Sungchul Ji

Molecular Theory of the Living Cell

Concepts, Molecular Mechanisms, and Biomedical Applications

Springer

Molecular Theory of the Living Cell

Sungchul Ji

Molecular Theory of the Living Cell

Concepts, Molecular Mechanisms, and Biomedical Applications

Springer

Sungchul Ji PhD
Dept. of Pharmacol. & Toxicol.
Ernest Mario School of Pharmacy
Rutgers University
Piscataway, NJ 08854, USA
sji@rci.rutgers.edu

ISBN 978-1-4614-2151-1 e-ISBN 978-1-4614-2152-8
DOI 10.1007/978-1-4614-2152-8
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2011945682

To my wife, Jaehyun Lee,
without whose advice, love and encouragement,
this book could not have been born.

Preface

There are three main objectives in writing this book – i) to summarize the key experimental observations on the living cell, ii) to develop a molecular theory of the living cell consisting of a set of concepts, molecular mechanisms, laws and principles, and iii) to apply the newly formulated theory of the living cell to solving concrete problems in biology and medicine, including the molecular mechanisms of force-generation in molecular motors (Chap. 8), morphogenesis (Chap. 15), the origin of life (Chap. 13), and evolution itself (Chap. 14).

The cell is arguably one of the most complex material systems in nature, in no small part because it is the building block of all living systems, including us. *We are cells, and cells are us*. To know how cells work, therefore, will contribute to understanding not only how our bodies work, which will advance medicine, but also how our mind works, which may help answer some of the age-old philosophical and religion-related questions from a new perspective. It is hoped that the molecular theory of the living cell presented in this book will contribute to the emergence of "the new science of human nature" that can lead "to a realistic, biologically informed humanism" (Pinker 2003). As a result of the research efforts of biologists around the world over the past several centuries, especially since the middle of the last century when the *DNA double helix* was discovered, we now have, as pointed out by de Duve (1991), a complete list of the components that constitute a living cell (e.g., see Table 17.2), and yet we still do not understand how even a single enzyme molecule works. There are tens of thousands of different kinds of enzymes in the human cell. We do not yet know how the cell expresses the right sets of genes at right times and right places for right durations in order to perform its functions under a given environmental condition.

Although many excellent books have been written on specialized aspects of the cell, such as the *Molecular Biology of the Cell* (Alberts et al. 2008), *Computational Cell Biology* (Fall et al. 2002), *Thermodynamics of the Machinery of Life* (Kurzynski 2006), and *Mechanics of the Cell* (Boal 2002), to cite just a few, there is a paucity of books that deal with the general principles, concepts, and molecular mechanisms

that apply to the living cell as a whole, with some exceptions such as Schrödinger's *What Is Life* written in the middle of the last century, Crick's *From Molecules to Men* (1966), Rizzotti's *Defining Life* (1996), and de Duve's *Blueprint of Life* (1991). The present book is probably the most recent addition to the list of the books on what may be called *theoretical cell biology* (in analogy to *theoretical physics*) that attempts to answer the same kind of questions raised by Schrödinger more than a half century ago (see Chaps. 16 and 21) and subsequently by many others.

During the course of writing the present book, I have often been reminded of a statement made by G. Simpson (1964) to the effect that physicists study principles that apply to all phenomena; biologists study phenomena to which all principles apply. For convenience, we may refer to this statement as the *Simpson thesis*. More recently, I came across another truism which may be referred to as the *de Duve thesis*: The problems of life are so fundamental, fascinating and complex that they attract the interest of all and can be encompassed by none (de Duve 1991, Preface).

True to *the Simpson thesis*, the present work deals with unusually wide-ranging topics, from inorganic electron transfer reactions (Sect. 2.2), single-molecule enzymology (Sect. 11.3), gene expression (Sect. 12.9), morphogenesis (Chap. 15), category theory (Chap. 21), the origin of life (Chap. 13), biological evolution itself (Chap. 14), personalized medicine (Chap. 18), to drug discovery (Chap. 19). True to *the de Duve thesis*, the readers will find numerous gaps in both the kinds of topics discussed (e.g., photosynthesis and immunology) and the factual details presented in some of the topics covered, reflecting the limitations of my personal background (as a physical-organic chemist-turned-theoretical-cell-biologist) in experimental cell biology and mathematical and computational skills.

Two revolutionary experimental techniques appeared more or less simultaneously and independently in the last decade of the twentieth century – the *DNA microarrays* (Sect. 12.1) (Watson and Akil 1999) and the *single-molecule manipulation* and *monitoring techniques* (Sect. 11.3) (Ishii and Yanagida 2000, 2007, van Oijen and Loparo 2010). With the former, cell biologists can measure tens of thousands of mRNA levels in cells simultaneously, unlike in the past when only a few or at most dozens of them could be studied at the same time. The DNA microarray technique has opened the window into a whole new world of complex molecular *interactions* underlying the phenomenon of life at the cellular level (see *interactomes*, Sect. 9.3), the investigation of which promises to contribute to deepening our understanding of the phenomenon of life as well as the phenomenon of mind on the most basic level (Pattee 1982, Thompson 2009).

In contrast to the DNA microarray technique which provides a global view of cell metabolism, the single-molecule measuring techniques (Ishii and Yanagida 2000, 2007, van Oijen and Loparo 2010) make it possible to probe cell metabolism at the level of single enzyme or DNA molecules. The single-molecule mechanical measurements are truly amazing, since, for the first time in the history of science, it is now possible to observe and measure in real time how a single molecule of *myosin*, for example, moves along an actin filament utilizing the free energy supplied by the hydrolysis of a single molecule of ATP (see Panel D in Fig. 11.33).

The theoretical investigations into the molecular mechanisms of *oxidative phosphorylation* in *mitochondria* that I began in 1970 as a postdoctoral fellow under David E. Green (1910–1983) at the Institute for Enzyme Research, University of Wisconsin, Madison, had led me to formulate the concept of the *conformon* in 1972–1985 (see Chap. 8) and the *Principle of Slow and Fast Processes* (also known as the *generalized Franck-Condon principle*) in 1974 (Sect. 2.2.3) and construct what appears to be the first *theoretical model* of the living cell called the *Bhopalator* in 1985 (Sect. 10.1). These theoretical models and related theoretical ideas and principles are summarized in this book, and an attempt has been made to apply them to analyze some of the rapidly expanding experimental data generated by the two revolutionary techniques mentioned above. In addition, these theoretical results have been utilized to formulate possible solutions to many of the basic problems facing the contemporary molecular, cell, and evolutionary biology.

When I formulated the concept of the *conformon* in 1972 (see Chap. 8) in collaboration with D. E. Green, I did not realize that I would be spending a good part of the next four decades of my life doing theoretical research on this concept and related physical, chemical, and philosophical principles, including the g*eneralized Franck-Condon principle* (GFCP), or the *Principle of Slow and Fast Processes* (PSFP) (Sect. 2.2). If *conformons* do indeed exist in biopolymers as appears likely on the basis of the currently available experimental data and theoretical considerations (see Chap. 8 and Sect. 11.4), the following generalizations may hold true:

1. The cell is an organized system of *molecular machines,* namely, biopolymers (DNA, RNA, proteins) that carry out microscopic work processes including enzymic catalysis, active transport, molecular motor movement, gene expression, DNA repair, and self-replication.
2. Conformons are packets of mechanical energy stored in sequence-specific sites within biopolymers derived from *chemical reactions based on generalized* Franck-Condon mechanisms (Sect. 8.4).
3. Therefore, the living cell is a supramolecular machine driven by chemical reactions mediated by conformons.

These statements can be schematically represented as follows:

CHEMICAL REACTIONS $\longrightarrow$ ***Conformons*** $\longrightarrow$ **LIFE** (0–1)

The most recent and most direct experimental verification to date of the conformon concept was reported by Uchihashi et al. (2011, Junge and Müller 2011; see Sect. 7.1.5) who, using the high-speed atomic force microscopy, succeeded in visualizing the propagation of the conformational waves (or *conformons*) of the β subunits of the isolated F_1 ATPase stator ring. It now appears that the conformon concept has been verified more than four decades after it was proposed by Green and Ji (1972a,b, Ji 1974, 1991, 2000; Chap. 8 in this book).

In (Ji 1991), conformons were postulated to mediate what I elected to call *the cell force*. The cell force was invoked to account for the *functional stability* of the living cell in analogy to the strong force which was invoked by physicists to account

for the *structural stability* of the atomic nuclei (Han 1999; Huang 2007). One of the most significant findings resulting from writing this book, I believe, has been the recognition that the whole-cell RNA metabolic data measured with microarrays may provide the first experimental evidence for the cell force. This is discussed in Chaps. 12 and 13.

My desire to test the validity of Scheme (0–1) as objectively and as rigorously as possible has led me to explore a wide range of disciplines during the past four decades, including not only biology, physics, chemistry, engineering, and computer science but also mathematics, linguistics, semiotics, and philosophy. The numerous principles, laws, and concepts that I have found necessary to account for the phenomenon of life on the molecular and cellular levels have been collected and explained in Part I of this book. Part II applies these principles, laws, and concepts to formulate a comprehensive *molecular theory of life* which I have at various times referred to as *biognergetics* (Ji 1985), *biocybernetics* (Ji 1991), *microsemiotics* (Ji 2002a), *molecular information theory* (Ji 2004a), and *renormalizable network theory of life* (Sect. 2.4), depending on the points of emphasis or prescinding (to use a Peircean idiom (Sect. 6.2.12)). The molecular theory of life developed in Part II is then utilized in Part III to formulate possible solutions to some of the basic problems facing the contemporary molecular and cell biology, including the definitions of the gene and life, mechanisms of molecular machines, morphogenesis and evolution, and the problems of interpreting DNA microarray data (Ji et al. 2009a) and the single-molecule enzymological data of Lu, Xun, and Xie (1998); Xie and Lu (1999); and Ishijima et al. (1998). Possible applications of the molecular theory of the living cell developed in this book to drug discovery research and personalized medicine are also included in Chaps. 18 and 19.

Piscataway, NJ, USA Sungchul Ji

Acknowledgments

Through the generous scholarship acquired for me by Prof. Chester Wood of the University of Minnesota, Duluth (UMD), whom I had met in Seoul, Korea, when I was working as the English translator/interpreter for Dean Kyun Sang Lee of the College of Engineering, Seoul National University, I came to this country in 1962 to continue my education at UMD, graduating in 1965 with BA in chemistry and mathematics. I am grateful to Mr. and Mrs. Willard B. Matter and Rev. and Mrs. William L. Halfaker of Duluth, Minnesota for their kindness with which they invited me into their homes as a house guest while I attended UMD.

After obtaining a Ph.D. degree in physical organic chemistry from the State University of New York at Albany in 1970 and having taught chemistry at the Mankato State College for the previous 2 years while writing my thesis, I embarked on an unusually long postdoctoral journey, from 1970 to 1982, doing research successively in theoretical bioenergetics and mitochondriology (Enzyme Institute, University of Wisconsin, Madison), experimental biophysics (Johnson Research Foundation, University of Pennsylvania School of Medicine, Philadelphia), microcirculation physiology and tissue photometry (Max Planck Institute of Systems Physiology, Dortmund, West Germany), and organ and biochemical toxicology (Department of Pharmacology, University of North Carolina School of Medicine, Chapel Hill). I want to thank David E. Green, Britton Chance, Manfred Kessler, and Ronald Thurman for their professional guidance and support for my research during these years.

Since coming to Rutgers in 1982, my research efforts have benefited from the light teaching and administrative duties placed on me and from the free and friendly scholarly atmosphere of the Department of Pharmacology and Toxicology, Ernest Mario School of Pharmacy (EMSP), fostered under the leadership of Deans John L. Colazzi and Christopher Molloy and Chairs Robert Snyder and Debra Laskin. My research in experimental and theoretical toxicology and cell biology was also aided, directly or indirectly, by many of my colleagues at EMSP, including Fredrick Kauffman, Kenneth Reuhl, Mike Iba, and Andrew Gow, and by the many bright

undergraduate and Pharm. D. students who took my courses titled *Theoretical Aspects of Pharmacology* (since 2000) and the *Theoretical and Computational Cell Biology* (since 2005).

I want to express my special thanks to Joel Lebowitz for introducing me to Harry Blom, the physics editor of Springer, New York, during the cocktail party at the 96th Statistical Mechanics Conference held at Rutgers in December, 2006. It was Harry with whom I began to communicate about my interest in writing a book on *theoretical cell biology*, a novel topic. I am grateful to Harry for his acceptance and encouragement for me to write this book. I am also grateful to my current editor, Christopher Coughlin, for his patience and helpful advices given to me throughout the 3 years of my book writing and to Project Manager, Ms. Jayanandan Greetal-Carolyn for her efficient cooperation.

Finally, I want to thank the authors and publishers who gave me the permissions to use their figures that appear in this book as indicated in appropriate places.

Contents

Chapter 1
Introduction

The cell doctrine stating that all living systems are built out of one or more cells was formulated by M. J. Schleiden and T. Schwann in 1838–1839 (Swanson 1964; Bechtel 2010). Since then an enormous amount of experimental data has been accumulating in the literature and on the World Wide Web, pre- and post-Google, on the structure and function of the cell, based on which many authoritative books have been written, one of the most recent publications being *The Molecular Biology of the Cell*, Fifth Edition, by Alberts and his colleagues (2008). Other publications include "Computational Cell Biology" (Fall et al. 2002) and *Mechanics of the Cell* (Boal 2002), which are highly mathematical and computer model based and deal with rather specialized subfields within molecular cell biology. To the best of my knowledge (as of January, 2012) there has been no general book published that deals with the *molecular theory* of the living cell as a whole, except, as mentioned in the *Preface*, the books by Schrödinger (1998), Crick (1966), and Rizzotti (1996). The present book may be viewed as the twenty-first-century version of *What Is Life?* that has been updated by taking into account the biological knowledge that has accumulated since 1944 when *What Is Life?* was published. The molecular theory of life formulated by Schrödinger and that described in this book are compared in Sects. 16.2 and 16.6 and Chap. 21.

To emphasize the importance of *theory* in relation to *experiment* in biology, I elected to entitle the present book after the title of the book by Alberts et al. (2008) by (1) replacing *Biology* with *Theory* and (2) adding the adjective *Living* in front of the word *Cell*, resulting in *The Molecular Theory of the Living Cell*. The first modification highlights the difference between the *theory* of life emphasized in this book and the *experiment* on life comprehensively summarized in Alberts et al. (2008). The second modification emphasizes the difference between the *static picture* of the cell normally found in textbooks (analogous to *sheet music*) and the *dynamic* picture of the cell (analogous to *audio music*) emphasized in the present book. Also, unlike the books by Alberts et al. and by others that focus on experimental data obtained from broken (and hence "dead") cells, the present book attempts to understand the essential characteristics of cells that are unbroken and

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_1,

"alive," by developing a molecular *theory* of life based on both the experimental findings on dead cells and theoretical concepts applicable to *living* cells.

The concept of "theory" in biology is relatively new and seemingly alien to most practicing biologists. Biologists have learned throughout the recent history of molecular cell biology that many breakthroughs in biology are possible without any deep biological theory (witness: the discovery of the DNA double helix, the deciphering of the genetic code, the completion of the human genome sequencing project, and many fundamental findings in stem cell research [Holden and Vogel 2008]). As a consequence, biologists may have unwittingly come to entertain the view that no deep theory, comparable to quantum mechanics in physics and chemistry, is needed in biology. In fact many bioscientists may hold the opinion that living systems are too complex for any deep theoretical approaches to be possible, as one of the most respected living biologists whom I know once challenged me: *Why do theory when you can solve problems by doing experiments?* Such a perspective on theory found among many biologists contrasts with that of contemporary physicists who most often carry out experiments in order to test the predictions made by theory (Moriyasu 1985). It is hoped that the publication of the present book will contribute to establishing a culture in biology wherein theory is viewed as essential as experiments in solving problems in biology.

To gauge what a future *molecular theory of biology* may look like, it may be useful to survey other fields of human inquiries where *experiment* and *theory* have established firm relations. As summarized in Table 1.1, physics, chemistry, and linguistics appear to have progressed through three distinct stages of development, viewed either globally/macroscopically or locally/microscopically. Some of the boxes in the table are empty by definition. Assuming that biology will also follow the three stages of *description*, *organization*, and *theory building*, I have filled in the boxes belonging to Biology based primarily on my own research experience over the past four decades (i.e., 1970–2012). It is possible that there are many other candidates that can fill these boxes and that any of my own theories may be replaced by some of these in the future. There are a total of ten theories listed in the last column of the Biology section, all of which are discussed throughout this book in varying details.

Table 1.1 The three stages of the development of human knowledge. "TOE" stands for the Theory of Everything. Examples of each field are selected from two levels – global (or macroscopic) and local (or microscopic). Boxes labeled (3, 1), (3, 2), (6, 1), (6, 2), (9, 1), (9, 2), (12, 1), and (12, 2) are empty because the third row of each field applies to the "Theory building" column only

Field		Description	Organization	Theory building
Physics	1. Global	Astronomy	Kepler's laws	Newton's laws of motion
				Einstein's relativity
	2. Local	Atomic line spectra	Lyman, Balmer, Ritz-Paschen, etc., series	Bohr's atomic model
				Quantum mechanics
	3. TOE	(3, 1)	(3, 2)	Standard model
				Superstring theory
Chemistry	4. Global	Chemical reactions	Chemical kinetics	Thermodynamics
				Transition-state theory
	5. Local	Molecular structures	Periodic table	Statistical mechanics
				Electron density functional theory
	6. TOE	(6, 1)	(6, 2)	Quantum statistical mechanics (?)
Linguistics	7. Global	Descriptive linguistics	Chomsky's Universal Grammar (?)	F. de Saussure's semiology (?)
	8. Local	Descriptive linguistics	Grammars	F. de Saussure's linguistics (?)
			Lexicon	
	9. TOE	(9, 1)	(9, 2)	Peirce's semiotics (Sect. 6.2)
Biology	10. Global	Behavioral biology	Physiology	Darwin's theory of evolution
		Human genome project	Human anatomy	Prigogine's dissipative structure theory
		Transcriptomics	Cell doctrine	Cell language theory
		"Synthetic" stem cells	Cell structure and function	IDS-cell function identity hypothesis (Sects. 3.1, 6.1.2, 10.2)
			Reprogrammable genome	
	11. Local	Single-molecule mechanics	DNA double helix	Molecularized second law *of thermodynamics* (Sect. 2.1.4)
			Genetic code	Generalized Franck–Condon *principle* (Sect. 2.2.3)
			Metabolic pathways	Conformon theory of molecular machines (Chap. 8)
			Single-molecule enzymology	
	12. TOE	(12, 1)	(12, 2)	Biocybernetics (Ji 1991)
				Renormalizable network *Theory* (Sect. 2.4)
				Microsemiotics (Sect. 6.2.4)

Part I
Principles, Laws, and Concepts

Chapter 2
Physics

2.1 Thermodynamics of Living Systems

2.1.1 Three Thermodynamic Systems: Isolated, Closed, and Open

Thermodynamics is the scientific study of the production, transformation, and storage of heat and other forms of energy in material systems, including organisms. Thermodynamic systems can be divided into three classes – *isolated, closed*, and *open* (Prigogine 1980; Kondepudi and Prigogine 1998; Kurzynski 2006). Isolated thermodynamic systems do not exchange any *energy* nor *matter* with their environment; closed systems can exchange *energy* but not *matter* with their environment; and open systems can exchange both *energy* and *matter* with their environment. Obviously living systems are open thermodynamic systems. It should be pointed out that physicists often use the term "closed systems" in the sense of "isolated systems" in chemistry. Not distinguishing between *closed* and *isolated* systems can lead to confusions in thermodynamic discourses. For example, the entropy of an isolated system (e.g., the Universe) increases with time according to the Second Law of thermodynamics, but the entropy of a closed system (e.g., a refrigerator) need not increase with time.

Thermodynamic systems can be divided into two distinct groups based on another criterion, namely, whether or not a given thermodynamic system involves any dissipation of free energy. *Free energy* is different from *energy* in that it is a function not only of energy, E, a measure of the capacity of a system to do work, but also of entropy, S, a measure of the quality of energy. For example, the *Gibbs free energy*, G, of a thermodynamic system is defined as

$$\Delta G = \Delta E + P\Delta V - T\Delta S \tag{2.1}$$

where P, V, and T are pressure, volume, and temperature, respectively, of the thermodynamic system under consideration, and the symbol ΔX is defined as the difference in variable X between the initial and the final states of the system,

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_2,

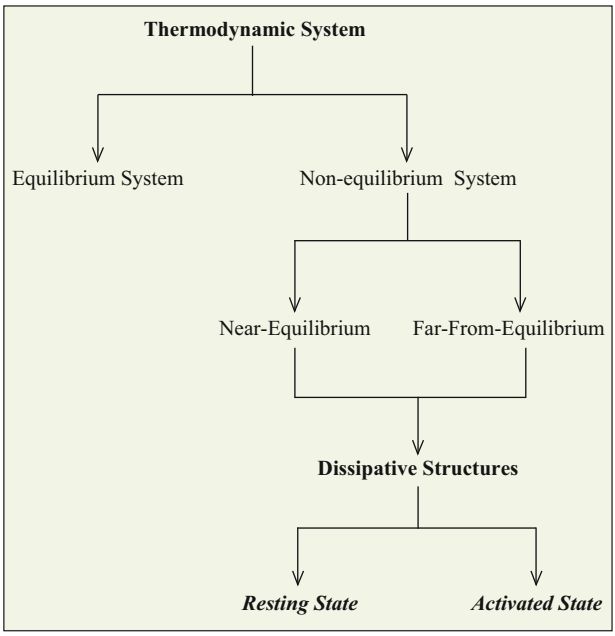


Fig. 2.1 The relationship between thermodynamic systems and dissipative structures

i.e., $\Delta X = X_{final} - X_{initial}$. The importance of Gibbs free energy in biology stems from the fact that under biological conditions (most often characterized by constant pressure and temperature), all spontaneous changes are accompanied by Gibbs free energy decreases, i.e., by *negative Gibbs free energy changes*, $\Delta G < 0$.

Equilibrium structures do not dissipate any free energy, but *dissipative structures* do (i.e., $\Delta G < 0$), as the name indicates (Prigogine 1977, 1980). In addition, dissipative structures can lead to the organization of matter in space (e.g., the flame of a candle) or in time (e.g., oscillating chemical concentrations in a test tube) (Babloyantz 1986). Organisms are excellent examples of dissipative structures (Prigogine 1977, 1980).

Though it had been known for a long time that living systems must obey the same laws of thermodynamics that originated from the study of nonliving systems, such as the steam engine invented in the 1700s, the first serious attempt to formulate the theoretical connection between thermodynamics and biology seems to have been made by I. Prigogine (1917–2003) and his groups at the Free University of Brussels in Belgium and the University of Texas at Austin (Prigogine 1977, 1980; Nicolis and Prigogine 1977; Kondepudi and Prigogine 1998; Kondepudi 2008). Prigogine and his coworkers have established the concept that irreversible physicochemical processes occurring in *far from equilibrium* systems are necessary for any constructive process, variously referred to as "self-organizing processes," "self-organization," or "dissipative structures." These and related terms are diagrammatically represented in Fig. 2.1.

Equilibrium structures such as atoms can exist in two states – *ground state* and *excited state*, and the transitions between them require absorbing or emitting/releasing energy as in electronic transitions of atoms giving rise to atomic line spectra (see Fig. 10.5b) (Moore 1963). Nonequilibrium structures divide into two classes – near-equilibrium systems obeying the *Onsager reciprocity relation* (Prigogine 1980, pp. 84–90) and far-from-equilibrium systems exhibiting nonlinear behaviors such as amplification, self-organization, *metastability* (Kelso 1995; Kelso and Engstrøm 2006), and *deterministic chaos* (Domb 1996; Prigogine 1980, pp. 103–150). Although chemical reaction-diffusion systems have been claimed to require far-from-equilibrium conditions in order to exhibit self-organization (Prigogine 1980, pp. 103–150), we cannot exclude the possibility that enzyme-catalyzed chemical reaction-diffusion systems can self-organize in space and time even at near-equilibrium in living systems due to the *nonlinear behaviors inherent in enzymes themselves*. If this conjecture proves to be true, the far-from-equilibrium condition of Prigogine may not be universally necessary for biological organizations. Dissipative structures such as cells can exist in two states – "resting," and "activated" or "energized." Examples of resting dissipative structures include quiescent immune cells such as Kupffer cells in the liver (Laskin 2009; Laskin et al. 2010) and quiescent neurons, and the examples of activated dissipative structures are exemplified by immune cells activated by cytokines (Laskin et al. 2010) and neurons exhibiting function-related firing patterns triggered by neurotransmitters.

2.1.2 Free Energy vs. Thermal Energy in Enzymic Catalysis

Thermal fluctuations (also called *Brownian motions*) are essential for life (see Sects. 11.3.3 and 12.12). According to the *conformon theory* of enzymic catalysis (Ji 1974a, b, 2000), (1) enzymes require thermal fluctuations for their activities, (2) thermal fluctuations of enzymes require heat, and hence (3) enzymes need heat to function. Despite their obvious importance, the *thermal motions* and *thermal energies* are often viewed by biologists as irrelevant or even harmful to living processes on the molecular level.

It is important to distinguish between two kinds of energy – *free energy* and *thermal energy*. Free energy (e.g., Gibbs free energy, G) is a *useful form of energy*, being a function of both *energy* (E) and *entropy* (S) (Kondepudi and Prigogine 1998; Kondepudi 2008; Moore 1963) as already indicated (see Eq. 2.1), whereas thermal energy cannot be utilized to do any useful work without temperature gradient. Life depends on free energy which is needed to "pump up" living systems. To use thermal energy without temperature gradient is tantamount to violating the Second Law of thermodynamics. This is probably why biologists have been reluctant to implicate any thermal energy in living processes (which mostly occur under *homeothermic conditions*, i.e., without any temperature gradient). But, according to the conformon theory of enzymic catalysis, thermal energy can be utilized by enzymes "transiently" without violating the Second Law, even in the absence of any sustained temperature

gradients (Ji 1974b, 1979, 2000). Enzymes are like someone borrowing a large amount of money, M, from a bank overnight and paying it back before the bank opens the next morning. The important ingredient here is this: The money, M′, used to pay the bank back before it opens is not the same as M borrowed from the bank during the night, because M was used to complete a business transaction during the night which led to M′ (which is assumed to be greater than M), out of which M was paid back. In other words, although the *amount* of the money paid back is the same as that of the money borrowed from the bank overnight, the *identity* of the money, M′, can be different from that of the money, M, borrowed overnight. This analogy explains what is meant by thermal energy playing an essential role in living processes. Thermal energy is analogous to M and free energy is analogous to M′. So, just as the profit, M′−M, from the above imaginary business transaction required the initial investment of money M borrowed from the bank, so the free energy released, M′, from, say, the oxidation of NADH to NAD^+, requires the initial input of thermal energy, M, without which no catalysis can occur nor free energy released from chemical reactions. We may refer to this analogy between *energies* and *monies* as the "*overnight-bank-loan analogy* (OBLA)" enzymic catalysis.

The content of OBLA is consistent with the Second Law of thermodynamics reformulated in (McClare (1971) (see Sect. 2.1.4 below). McClare introduced time into his reformulation of the Second Law so that the law now becomes applicable to systems at the molecular level. If McClare's version of the Second Law is valid, the application of the traditional version of the Second Law to molecular processes such as Brownian motions may lead to invalid conclusions or contradictions.

Free energy is necessary but not sufficient for catalysis or for life. You can have a cell population in a test tube with high concentration of nutrients such as glucose and oxygen, but cells cannot use these nutrients to do any useful work such as pumping ions or crawling around at 0°C, simply because enzymes cannot work at this temperature due to lack of sufficient thermal energies or thermal fluctuations. We can therefore make the following generalization:

> Enzymes must first be "heated up" before they can catalyze chemical reactions to drive living processes (2.2)

Equivalently, we can state that:

> Living processes cannot occur unless a sufficient amount of thermal energy is provided first followed by free energy. (2.3)

Statement 2.3 may be referred to as the "thermal-energy-first-free-energy-later (TEFFEL)" hypothesis.

2.1.3 The First Law of Thermodynamics

This law states that the energy of the Universe (or of any isolated system) remains constant. In other words, the amount of energy of an isolated system cannot be

increased or decreased; only its form can be changed. Since energy, E, and matter, m, are equivalent and interconvertible according to *Einstein's special relativity theory*, i.e., $E = mc^2$, where c is the speed of light, 10^{10} cm/s (Shadowitz 1968), the term energy in the expression of the First Law of thermodynamics should, strictly speaking, be replaced by *energy and matter*, which is often written as "energy/matter" or more briefly as "mattergy." That is, according to the First Law of Thermodynamics, it is the mattergy of the Universe that is conserved and not its matter or energy separately. I will adopt 'mattergy' throughout this book.

2.1.4 The Second Law of Thermodynamics

The most important contribution that Colin McClare (1937–1977) made to biology in his short life may be to have introduced time explicitly in 1971 in his reformulation of the Second Law of Thermodynamics so that it can be applied to molecules (McClare 1971). Before his work, classical thermodynamicists (since around 1850) believed that the Second Law was a statistical law and hence cannot be applied to individual molecules. The classical formulation of the Second Law (e.g., by Kelvin) states that:

> It is impossible to devise any engine which, working in a cycle, shall produce no effect other than the extraction of heat from a reservoir and the performance of an equal amount of mechanical work. (2.4)

McClare reformulates the Second Law in a similar vein but with an explicit implication of time τ:

> It is impossible to devise an engine, of any size whatever, which, acting in a cycle which takes a time τ, shall produce no effect other than the extraction of energies, which have equilibrated with each other in a time less than τ, from a reservoir at one temperature and the conversion of these energies into a form in which they would remain stored for longer than τ; either at a higher temperature, or in a population-inversion. (2.5)

We may refer to Statement 2.5 as the *microscopic version of the Second Law* (or the *McClare version of the Second Law*), in contrast to the classical one which would then be referred to as the *macroscopic version*. These two versions of the Second Law may be related to each other as Newtonian (macroscopic) mechanics is related to quantum (microscopic) mechanics.

Consistent with the microscopic version of the Second Law, there appears to be at least two mechanisms by which chemical energy can be converted to mechanical energy (as happens in many biological systems such as the actomyosin system, molecular motors, and ion pumps) (see Chap. 8 and Sect. 11.3). One is the *resonance mechanism* proposed by McClare himself (1971, 1974), and another is the *conformon mechanism* that I proposed in the same meeting where McClare presented his theory (see Fig. 3 in Ji (1974b)).

In (McClare 1974, p. 108), McClare's resonance-based mechanism of chemical-to-mechanical energy conversion was criticized by G. Weber of the University of Illinois, Urbana, but the Franck–Condon principle-based conformon mechanism is

immune to such criticisms. The conformon mechanism (Chap. 8) can utilize thermal energy to catalyze chemical reactions without violating the Second Law, because enzymes can store thermal energy *transiently*, i.e., *for a time shorter than* τ, the cycling (or turnover) time of enzymes. In other words, although McClare's molecularization of the Second Law is valid, his suggested mechanism of chemical-to-mechanical energy conversion based on resonance mechanism may suffer from the problem of thermalization, since the resonance energy stored in electronic excited states of most enzymes cannot last for times longer than τ before being dissipated into heat and hence is unlikely to be utilized by molecular machines in living cells.

2.1.5 *The Third Law of Thermodynamics and "Schrődinger's Paradox"*

The Third Law of Thermodynamics was developed by Walter Nernst (1864–1941) of the University of Gőttingen during the years 1906–1912 and can be stated in several equivalent ways, including the following (http://en.wikipedia.org/wiki/Third_law_of_thermodynamics) (Atkins 2007).

> The entropy of most pure substances approaches zero as the absolute temperature approaches zero. (2.6)

> If the entropy of each element in some (perfect) crystalline state be taken as zero at the absolute zero of temperature, every substance has a finite positive entropy; but at the absolute zero of temperature the entropy may become zero, and does so become in the case of perfect crystalline substances. (G. N. Lewis and M. Randall 1923) (2.7)

Statements 2.6 and 2.7 can be expressed algebraically thus:

$$S \geq 0 \tag{2.8}$$

where S is the entropy of a thermodynamic system. Equation 2.8 is in turn equivalent to the Statement 2.9:

> The entropy of a thermodynamic system cannot be negative. (2.9)

Statement 2.9 is particularly useful in evaluating the concept of "negative entropy" first introduced by Schrödinger (1998) in 1944 with the following definition:

$$-S = k \log (1/D) \tag{2.10}$$

where k is the Boltzmann constant and D stands for "disorder." Schrődinger derived Eq. 2.10 by simply taking the negative of both sides of the entropy formula of

Boltzmann (1844–1906), Eq. 2.11, after replacing W with D, where W is the number of possible microstates compatible with the macrostate of a system (http://en.wikipedia.org/wiki/Boltzmann's_entropy_formula):

$$S = k \log W \tag{2.11}$$

Schrődinger then concluded that *negative entropy* is a measure of *order*:

> Hence the awkward expression "negative entropy" can be replaced by a better one: entropy, taken with the negative sign, is itself a measure of order. (2.12)

Evidently Eq. 2.10 defining the concept of "negative entropy" violates the Third Law according to which entropy cannot be negative; see Eq. 2.8. In other words, the *concept of "negative entropy" violates the Third Law of thermodynamics*. Since Eq. 2.10 violates the Third Law, its consequent, Statement 2.12, must also violate the same law, leading to the following conclusion:

> Negative entropy cannot be a measure of order. (2.13)

So we are now confronted with the following question: How can the same equation, Eq. 2.10, give rise to two opposing conclusions, Statements 2.12 and 2.13? One possible answer to this puzzle may be provided if it can be assumed (1) that there are two aspects to Eq. 2.10 – the formal (or syntactic) and physical (or semantic) aspects – and (2) that Eq. 2.10 is true formally (since it can be derived from Eq. 2.11 *logically,* by multiplying both sides of the equation with −1 and equating W with D) but untrue physically (since it *violates the Third Law* of thermodynamics). In other words, Eq. 2.10 that Schrődinger made famous among the generations of physicists, chemists, and biologists since 1944 is *paradoxical*. For this reason, we may refer to Eq. 2.10 and its equivalents as Schrődinger's *paradox* which can be defined more broadly as follows:

> Schrődinger's paradox refers to the mathematical equations, concepts, or general statements that are formally true but physically meaningless. (2.14)

Although "negative entropy (NE)" (an *absolute* value) cannot exist, due to the Third Law, the concept of "negative entropy changes (NEC)" (a *differential* value) is both *formally* sound and *physically* true and meaningful since NEC can be equated with *order* or *organization* without violating any laws of physics. In other words, although *entropy* cannot be negative, *entropy change* can be negative, zero, or positive:

$$\Delta S = S_A - S_B > 0 \tag{2.15}$$

$$\Delta S = S_A - S_B = 0 \tag{2.16}$$

$$\Delta S = S_A - S_B < 0 \tag{2.17}$$

where S_A and S_B refer to the absolute entropy contents of thermodynamic systems A and B, respectively, or two different sates of a given thermodynamic system, A being the final and B the initial states.

It is important to distinguish between an *absolute value* and a *differential one*, because conflating these two kinds of values can lead to paradoxes. For example, RNA levels in a cell are differential values that are determined by the balance between two opposing processes, RNA synthesis (or transcription) and RNA degradation, whereas the RNA level in a test tube without RNA degrading enzymes would be an absolute entity. Not distinguishing between these two distinct RNA entities have led to numerous errors in interpreting DNA microarray data since the mid-1990s (see Chap. 12) (Ji et al. 2009a). Similarly, conflating "entropy" (an absolute entity) and "entropy change" (a differential entity) can be viewed as the root cause for Schrődinger's paradox, Statement 2.14.

It would be convenient to adopt the term "negentropy" first introduced by Brillouin in 1953 to *formally* (or syntactically) represent either "negative entropy (NE)" (an absolute entity) or "negative entropy change (NEC)" (a differential entity). Since, *physically* (or semantically), NE does not exist, "negentropy" by default would stand for "negative entropy change." Using "negentropy" in this carefully defined sense, we can formulate Statement 2.18 which is physically meaningful:

> Negentropy is a measure of order. (2.18)

The seemingly contradictory Statements 2.13 and 2.18 can be combined into one true statement as shown below:

> Negentropy defined as "negative entropy change" can, but negentropy defined as "negative entropy" cannot, be a measure of order. (2.19)

It may be convenient to refer to Statement 2.19 as the *negentropy principle of order* (NPO).

There may be many situations similar to *Schrődinger's paradox,* Eq. 2.10. Two examples are (1) *Maxwell's Demon*, and (2) *Brillouin's NPI* (Negentropy Principle of Information):

1. Maxwell introduced his famous demon in 1871 (Brillouin 1951):

> He will, thus, without expenditure of work raise the temperature of B and lower that of A, ... (2.20)

It is asserted here that Statement 2.20 is an example of *Schrődinger's paradox*, because it contains a phrase that is *syntactically* (or formally) *sound* but *physically* (or semantically) meaningless in view of the fact that the Second Law prohibits changing temperatures without dissipating free energy (i.e., *without expending work*). Thus, it may be concluded that Maxwell's demon cannot exist or violates the Second Law.

2. In my opinion, another prominent example of *Schrődinger's paradox* is what is known as "Negentropy Principle of Information (NPI)" (Brillouin 1951, 1953, 1956), according to which information is negentropy:

$$\textbf{Information} = \textbf{negentropy}\,(\text{negative entropy}) \tag{2.21}$$

It is here asserted that Eq. 2.21 is equivalent to Statement 2.12 with "order" replaced with "information" and hence untrue. The true relation between *negentropy* and *information* can be obtained by simply replacing "order" with "information" in Statement 2.19, since "order" and "information" can be related in the sense that "ordering" entails *reducing uncertainty* which characterizes information (Klir 1993):

> Negentropy defined as "negative entropy change" can, but negentropy defined as "negative entropy" cannot, be a measure of information. (2.22)

In other words, Statement 2.22 asserts that the *negentropy-information relation* is paradoxical just as *negentropy-order relation* is, because the truth or the falsity of the relations critically depends on whether the term *negentropy* is defined as an *absolute* entity or a *differential* one.

2.1.6 Are There More Laws of Thermodynamics?

It is proposed here (see Table 2.1) that:

> Thermodynamics can be defined as the scientific study of heat transfer, transduction, and production on both the macroscopic and microscopic scales. (2.23)

Heat transfer or diffusion occurs along temperature gradients, from hot to cold; heat transduction is involved when the steam engine converts thermal energy to mechanical energy, the maximum efficiency, ε, being given by $\varepsilon = 1 - T_{sink}/T_{source}$ (Atkins 2007; Kondepudi 2008); and heat is produced when exothermic chemical reactions occur transforming matter into heat energy obeying Einstein's equation, $E = mc^2$, although the changes in the mass, $\Delta m = m_{reactant} - m_{product}$, that accompany chemical reactions are usually too small to be detected using

Table 2.1 The domains of thermodynamics. Thermodynamics can be defined as the study of heat *production, transfer*, and *transformation* at both the macroscopic and microscopic levels

		Thermodynamics	
		Abiotic	Biotic
Scale	*Macroscopic*	Classical thermodynamics	Classical biology
	Microscopic	Statistical thermodynamics and quantum mechanics	Molecular biology

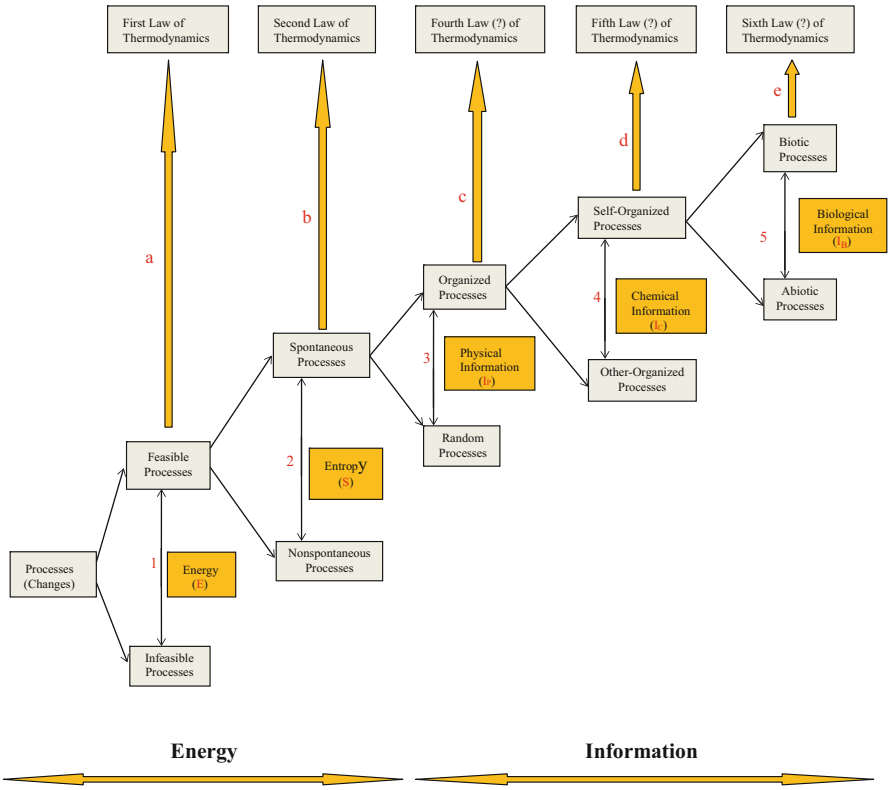


Fig. 2.2 The five levels of bifurcations of natural processes. Each bifurcation is postulated to be associated with a fundamental concept (e.g., entropy) and a law (e.g., the Second Law of Thermodynamics) as indicated in the *boxes* above an *arrow*

current technology. Based on Definition 2.23, we can infer that physicochemical systems that involve heat changes are the legitimate domain of thermodynamic investigations, and such physical chemical systems include everything and every process in the Universe, from subatomic to cosmological processes. Thus, it may be concluded that thermodynamics is the most comprehensive of all the natural sciences developed so far in human history. Since living processes, from enzymic catalysis (see Sect. 11.3.3) to physiology of the human body, critically depend on heat, the scientific study of enzymes and the human body belongs to the domain of thermodynamics, although traditional thermodynamics has mainly focused on the study of abiotic systems such as steam engines and refrigerators so that simple mathematical tools could be applied.

Processes or changes can be classified into two groups – *feasible* and *infeasible*, depending on whether or not the process under consideration obeys the First Law of

thermodynamics (FLT) (see Step 1 in Fig. 2.2) (Atkins 2007). FLT states that the energy and matter (or more briefly *mattergy*) of the Universe are (or is) conserved. *Feasible* processes can be divided into two classes – *spontaneous* and *nonspontaneous*. Spontaneous processes increase, and nonspontaneous processes decrease, the entropy of the Universe (see Step 2). *Spontaneous* processes can be divided into *organized* processes exhibiting some patterns and regularities and *random* processes showing no recognizable patterns, depending on whether or not physical information (I_P) (e.g., the universal constants) affect or constrain the processes under consideration (see Step 3). Organized processes divide themselves into *self-organized* (e.g., Belousov–Zhabotinsky reaction) and *other-organized* processes (e.g., Bernard convection cells) (Sect. 3.1), depending on whether the organization is driven by chemical reactions (encoding chemical information, I_C) occurring inside or outside the thermodynamic system under consideration (see Step 4). Finally, *self-organizing* processes can be divided into *biotic* (i.e., living) and *abiotic* (i.e., nonliving) processes, depending on whether or not the processes under consideration are parts of (or associated with) self-reproducing systems controlled by biological information, I_B (see Step 5). The first two laws of thermodynamics are related to *free energy* (or *energy* more conveniently), while the last three "suggested" laws concern *information* defined at the three distinct levels of *physics, chemistry*, and *biology*, designated as I_P, I_C, and I_B, respectively. This seems consistent with the *information–energy complementarity principle* formulated in the early 1990s (Ji 2002b, 2004b). The contents of the suggested laws may be stated as follows:

4th Law: *Not all spontaneous processes are random.*
5th Law: *Not all organized processes are driven by external forces.*
6th Law: *It is impossible to self-reproduce without biological information.*

If the bifurcation scheme shown in Fig. 2.2 is correct, it may be concluded that thermodynamics has two *complementary* aspects – the *energetic* and the *informatic*. Classical thermodynamics mainly deals with the energetic aspect of thermodynamics while the informatic aspect of thermodynamics has been almost totally ignored, except in statistical mechanics where Boltzmann introduced the concept of information in the form of the number of microstates, W (called "complexion"), in his equation for entropy (see Eq. 2.11). Just as classical mechanics encountered a conceptual crisis about a century ago when it encountered the phenomenon of blackbody radiation which was not resolved until the quantum of action was invoked and quantum mechanics was formulated (see Rows 4, 5, and 6 of the second column in Table 2.2), so it may be that classical thermodynamics is facing a conceptual crisis with the discovery of the phenomena of self-reproduction, morphogenesis (also called ontogenesis) and biological evolution (also called phylogenesis) which may not be resolved until novel concepts such as gnergons are introduced and a new field of inquiry such as *gnergetics* is established (see Rows 4 and 5 of the third column in Table 2.2).

Table 2.2 Is classical thermodynamics at a cross-road, just as classical mechanics was about a century ago?

	Classical mechanics	Classical thermodynamics
1. Object of study	Moving objects	Heat
2. *Kinematics*: description of the space and time coordination of moving objects or changes without regard to causes	Astronomy (describing the movement of planets around the sun, etc.)	Conservation of energy
	Descriptive chemistry	Entropy production in irreversible processes
	Descriptive physiology	Heat flow from hot to cold
	Descriptive pharmacology (e.g., therapeutic index)	Free energy decrease in spontaneous chemical reactions
	Descriptive molecular biology	
3. *Dynamics*: study of the causes of motions or changes	Universal gravitation	Role of boundary conditions in self-organizing chemical reaction-diffusion systems (?)
	Mass-induced spacetime deformation	
4. Crisis	Blackbody radiation (i.e., the ultraviolet catastrophe)	Self-reproduction
		Genetic code
		Morphogenesis
		Biological evolution
5. Resolution	Quantum of action (1900)	Constructal law[a]
		Gnergons[b] (?)
6. New field	Quantum mechanics (1900–1925)	Gnergetics[c] (twenty-first century?)

[a]The new physical law formulated by Bejan (1997; Bejan and Lorente 2010) who claims that "For a finite-size system to persist in time (to live), it must evolve in such a way that it provides easier access to the imposed (global) currents that flow through it"

[b]Discrete units (-ons) of information (gn-) and energy (-erg-), as exemplified by conformons (Chap. 8). Direct experimental evidence have been obtained in recent years for conformons in DNA (Sect. 8.3) and myosin head (Sect. 8.4)

[c]The study of both information (gn-) and energy (-ergy) changes in thermodynamic systems, both macroscopic and microscopic (Ji 1985a)

2.2 The Franck–Condon Principle (FCP)

2.2.1 FCP and Born–Oppenheimer Approximation

The Franck–Condon Principle originated in molecular spectroscopy in 1925 when J. Franck proposed (and later Condon provided a theoretical basis for) the idea that, when molecules absorb photons to undergo an electronic transition from the ground state (see E_0 in Fig. 2.3) to an excited state (E_1), the electronic transition occurs so rapidly that heavy nuclei do not have time to rearrange to their new equilibrium positions (see q_{01}). In effect, this means that the photon-induced electronic transitions are most likely to occur from the ground vibrational level (i.e., $\nu'' = 0$) of the ground electronic state to an excited vibrational level (i.e., $\nu' = 2$) of the upper

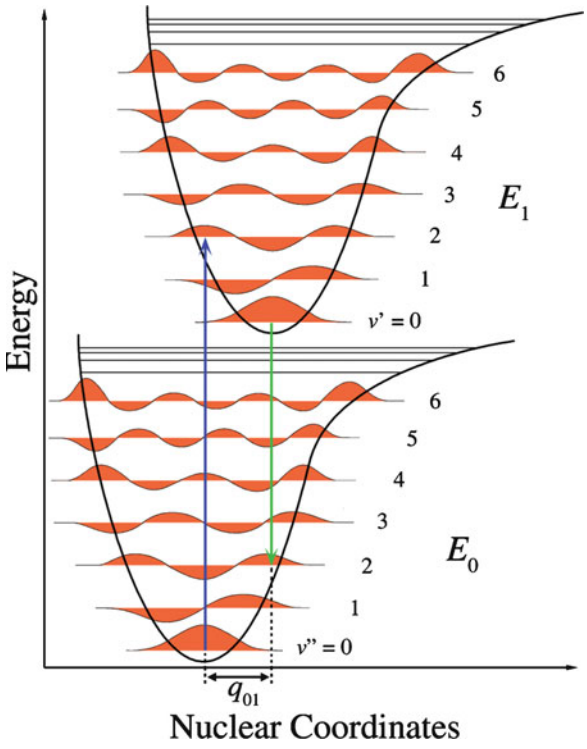
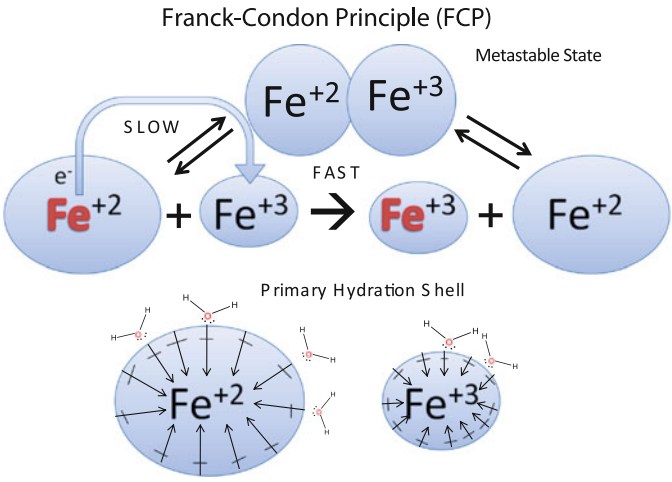


Fig. 2.3 A schematic representation of the Franck–Condon principle (Reproduced from http://en.wikipedia.org/wiki/Franck-Condon_principle). The *upward arrow* indicates the most favored vibronic (i.e., both vibrational and electronic) transition predicted by the Franck–Condon principle. The *downward arrow* indicates electron transfer from the electronic excited state, E_1, to the ground electronic state, E_0. See text for more detail

electronic state (see the vertical upward arrow in Fig. 2.3) which rapidly decays to the ground vibrational level, $v' = 0$, from which electron transfer is most likely to occur to the excited vibrational level of the ground electronic state, i.e., $v'' = 2$ (see the downward arrow), with the concomitant emission of the photon or fluorescence. A year later, Born and Oppenheimer justified what later became known as the Franck–Condon principle in terms of the large mass difference between the electron and average nuclei in a molecule (Born and Oppenheimer 1927). The proton is 1,836 times as massive as the electron.

The Born–Oppenheimer approximation is also known as the "adiabatic pathway" meaning that there is a complete separation between nuclear and electronic motions within atoms. Although this approximation has been found to be generally valid in atomic and molecular spectroscopy and in chemical reactions, there are also well-established exceptions, which are referred to as "nonadiabatic pathways," or "non-Born–Oppenheimer coupling" (Bowman 2008; Garand et al. 2008).



(Drawn by Julie Bianchini, 2008)

Fig. 2.4 The Franck–Condon principle in action in one of the simplest chemical reactions known, i.e., the one-electron redox reaction of the iron ions. (*Lower*) Due to the greater charge density around the ferric ion (Fe^{+3}), as compared with that around the ferrous ion (Fe^{+2}), water dipoles (depicted as *crossed arrows*) are more strongly attracted to the former than to the latter, forming smaller and tighter primary hydration shell around Fe^{+3} than around Fe^{+2}. (*Upper*) The electron transfer process is much faster than the nuclear rearrangements accompanying hydration shell changes (due to the proton being ~2,000 times more massive than the electron). The hydration shells around the Fe^{+3} and Fe^{+2} ions contract and expand (i.e., "breath") periodically as a consequence of thermal fluctuations or Brownian motions (not shown) (Drawn by Julie Bianchini, 2008)

2.2.2 *Franck–Condon Principle in Chemistry*

It is well established in inorganic electron transfer reactions that electron transfer processes must be preceded by the reorganization of the *solvation* (also called hydration) *shells* surrounding reactants (Reynolds and Lumry 1966). It was Libby (1952) who accounted for this phenomenon based on the Franck–Condon principle, suggesting that, *before the fast electron transfer can occur, the slower nuclear rearrangements of water molecules in the hydration shells must take place*. This is schematically illustrated in Fig. 2.4. The overall reaction involves the transfer of one electron from the ferrous ion, Fe^{+2}, to the ferric ion, Fe^{+3}. Due to the charge difference, the hydration shell around the ferric ion is more compact than the hydration shell around the ferrous ion. Despite this, there is a finite probability that the two hydration shells assume similar sizes at some time points (as the result of thermal fluctuations) as depicted by the two identically sized spheres partially overlapping in the upper portion of Fig. 2.4. Such a transient, metastable state is known as the *Franck–Condon state* or the *transitions state*, and it is only in this state that one electron can be transferred from Fe^{+2} to Fe^{+3} resulting in the electron

being on either of the iron ions. That is, in the Franck–Condon state, the two iron ions are chemically equivalent, within the limits set by the *Heisenberg Uncertainty Principle* (Reynolds and Lumry 1966). The Franck–Condon complex (i.e., the reaction system at the Franck–Condon state) can now relax back to the reactant state or proceed forward to the product state, depending on the sign of the Gibbs free energy change, ΔG, accompanying the redox reaction. If ΔG given by Eq. 2.24 is negative, the reaction proceeds forward (from left to right), and if it is positive, the reaction proceeds backward (from right to left).

$$\Delta G = G_{final} - G_{initial} = \Delta G^0 - RT \log \left[{}^*Fe^{+2} \right] / \left[Fe^{+3} \right] \tag{2.24}$$

where G_{final} and $G_{initial}$ are the Gibbs free energy levels of the final and initial states of the reaction system, ΔG^0 is the standard Gibbs free energy (i.e., ΔG at unit concentrations of the reactants and products), R is the universal gas constant, T is the absolute temperature of the reaction medium, $[{}^*Fe^{+2}]$ is the concentration of the radioactively labeled ferrous ion (to be distinguished from the unlabeled ferrous ion, Fe^{+2}), and $[Fe^{+3}]$ is the concentration of the ferric ion.

2.2.3 The Generalized Franck–Condon Principle (GFCP) or the Principle of Slow and Fast Processes (PSFP)

It was postulated (Ji 1974a) that the *Franck–Condon principle* need not be restricted to electron transfer processes in molecular spectroscopy or inorganic electron transfer reaction in aqueous media but could be extended to physicochemical processes that involve coupling between two processes whose rates differ significantly. The generalized version of the Franck–Condon principle was also referred to as the *Principle of Slow and Fast Processes* (PSFP) (Ji 1991, pp. 52–56), which states that:

> Whenever an observable process, P, results from the coupling of two partial processes, one slow (S) and the other fast (F), with F proceeding faster than S by a factor of 10^2 or more, then S must precede F. (2.25)

Statement 2.25 as applied to enzymic catalysis can be schematically represented as follows:

$$(A^\circ + B)_r \leftrightarrow \left[(A^\circ + B)^\ddagger \Leftrightarrow (A + B^\circ)^\ddagger \right] \leftrightarrow (A + B^\circ)_p \tag{2.26}$$

where A and B are the donor (or source) and the acceptor (or sink) of a particle denoted by ° (which can be any material entities, either microscopic or macroscopic), and the parentheses indicate the immediate environment (also called microenvironment) surrounding the reactant system, i.e., $(A^\circ + B)_r$, or the product system, i.e., $(A + B^\circ)_p$, where the subscripts r and p stand for reactant and product,

Table 2.3 The application of the generalized Franck–Condon principle to biological processes at different levels of organization (Reproduced from Ji 1991, p. 54)

	Partial processes	
Overall process (P)	Fast (F)	Slow (S)
1. Enzymic catalysis	Covalent bond rearrangements (i.e., electronic transitions)	Conformational rearrangements of catalytic groups (i.e., nuclear rearrangements)
2. Gene expression	Enzymic reactions	Conformational rearrangements of double-stranded DNA
3. Memory	Input of signals to neurons	Rearrangements of genes in DNA(?)
4. Morphogenesis	Gene expression	Rearrangements of the connections between cells and between cells and extracellular matrix(?)
5. Evolution	Events in individual organisms	Rearrangements of physical and social environments of organisms

respectively. The superscript ‡ denotes the so-called Franck–Condon state which is intermediate between the reactant and product states so that the particle now loses its preference for either A or B and can be associated with A or B with equal probability within the constraints imposed by the Heisenberg uncertainty principle (Reynolds and Lumry 1966). The Franck–Condon states, connected by a double-headed arrow, $\Leftrightarrow$, and enclosed within the square brackets, can be either two distinct states separated by a free energy barrier large relative to thermal energies or may be two aspects of a common resonance state (Ji 1974a), in which case the free energy barrier between the two states are less than, or comparable to, thermal energies (i.e., 0.6 kcal/mol at physiological temperatures).

So generalized, the Franck–Condon principle can be applied to a wide range of biological processes as pointed out in Table 1.12 in Ji (1991), which is reproduced as Table 2.3.

The processes accounted for by GFCP include ligand binding to receptors (Sect. 7.1), enzymic catalysis (Sect. 7.2), ion pumping (Sect. 8.5), action of molecular motors (Sects. 8.4, 11.4), gene expression, cell migration, morphogenesis (Sect. 15.1), and biological evolution itself (Chap. 14).

After over two decades since the list in Table 2.3 was prepared, the list of the fields where GFCP has been found to apply has grown from five to ten (see Table 2.4).

The photosynthetic reaction centers (PSRC) may provide a good example of the *slowing down by increasing mass* (SDBIM) principle in action: PSRC may be viewed as molecular machines that have evolved to couple fast-moving photons (i.e., light) and slow-moving proteins in five steps:

$$\textbf{Photons} \rightarrow \textbf{Electrons} \rightarrow \textbf{Protons} \rightarrow \textbf{Cofactors} \rightarrow \text{IntrinsicMembraneProteins} \rightarrow \text{Extrinsic Membrane Proteins} \quad (2.27)$$

Table 2.4 The universality of the Generalized Franck–Condon Principle (GFCP), or the Principle of Slow and Fast Processes (PSFP). GFCP (or PSFP) has been postulated to act at the levels of molecules, chemical reactions, the origin of life, receptors, enzymes, photosynthesis, cells, brain processes, and the biological evolution

Level	Fast (F)	Slow (S)	Overall process (P)
1. Molecules (Fig. 2.3)	Electronic transitions (intramolecular)	Nuclear movements (intramolecular)	Absorption or emission of photons
2. Chemical reactions (Fig. 2.4)	Electron transfer (intermolecular)	Nuclear movements (intermolecular)	Oxidation–reduction reactions
3. Origin of life (Fig. 13.3)	Thermal motions	Heating–cooling cycle attending the rotation of the Earth	Self-replication
4. Ligand receptors (Fig. 7.1)	Ligand diffusion into and out of the binding pocket	Conformational change of the receptor	Molecular recognition by receptors and enzymes
5. Enzymes (Fig. 7.5)	Electronic rearrangements	Conformational changes of enzymes	Enzymic catalysis
6. Photon receptors	Light-induced electronic excitation of chromophores	Conformational change of reaction center proteins	Photosynthesis (conversion of radiation energy to chemical energy)
7. Metabolic network	Local metabolic fluctuations	Intracellular microenviron-mental changes	Gene-directed intracellular processes
8. Cells	Intracellular metabolic fluctuations	Extracellular environmental changes	Goal-directed cell functions (i.e., space- and time-dependent gene expression)
9. Brains (Fig. 15.21)	Neuronal firings	Neural assembling and disassembling	Micro–macro coupling through neural synchrony
10. Evolution	(a) DNA/RNA polymerization reactions (Devo)	(a) Conformational changes of DNA and chromatins	(a) Gene expression
	(b) Life cycles of organisms (Evo)	(b) Geological and environmental changes	(b) Natural selection

Another example may be provided by the muscle (see Fig. 15.19):

$$\textbf{Actomyosin} \rightarrow \textbf{Myofilaments} \rightarrow \textbf{Myofibrils} \rightarrow \textbf{MuscleFiber} \rightarrow \textbf{Fascicle} \rightarrow \textbf{Muscle} \tag{2.28}$$

Wang et al. (2007) conclude that:

> [I]nitial photosynthetic charge separation is limited by protein dynamics rather than by a static electron transfer barrier . . .

which seems to support the predictions made by the generalized Franck–Condon principle that the fast electron transfer processes would be rate-limited by the slow conformational changes of the proteins constituting the photosynthetic reaction centers. The results of Wang et al. (2007) may turn out to be the strongest experimental support so far for the validity of the GFCP as applied to enzymic processes.

2.3 Complementarity

2.3.1 Complementarity vs. Supplementarity

The term "complementary" first appears in William James' book, *Principles of Psychology* (1890), in the context of the idea that human consciousness consists of two parts:

> [I]n certain persons, atleast, the total possible consciousness may be split into parts which coexist but mutually ignore each other, and share the objects of knowledge between them. More remarkable still, they are *complementary*. . ..

There is a great similarity between the concept of complementarity that James introduced into psychology in 1890 and that Bohr introduced into physics about four decades later. Whether Bohr's *complementarity* was influenced directly or indirectly by James' notion of *complementarity* is a challenging question for philosophers of science to answer.

The concept of complementarity emerged in 1926–1927 from the intense discussions that transpired between Bohr and his then-assistant Heisenberg in the wake of the latter's discovery of the *matrix mechanics* and *uncertainty relations* (Lindley 2008). Bohr discussed his philosophy of *complementarity* in public for the first time at a meeting held in Como, Italy, in 1927 and published the first paper on complementarity in 1928 (Bohr 1928; Camillieri 2007). In 1958, Bohr summarized the concepts of *supplementarity* and *complementarity* as follows (Bohr 1958):

> Within the scope of classical physics, all characteristic properties of a given object can in principle be ascertained by a single experimental arrangement, although in practice various arrangements are often convenient for the study of different aspects of the phenomenon. In fact, data obtained in such a way simply supplement each other and *can be combined* into a consistent picture of the behavior of the object under investigation. In quantum mechanics, however, evidence about atomic objects obtained by different experimental arrangements exhibits a novel kind of *complementary relationship*. (2.29)

> Indeed, it must be recognized that such evidence which appears contradictory when combination into a single picture is attempted exhausts all conceivable knowledge about the object. Far from restricting our efforts to put questions to nature in the form of experiments, the notion of *complementarity* simply characterizes the answers we can receive by such inquiry, whenever *the interaction between the measuring instruments and the objects forms an integral part of the phenomenon* . . . (my italics)

The *supplementary* and *complementary* relations defined above can be conveniently represented as triadic relations among three entities labeled A, B, and C. *Supplementarity* refers to the relation in which the sum of a pair equals the third:

$$\text{Supplementarity: } C = A + B \tag{2.30}$$

As an example of supplementarity, Einstein's equation in special relativity, $E = mc^2$ (Shadowitz 1968), may be cited. Energy (A) and matter (B) may be viewed as extreme manifestations of their source C that can be quantitatively combined or added to completely characterize C. As already indicated there is no common word to represent the C term corresponding to the combination of *matter* and *energy*. Therefore, we will adopt in this book the often-used term "mattergy" (meaning *matter* and ener*gy*) to represent C. Through Einstein's equation, matter and energy can be interconverted quantitatively. The enormity of the numerical value of c^2, namely, 10^{21}, justifies the statement that:

Matter is a highly condensed form of energy. (2.31)

In contrast to supplementarity, *complementarity* is nonadditive: i.e., A and B cannot be combined to obtain C. Rather, C can be said to become A or B depending on measuring instruments employed: i.e., C = A or C = B, depending on measurement. We can represent this complementary relation symbolically as shown in Eq. 2.32:

$$\text{Complementarity: } C = A\hat{}B \tag{2.32}$$

where the symbol ^ is introduced here to denote a "complementary relation." Equation 2.32 can be read in two equivalent ways:

A and B are *complementary aspects* of C. (2.33)

C is the *complementary union* of A and B. (2.34)

Statements 2.33 and 2.34 should be viewed as short-hand notations of the deep philosophical arguments underlying complementarity as, for example, discussed recently by Plotnitsky (2006) and Camillieri (2007). The principles of *complementarity* and *supplementarity* defined above may operate not only in physics but also in biology as first suggested by Bohr (1933; Pais 1991). In other words, it may be said that:

Physics and biology are symmetric with respect to the operation of supplementarity and complementarity principles. (2.35)

We will refer to Statement 2.35 as the *Symmetry Principle of Biology and Physics* (SPBP). SPBP is supported by the symmetry evident in Table 2.5.

In Table 2.5, two new terms appear, "mattergy" (see Item 2) and "liformation" (Item 7) whose meanings are explained in footnotes. One of the most significant conclusions resulting from Table 2.5 is the assertion that *life* and *information* are intimately related in biology just as *matter* and *energy* are related in physics (see Items 1, 2, 6, and 7), leading to the coining of the new term "liformation" in analogy

Table 2.5 *The Symmetry Principle of Biology and Physics* (SPBP): the principles of *supplementarity* and *complementarity* in action in physics and biology. "Wavecles" are complementary unions of waves and particles, and "quons" are quantum mechanical objects exhibiting wave or particle properties depending on the measuring apparatus employed (Herbert 1987). "Gnergy" is defined as a complementary union of information (gn-) and energy (-ergy) (Ji 1991, p. 152). In other words, energy and information (or more accurately *mattergy* and *liformation*) are the complementary aspects of gnergy

	Physics	Biology
Supplementarity (from Special Relativity Theory)	1. Matter-energy equivalence $E = mc^2$	6. Life-information equivalence[a]
	2. Matter-energy or "Mattergy"[b]	7. Life-information or "Liformation"[c]
	3. *Matter is a highly condensed form of energy*"	8. *Life is a highly condensed form of information*
Complementarity (from Quantum Mechanics)	4. Wave–particle[d] complementarity Kinematics–dynamics Complementarity[e]	9. "Liformation-mattergy" complementarity
	5. "Wavicles" or "Quons"[f]	10. "Gnergons"[g]

[a]Just as the *matter-energy equivalence* was unthinkable before Einstein's special relativity theory published in 1905 (Shadowitz 1968), so it is postulated here that the *life-information equivalence* was unthinkable prior to the emergence of molecular theories of life that began with Watson and Crick's discovery of the DNA double helix in 1953

[b]The term often used to denote the equivalence between (or supplementary union of) matter and energy as indicated by $E = mc^2$ (Shadowitz 1968)

[c]A new term coined here to represent the postulated supplementary relation (or the equivalence or continuity) between life and *information*, in analogy to mattergy, embodying the supplementary relation between matter and energy

[d]The Airy pattern (see Fig. 4.2 in Herbert 1987) may be interpreted as the evidence for a *simultaneous* measurement of both waves and particles of light, and if such an interpretation proves to be correct, it would deny the validity of the wave–particle complementarity and support the notion of the wave–particle supplementarity

[e]The kinematics–dynamics complementarity is a logically different kind of complementarity that was recognized by Bohr in addition to the wave–particle complementarity (Murdoch 1987, pp. 80–88)

[f]Any material entities that exhibit both wave and particle properties, either simultaneously (as claimed by L. de Broglie and D. Bohm) or mutually exclusively (as claimed by N. Bohr) (Herbert 1987)

[g]Gnergons are defined as discrete units of gnergy, the complementary union of information and energy (Ji 1991). Gnergy is a *type* and gnergons are its *tokens* (see Sect. 6.3.9)

to "mattergy" (see Items 2 and 7). Another important insight afforded by the symmetry inherent in Table 2.5 is the "liformation–mattergy complementarity" (see Item 9), which may be related to the view recently expressed by Lloyd (2006, p. 38), if *computation* can be identified with *liformation* or information processing:

> The computational universe is not an alternative to the physical universe. The universe that evolves by processing information and the universe that evolves by the laws of physics are one and the same. The two descriptions, computational and physical, are complementary ways of capturing the same phenomena. (2.36)

To highlight the symmetry, properties embedded in Tables 2.5 and 2.6 are prepared as its geometric version. Please note that the terms enclosed in double quotation marks are predicted by the symmetry inherent in the table. That is, the symmetry properties of the table entail their existence.

The gnergy triangle in Table 2.6 has three nodes. Since Mattergy and Liformation can be decomposed into matter and energy, and life and information, respectively, resulting in five nodes, the gnergy triangle can be alternatively represented as a body-centered tetrahedron which possesses five nodes (see Fig. 10.7).

If the above symmetries turn out to be true, the following three inferences may be made:

1. Biology and physics may be more deeply related with each other than previously thought.
2. Information cannot exist without life (nor vice versa), just as energy cannot exist without matter (as in chemical reactions) due to $E = mc^2$.
3. The Universe may be described in two complementary ways – the energy/matter-based and the information/life-based, in agreement with Statement 2.36 (Lloyd 2006).

If these inferences turn out to be valid, especially inference (3), they may have important implications for philosophical discourses on the phenomenon of life, including the problem of vitalism (Crick 1966).

2.3.2 *Information–Energy Complementarity and "Gnergy"*

Gnergy was originally defined as *the complementary union of information and energy* that drives all self-organizing processes in the Universe (Ji 1991, 1995). Although *information–energy complementarity* is now more accurately expressed as *liformation–mattergy complementarity* for the reasons provided in Tables 2.5 and 2.6, gnergy may continue to be thought of as the complementary union of *information* and *energy* for the sake for brevity.

Unless indicated otherwise, "information" refers to "chemical" and "genetic" information among many other kinds of information (e.g., physical information, mathematical information, literary information), and "energy" will refer to "free energy" or the "useful form of energy," for example, for living systems under physiological conditions, among many other kinds of energies (e.g., thermal energy, nuclear energy, gravitational energy). It is important to realize that information (e.g., software, the mechanical structure of a car) and energy (e.g., electricity, gasoline) can be separated only in macroscopic machines, and not in molecular machines that are *structurally flexible and deformable* (e.g., molecular motors, including ATP-driven proton pumps). Because of the structural deformability, it is claimed here that information and energy cannot be separated on the microscopic level and exist as a *fused* entity which has been referred to as the *gnergon* (a term coined by combining three Greek roots, *gn-* meaning information, *-erg-* meaning

Table 2.6 The Symmetry Principle of Biology and Physics represented diagrammatically. Based on the postulated symmetry, the new term, mattergy, was coined. The inverted T symbolizes the *supplementarity* relation, and the triangle symbolizes the *complementarity* relation

Principles	**Physics**	**Biology**
Supplementarity:	Mattergy Matter — Energy	'Liformation' Life — Information
Complementarity:	Quons Particle — Wave	'Gnergy' Mattergy — 'Liformation'

work or energy, and *-on* meaning discrete entity or particle). Gnergons are discrete units of gnergy. One concrete example of gnergons in action in molecular and cell biology is the *conformon*, the mechanical energy stored in sequence-specific sites within biopolymers as conformational strains (for the experimental evidence for conformons, see Chap. 8).

The concept of gnergy embodies the *principle of information and energy complementarity* (PIEC), according to which gnergy is responsible for driving all self-organizing processes in the Universe, including the origin of life, physicochemical processes occurring in the living cell such as self-replication and chemotaxis, cognitive processes in the human brain, biological evolution, and the evolution of the Universe Itself. According to PIEC, the ATP molecule which plays a fundamental role in most, if not all, self-organizing processes inside the cell carries not only *energy* as is usually assumed (about 16 kcal/mol under physiological conditions) but also *chemical information* encoded in its three-dimensional molecular shapes. Thus, it can be predicted that, for some biochemical processes driven by ATP, ATP cannot be replaced by deoxy-ATP even though the latter can be hydrolyzed by ATPase to generate the same amount of free energy, because the deoxy-ATP molecule does not have the same information (i.e., molecular shape) as ATP. An analogy may be suggested here: Although a US dollar bill and a Korean 1,000-Won bill have approximately the same monetary value (analogous to *energy*), the latter cannot replace the former in a vending machine in the US because it has different *information* (e.g., a different shape, color, and size) from that of a US dollar bill.

PIEC is expected to be manifested in the Universe in many different guises. The wave–particle complementarity is perhaps the best-known example of PIEC in

science, and the principle of matter–symbol complementarity (PMSC), championed by H. Pattee (1982, 1995, 1996), may be viewed as another important manifestation of PIEC. According to PMSC (later re-named as *the von Neumann–Pattee principle of matter–sign complementarity* (Ji 1999b)), all self-reproducing systems have two complementary aspects – (1) *physical law-governed material/energetic aspect* and (2) *the evolutionary rule-governed informational (or symbolic) aspect*. According to Pattee, open-ended evolution is possible if and only if evolving systems have both these two complementary aspects (Pattee 1995; Umerez 2001).

2.3.3 Complementarian Logic

In order to capture the essential characteristics of Bohr's *complementarity*, the author formulated what is referred to as "complementarian logic" in Ji (1995) that comprises three logical elements:

1. *Exclusivity*. A and B are mutually exclusive in the sense that A and B cannot be measured/observed/thought about simultaneously within a given context. For example, light under most experimental conditions exhibit wave or particle properties, depending on the measuring apparatus employed, but it is impossible to measure these properties simultaneously under a given measuring environment. Even the Airy experiment (Herbert 1987, pp. 60–64) may not be an exception although the Airy pattern shows both the particle property (as the dots) and the wave property (as the concentric circles) on the same record, since they were not recorded simultaneously. That is, dots appear first and then the concentric waves appear gradually over time when enough dots accumulate on the screen. Thus, the particle property and wave property of light were not measured/recorded *simultaneously*, thereby satisfying the exclusivity criterion.

   It is also interesting to note that, on the *formal* level (Murdoch 1987, pp. 34–36), particle and wave properties are not exclusive in the sense that they are related to each other through the de Broglie equation,

$$\lambda = h/mv \tag{2.37}$$

   where λ is the wavelength associated with a particle of mass m moving with velocity v, and h is the Planck constant. Therefore, at least on the formal level (in contrast to the real or physical level), the wave and particle properties of light are derivable from each other just as energy and matter are derivable from each other based on $E = mc^2$. However, whether this mutual derivability on the formal level can be physically realized depends on the availability of the mechanisms (and environment) to implement such an interconversion. In the case of the energy–matter equivalence, there exist physical mechanisms by which energy and matter can be interconverted as in chemical reactions or nuclear reactions. However, it is not certain whether particles can be converted

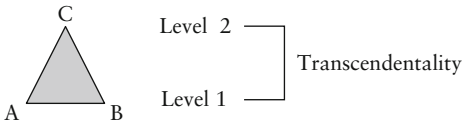


Fig. 2.5 An iconic representation of the *complementarian logic*. Each node is occupied by one of the three entities constituting a complementary relation (e.g., wave, particle, light), and the edges have the following meanings: A-B = Exclusivity; A-C or B-C = Essentiality; Levels 1 and 2 = Transcendentality.

into waves and waves into particle. Hence *complementarity* and *supplementarity* may be distinguished on the basis of the Exclusivity criterion. If the condition is found under which particles and waves can be interconverted, then complementarity and supplementarity may lose their distinction under such conditions. For convenience, we may refer to such conditions as *the U point*, where the capital letter U stands for *uncertainty*, and the parameter whose numerical value characterizes the U point may be denoted by U in analogy to the Planck constant *h* that characterizes the point where quantum effects become nonnegligible. Thus, in terms of the concept of the U point, the Exclusivity criterion and hence the distinction between complementarity and supplementarity are meaningful only above the U point and lose their meanings below it, just as space and time lose their individuality when objects move with speeds close to that of light, c, or just as the de Broglie waves lose their practical consequences when the momentum of moving objects becomes large.

2. *Essentiality*. A and B are both essential for completely describing/understanding a third term C. Light cannot be described completely in terms of either particle or wave properties alone but both these properties are *essential* to our understanding of the nature of light or any other "quantum objects" often called "quons" or "wavicles" (Herbert 1987, p. 64).
3. *Transcendentality*. C transcends the level of description where A and B have meanings and serves as the source of, or as the ground for, the irreconcilably opposite A and B. The quality of light as directly perceived through the human eye transcends the level of instrument-mediated observations/measurements where it is registered as either waves or particles.

These three elements of the complementarian logic can be represented diagrammatically as a triangle (Fig. 2.5):

The complementarian logic helps to distinguish *supplementarity* from *complementarity* because the former does not satisfy the conditions of Exclusivity and Transcendentality. Thus, most of the over 200 "complementary pairs" that Kelso and Engström (2006) list in their book, Complementary *Nature*, may be considered as "supplementary pairs" according to the complementarian logic.

Complementarity began its philosophical career as Bohr's interpretation of quantum mechanics (Murdoch 1987; Lindley 2008; Plotnitsky 2006), but the complementarism (see Sect. 2.3.4) that I formulated in the mid-1990s (Ji 1993,

1995), although inspired by Bohr's complementarity initially, is based on the complementarian logic (see above) whose validity is no longer solely dependent upon the validity of Bohr's complementarity and can stand on its own feet. The wave–particle duality, which served as the model for the complementarian logic, may or may not obey all the three logical criteria (especially the exclusivity criterion), depending on how one interprets experimental data such as the Airy patterns (Herbert 1987, pp. 60–64) and de Broglie equation, Eq. 2.37.

2.3.4 The Principle of Generalized Complementarity and Complementarism

The term "complementarity" was introduced in 1927 by Niels Bohr (Pais 1991) in an attempt to describe the novel situations arising from (1) the wave–particle duality of light and (2) the Heisenberg uncertainty principle (Murdoch 1987; Plotnitsky 2006; Lindley 2008; Camillieri 2007). But Bohr did not give any rigorous definition of complementarity in his writings. One exception may be the following quotation from (Bohr 1934), where he states that the *quantum of action:*

> [F]orces us to adopt a new mode of description designated as complementary in the sense that any given application of classical concepts preclude the simultaneous use of other classical concepts which in a different connection are equally necessary for the elucidation of the phenomena.

The Bohr's concept of complementarity so defined is not universally accepted by contemporary physicists (Herbert 1987; Bacciagaluppi and Valenti 2009), and there are recent reports in the physics literature claiming to have invalidated the wave–particle complementarity (e.g., google "wave nature of matter"). Although Bohr popularized the term "complementarity" beginning in 1927, the main semantic content of this word was known to philosophers as early as fourth to sixth century BCE (e.g., Lao-tzu, and Aristotle). Complementarity, in this broad sense of the word, appears to reflect the following three characteristics of human language:

1. Words evolve to represent familiar concepts (e.g., waves, particles).
2. As human experience expands, new concepts are formed in the human mind which cannot be adequately represented by familiar words, often leading to paradoxes (e.g., wave–particle duality).
3. New words are coined to represent new experiences (e.g., wavicles, or quons, gnergy, etc.).

On the basis of this reasoning, it may be suggested that the definition of complementarity entails using three key terms, A and B, which are familiar but have mutually incompatible or contradictory meanings, and C which represents a new concept foreign to A and B and yet capable of reconciling the opposition between them. The A-B-C "triads" collected in Table 2.7 all appear to comply with the three characteristics of human language given above.

Table 2.7 Some examples (numbered 1–14) of complementarities found in physics, biology, and philosophy. The term "quons" refer to quantum objects (e.g., photons, electrons) that exhibit wave–particle duality

Fields	Familiar concept (macroscopic, commonsensical, traditional, superficial) (A and B)	Unfamiliar concept (microscopic, specialized, nontraditional, deep) (C)
Physics	1. Waves and particles	Quons (or wavicles) (Herbert 1987)
	2. Kinematics and dynamics	Quantum mechanics
Biology	3. Information and energy	Gnergy (Ji 1985a, 1991)
	4. Living and nonliving	Biomolecular processes
Philosophy	5. Matter and form	Hylomorph (Aristotle)
	6. Extension and thought	Substance (also called Nature, or God) (Spinoza)
	7. Secondness and thirdness	Firstness (Peirce)?
	8. Mind and body	Flesh (Merleau-Ponty) (Dillon 1997)
	9. Mind and matter	Implicate order (Bohm 1980)
	10. Yin and Yang	Tao (Lao-tzu)
	11. Global and local	Complementarism? (Pais 1991; Ji 1995)
	12. Forest and trees	Complementarism? (Pais 1991; Ji 1995)
	13. Whole and parts	Complementarism? (Pais 1991; Ji 1995)
	14. Holism and reductionism	Complementarism? (Pais 1991; Ji 1995)

In agreement with Bohr, I believe that the complementarity concept as used in physics and the Taoist philosophy can be applied to biology. Furthermore, I have long advocated the idea that *information* and *energy* constitute *a new complementary pair* (i.e., A and B in Fig. 2.5) with gnergy serving as their source, i.e., the C term. Organisms and abiotic objects may be another example of the complementary pair, with molecular biological processes (e.g., enzyme-catalyzed chemical reactions, molecular motor actions) serving as the C term. If this reasoning is valid, we can conclude that biomolecular processes can be viewed as either living or nonliving, depending on the context, namely, the way one measures (or observes) them, just as light can be viewed as waves or particles depending on the measuring instruments employed. This would resolve the controversy about whether or not biochemical processes are living processes. *They are living when occurring inside the cell and not when occurring in a test tube*. That is, the meaning of biochemical processes is context-dependent. The importance of the context and perspectives in philosophical discourses have recently been emphasized in *transcendental perspectivism* of Krieglstein (2002), which should apply to biological theorizing with an equal force as illustrated in a recent review article in theoretical biology (Lesne 2008).

Bohm's idea of implicate order (Bohm and Hiley 1993) as the source of mind and matter may be accommodated within the complementarity framework described in Table 2.5. This is surprising because, within the field of quantum physics itself, Bohr and Bohm represent the two opposite schools of thought as regards their interpretation of quantum objects (i.e., acausal vs. causal interpretations) (Plotnitsky 2006).

Table 2.5 also includes the dichotomies (or dualities) between the *global* and the *local*, the *forest* and *trees*, *whole* and *parts*, or *holism* and *reductionism*. These dualities may reflect the same human cognitive limitations as exemplified by our inability to see both the forest and trees at the same time. Thus, we may refer to these dichotomies as the "forest–tree complementarity (FTC)" for convenience. The simple notion of FTC may help resolve the controversies arising between molecular neurobiologists (reductionism) and behavioral biologists (holism), just as the wave–particle complementarity helped settle the controversy between Einstein and his followers who believed in the primacy of particles over waves and Bohr and his school believing the opposite, namely, the primacy of waves over particle, in the early decades of the twentieth century. *The philosophical framework erected on the basis of the assumption that the complementarity principle of Bohr (generalized as the information–energy complementarity or the gnergy principle) applies to all self-organizing processes in the Universe has been named "complementarism" in the early 1990s* (Ji 1993, 1995), independently of Pais (1991) who coined the same term to represent Bohr's assertion that his complementarity concept can be extended to fields beyond physics.

2.3.5 *Two Kinds of Complementarities: Kinematics vs. Dynamics and Wave vs. Particle*

Kinematics refers to the study of the *space* and *time* (or spacetime in the relativistic frame of reference, where objects move with speeds close to that of light) coordination of moving objects *without considering the causes underlying the motion* (http://en.wikipedia.org/wiki/Kinematics), while *dynamics* refers to the study of the causal roles of the *energy* and the *momentum (or momenergy* in the relativistic frame of reference) (Wheeler 1990, pp. 110–121) underlying the motions of objects. Bohr referred to the *kinematic* relation as "space–time coordination" and the *dynamic* relation as "causality." The wave–particle complementarity which is more widely known than the kinematics–dynamics complementarity is "logically independent notion" according to Murdoch (1987, p. 67). It is interesting to note that Heisenberg had a different interpretation of Bohr's concept of the kinematics–dynamics complementarity (Camillieri 2007). The *wave–particle* and *kinematics–dynamics* complementarities are compared in Table 2.8.

The concepts of wave and particle are distinct, clearly separable, and logically compatible in classical mechanics but become inseparable, fused, or "logically incompatible" in quantum mechanics in the sense that they together, rather than separately, describe quantum objects or quons. In other words, the classical concepts of wave and particle cannot be applied to quons as they can be to classical objects. Murdoch (1987, p. 80) also states that:

Table 2.8 Two kinds of complementarity in physics. The quoted phrases are from Murdoch (1987, p. 67)

Complementarity	Classical mechanics	Quantum mechanics
Wave vs. particle	"Fall apart"	"Come together"
(*Logical incompatibility)*		
Position vs. momentum	"Go together"	"Fall apart"
Spacetime vs. momenergy		
Kinematics vs. dynamics		
(*Empirical or epistemic incompatibility*)		

> Kinematic and dynamic attributes in quantum mechanics are mutually exclusive in the sense that they cannot be simultaneously measured; they are, in this sense, espistemically incompatible.

As pointed out by Bohr (1934, p. 60), it is only in classical physics that momentum and energy can be measured precisely on the basis of spatio-temporal measurements (i.e., space and time "go together" with momentum and energy). In quantum physics, where effect of the quantum of action is large enough to be negligible, these properties are no longer deterministically related and hence "fall apart" (Murdoch 1987, p. 67).

The Heisenberg uncertainty relations/principle can be expressed in two equivalent forms (Murdoch 1987):

$$(\Delta q)(\Delta p) \geq h/2\pi \tag{2.38}$$

$$(\Delta t)(\Delta E) \geq h/2\pi \tag{2.39}$$

where Δq, Δp, Δt, and ΔE are the uncertainties about the position, momentum, time, and energy associated with moving objects, respectively, and h is the Planck constant. As evident in these equations, the two horizontal pairs, namely, q and p and t and E, are related by Heisenberg uncertainty principle, while the two vertical pairs, namely, q and t and p and E, are related *kinematically* and *dynamically*, respectively (Table 2.5) (Murdoch 1987, pp. 80–85).

We can represent these relations diagrammatically as shown in Table 2.9, where the Heisenberg uncertainty principle appears in the margins – the *horizontal* margin for the q and p conjugate pair, and the *vertical* margin for the t and E conjugate pair. Thus, we may refer to Eqs. 2.38 and 2.39 as the *horizontal uncertainty principle* and the *vertical uncertainty principle*, respectively. In contrast, Bohr's Complementarity Principle appears as *a diagonal* in the interior of the table. There are six complementary pairs listed in the diagonal boxes in Table 2.9 that are related to Bohr's complementarity concept:

1. The *wave–particle* complementary pair (Murdoch 1987, pp. 58–61).
2. The *kinematic–dynamic* complementary pair (Murdoch 1987, pp. 80–88).
3. The *spacetime–momenergy* complementary pair (just as "spacetime" is the combination of *space* and *time* that remains invariant in general relativity, so

Table 2.9 A tabular representation of the relation between the *Heisenberg Uncertainty Principle* (HUP) and *Bohr's Complementarity Principle* (BCP). The Planck constant, h, and the speed of light c are displayed in the upper-left hand corner of the table to emphasize the fact that both HUP and BCP are manifest only under the conditions *where molecular interactions play critical roles or* objects under consideration move with speeds close to that of light

h, c	q	p
t	1. Wave 2. Kinematics 3. Spacetime 4. Continuity 5. Group property (superposition) (A)	–
E	–	1. Particle 2. Dynamics 3. Momenergy 4. Discontinuity 5. Individuality (B)

"momenergy" is the combination of *momentum* and *energy* that remains invariant).

4. The *continuity* vs. *discontinuity* complementary pair may be viewed as the philosophical basis for the wave vs. particle duality to the extent that wave is continuous and particle is discontinuous in space.
5. The *group* vs. *individuality* complementary pair can also be viewed as a general principle that accommodates wave vs. particle duality, if we associate wave with superposition which presupposes more than one wave, i.e., a group of waves.

The phrase "A–B complementary pair" embodies the following notions:

1. A and B have well-defined meanings only in classical physics, i.e., in situations where the *quantum of action* (i.e., the *finite nonzero value of* the product of *energy* and *time*) has no measurable effects and thus can be ignored.
2. In quantum mechanics where the *quantum of action* has significant effects during the interactions between the object under observation and the measuring apparatus, the object can no longer be described in terms of A and B but only in terms of nonstandard, nonclassical models denoted by C in Fig. 2.5 that can be characterized as "neither A nor B," or as "both A and B."
3. In relativity theory where objects under observation move at speeds close to that of light, well beyond our ordinary experience, a similar complementarity principle may apply as pointed out by Bohr (1934, pp. 55, 98):

> In both cases we are concerned with the recognition of physical laws which lie outside the domain of our ordinary experience and which presents difficulties to our accustomed forms

> of perception. We learn that these forms of perception are idealizations, the suitability of which for reducing our ordinary sense impressions to order depends upon the practically infinite velocity of light and upon the smallness of the quantum of action. (2.40)

Of the five complementary pairs listed in Table 2.9 (Murdoch 1987, pp. 58–66; Bohr 1934, pp. 19, 61, 623), the first two are the consequences of the smallness of the quantum of action, $h = 6.63 \times 10^{-34}$ J s, and the third results from the constancy of the speed of light, $c = 3 \times 10^{10}$ cm/s, as already indicated. What is common to the first two (if not all) of the five complementarities may be the dichotomy of *continuity* vs. *discontinuity* as described by Murdoch (1987, p. 46):

> Bohr's view now was that when *continuity* obtains, the standard models are applicable, i.e., matter may be conceived of as corpuscular and radiation as undulatory; when, however, *discontinuity* prevails, the standard models break down, since they presuppose continuity, and the nonstandard models then suggest themselves . . .. (2.41)

It is interesting to note that the *quantum of action* is implicated only in the two margins of Table 2.9, in the form of Inequalities 2.38 and 2.39, but not in the diagonal boxes. This suggests that HUP and BCP belong to two different logical classes; i.e., one is about *measurement* (or results of measurements) and the other about *measurability* (or measuring conditions). To understand the difference between these two terms, it is necessary to return to Heisenberg's original explanation for his uncertainty relation, Inequality 2.38, based on his thought experiments with the "gamma-ray microscope."

Heisenberg describes his experiment thus (Murdoch 1987, p. 48):

> At the moment of the position determination, when the light-quantum is diffracted by the electron, the momentum of the electron is changed discontinuously. The shorter the wavelength of the light, i.e., the more accurate the position measurement, the greater the change in the momentum. At the moment the position of the electron is ascertained, its momentum can be known only within a magnitude that corresponds to this discontinuous change . . .. (2.42)

In short, Heisenberg originally thought that the reason for his uncertainty principle resided in the discontinuous change in the trajectory of the electron due to collision with the light-quantum. But Bohr claimed, according to Murdoch (1987, p. 49), that:

> [W]hat precludes the measurement of the momentum of the electron in the "gamma-ray microscope" experiment is not the discontinuity of the momentum change as such but rather the impossibility of *measuring* the change. What prevents measurement of the momentum change is the indispensability of the wave model for the interpretation of this experiment. The Compton-Simon experiment shows that the discontinuous change in momentum can be accurately determined provided the angle of scatter of the incident photon can be precisely determined. In the gamma-ray microscope' experiment, however, the angle of scatter cannot be determined within an uncertainty which is less than the angle 2θ subtended by the diameter of the lens: it is thus impossible to tell at what angle within the angular aperture of the lens the photon is scattered; . . . Bohr's point is that it is the wave–particle duality of radiation that makes it impossible to measure the momentum of the electron: while gamma radiation may appropriately be described in terms of the particle model, it is the indispensability of the wave model for the interpretation of the experiment that precludes the precise measurement of the momentum of the electron. (2.43)

Table 2.10 The liformation–mattergy complementarity and its predicted uncertainty principles. The symbol γ indicates the biological counterpart of the Plank constant whose characteristics are yet to be characterization

γ	Information (I)	Energy (E)
Life (L)	1. Liformation 2. Structure 3. Cell biology 4. Holism (A)	–
Matter (M)	–	1. Mattergy 2. Function 3. Molecular biology 4. Reductionism (B)

Table 2.11 Another version of the liformation–mattergy complementarity and its predicted uncertainty principles. The symbol γ indicates the biological counterpart of the Plank constant whose identity is yet to be characterized

γ	Life (L)	Matter (m)
Information (I)	1. *Liformation* 2. Function 3. Cell biology 4. Holism (**A**)	–
Energy (E)	–	1. *Mattergy* 2. Structure 3. Molecular biology 4. Reductionism (**B**)

Heisenberg later agreed with Bohr (Murdoch 1987, p. 51) that his uncertainty principle is a natural consequence of the wave–particle duality of light and the peculiarity of the measuring apparatus or the consequence of *the kinematic–dynamic complementarity* (Murdoch 1987, pp. 58–61).

Since the applicability of the *wave–particle pair* and the *liformation–mattergy pair* are symmetric with respect to the *complementarity principle* (see Statement 2.35, and Tables 2.5 and 2.6), we may be justified to construct two possible tables, each analogous to Table 2.9, that can be associated with the *liformation–mattergy* complementarity (see Tables 2.10 and 2.11). Of these two choices, Table 2.11 may be preferred because of its greater similarity to Table 2.9 with respect to the position of E.

New complementary pairs appear in Table 2.11, i.e., *liformation–mattergy, structure vs. function, cell biology vs. molecular biology,* and *holism vs. reductionism.* If the content of Table 2.11 is valid, it may be concluded that the structure–function dichotomy widely discussed in biology belongs to the same logical class as the kinematics–dynamics dichotomy in physics (compare Tables 2.8 and 2.10). If this conjecture is correct, the following generalization may be made:

> Just as the *kinematics* (i.e., the position–time coordination) and *dynamics* (i.e., energy-momentum changes or causality) of moving objects cannot be measured simultaneously in physics with arbitrary accuracy so it is impossible to measure the *structure* and *function* of an organism simultaneously. (2.44)

We may refer to Statement 2.44 as *the principle of the structure–function complementarity* (PSFC) in biology in analogy to the principle of *the kinematics–dynamics complementarity* (PKDC) in physics (Murdoch 1987, pp. 58–61). From Table 2.11, it is clear that PSFC is isomorphic with (or belongs to the same logical class as) the principle of *liformation–mattergy complementarity* which is a newer designation for what is more often referred to as the *information–energy complementarity* for brevity (Sect. 2.3.2) (Ji 1991, 2000). Table 2.11 suggests that the cell biology–molecular biology and holism-–reductionism pairs also belong to the liformation–mattergy complementarity class.

From Table 2.11, we can generate two inequalities in analogy to Inequalities 2.38 and 2.39:

$$(\Delta L)(\Delta m) \geq \gamma \tag{2.45}$$

$$(\Delta I)(\Delta E) \geq \gamma \tag{2.46}$$

where γ is a constant that is postulated to play a role in biology comparable to that of the Planck constant, namely, the *quantum of gnergy*, or the *gnergon*. The best characterized example of the gnergon is the *conformon*, the sequence-specific conformational strains of biopolymers that carry both *genetic information* and *mechanical energy* (Chap. 8). If we assume (based on the principle of excluded middle) that the minimum uncertainty in measuring information content of a conformon is 1 bit and that the minimum energy required to measure biological information is 1 kT or the thermal energy per degree, the minimum value of the product, $(\Delta I)(\Delta E)$, is 4.127×10^{-14} erg or 0.594 kcal/mol at $T = 298$ K, which may be considered to be the value of γ at this temperature (Ji 1991, pp. 119–122). If these conjectures are valid, Inequality 2.45 would suggest that:

> The more precisely one defines what life is, the less precisely can one define what the material constituents of the organism are. (2.47)

Conversely,

> The more precisely one determines what the material basis of an organism is, the less precisely can one define what life is. (2.48)

Statements 2.47 and 2.48 that are derived from the principle of Bohr's complementarity are consistent with the more general statement about the uncertainty in human knowledge, called the "Knowledge Uncertainty Principle" (KUP), to be discussed in Sect. 5.2.7. KUP can be viewed as a generalization of what was previously referred to as the *Biological Uncertainty Principle* (BUP) (Ji 1990, pp. 202–203, 1991, pp. 119–122).

If proven to be correct after further investigation, Statements 2.47 and 2.48 may find practical applications in medicine, science of risk assessment, and law, where the question of defining what life and death often arises.

The two forms of the Heisenberg uncertainty principle appearing in the margins of Table 2.8 are quantitative because they can be expressed in terms of quantifiable

entities, q, p, t and E. In contrast, many of the complementary pairs appearing in the interior of Tables 2.9 and 2.11 are qualitative. Hence, it may be concluded that:

> The Heisenberg uncertainty principle is quantitative: Bohr's complementarity principle is qualitative. (2.49)

If we can consider *quantity* and *quality* as complementary to each other in the sense of Bohr and the Taoist philosophy, the Heisenberg uncertainty principle (HUP) and Bohr's complementarity principle (BCP) would become complementary to each other, leading to the following statement:

> The Heisenberg uncertainty principle (HUP) and Bohr's complementarity principle (BCP) reflect the complementary aspects of reality. (2.50)

Statement 2.50 is obviously self-referential, reminiscent of the Mőbius strip, the Klein bottle, or recursion formulas in computer science discussed in Sect. 5.2.4. Hence, Statement 2.50 may be referred to as the "Recursivity of Complementarity and Uncertainty" (RCU).

It may be possible to represent the quantitative and qualitative complementarities geometrically. One possibility would be to use a pair of orthogonal axes, one representing the *quantitative complementarity* and the other the *qualitative complementarity*. The resulting plane may be interpreted as representing *reality*, the source of both these complementarities.

Another way to characterize the difference between HUP and BCP may be that HUP involves two variables (e.g., position and momentum of a moving object) that occur within a measurement system whereas BCP implicates two independent measurement systems that cannot be implemented simultaneously (e.g., two-slit experiment vs. photoelectric effect measurement). That is, HUP may be viewed as an *intra-system* principle while BCP as an *inter-system* principle.

The difficulty that Einstein and his followers have been encountering in unifying the gravitational and other forces of nature (i.e., the electroweak and strong forces) (Kaku and Trainer 1987) may be accounted for by BCP, if we assume that the measurement system, A, involving the gravitational force and that, B, involving the other forces are *complementary* in the sense of Bohr. Complementarism would predict that these complementary opposites, A and B, can be unified through the discovery of the C term, which was referred to as the cosmological DNA and suggested to be identical with superstrings (Ji 1991, pp. 154–163). If this conjecture is right, superstrings should contain not only *energy*/*matter* as now widely believed but also the *information* of the algorithmic type and/or the Shannon type as was suggested in Ji (1991, p. 155). If further research substantiates this idea, it may represent one of the rare examples of theoretical concepts (e.g., information intrinsic to material objects) flowing from biology to physics (see Fig. 2.6).

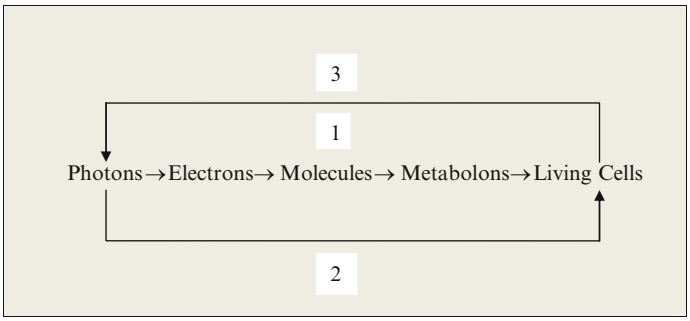


Fig. 2.6 A diagrammatic representation of the postulate that the *principle of complementarity* is *universal* and *circularly causal*. 1 = The progressive discovery of the principle of wave–particle complementarity from simple to complex material systems; 2 = the influence of physical principles on our understanding of living systems; 3 = the influence of the principles of biology on our understanding of nonliving systems

2.3.6 *Three Types of Complementary Pairs (or Complementarities)*

There are numerous complementary pairs suggested in the literature. Kelso and Engstrøm (2006) list over 450 pairs and Barab (2010) over 100, but only a small fraction of these "complementary pairs" appear to satisfy the three logical criteria of complementarity proposed in Sect. 2.3.3, and most of them satisfy only one or two of them. Therefore, it may be useful to classify complementary pairs (or complementarities) into three types as shown in Table 2.12.

Type I complementary pairs satisfy the *exclusivity* criterion only (see the second row in Table 2.12), as was the case for the two types of the consciousnesses that James invoked on the basis of his observation on a patient exhibiting the phenomenon of hysterical anesthesia (James 1890). The views of Einstein and Bohr may be said to exemplify a Type I complementarity, since their theories of quantum reality are mutually exclusive (determinism vs. contextualism) (Herbert 1987). The body and mind dichotomy as conceived by Descartes qualifies as an example of Type I complementarity, since mind and body are mutually exclusive according to Descartes. Type I complementarity may be referred to as the *Jamesian complementarity* or *psychological complementarity* since James (1890) introduced the adjective "complementary" into psychology.

Type II complementary pairs satisfy two of the three complementarian criteria – i.e., *Exclusivity* and *Essentiality* (see the third row in Table 2.12). The wave and particle attributes of photons (demonstrated by Einstein 1905) and electrons (predicted by Broglie in 1923 and experimentally confirmed about 5 years later) constitute Type II complementarity, since waves and particles are both mutually *exclusive* (at least under most experimental conditions, although exceptions

Table 2.12 A classification of complementarities (or complementary pairs) based on the three criteria of the complementarian logic (see Sect. 2.3.3)

Types of complementarities	Exclusivity (A)	Essentiality (B)	Transcend-entality (C)	Examples
I (Jamesian or psychological complementarity)	+			W. James (1890) (hysterical anesthesia) Einstein–Bohr debate (Herbert 1987) Descartes (mind–body dichotomy)
II (Bohrian or physical complementarity)	+	+		N. Bohr (wave–particle duality; kinematic–dynamic complementarity[a])
III (Lao-tsian or philosophical complementarity)	+	+	+	Complementarism (information and energy as the complementary aspects of gnergy) Lao-tse (Yin and Yang as the complementary aspects of the Tao) Aristotle (matter and form are the two aspects of hylomorph) Spinoza (humans can know only the thought and extension aspects of substance) Merleau-Ponty (Dillon 1997) (mind and body as the complementary aspects of flesh)

[a]See Sect. 2.3.5

may exist as in the Airy pattern formation by electrons; Sect. 2.3.3) and *necessary* for the complete characterization of quons (Herbert 1987). It appears to me that the Airy pattern can be accounted for equally well by two opposing views on quantum reality – the Bohrian perspective based on nonreality of dynamic attributes of quons and the Bohmian view that quons possess wave and particle properties simultaneously and intrinsically (Herbert 1987). Another way to describe the difference between the Bohrian and Bohmian perspectives is to state that:

> Wave and particle attributes of quantum entities or quons are complementary according to Bohr and supplementary according to Bohm. (2.51)

(See Statement 2.29 for the definitions of complementarity and supplementarity).

Since the concepts of *complementarity* and *supplementarity* are themselves mutually exclusive, it may be stated that the Bohrian and Bohmian views on quons are of the Type I complementarity as is the Einstein–Bohr debate.

The *kinematic–dynamic complementarity* is considered to be of Type II as well, since kinematics and dynamics are mutually exclusive (i.e., one cannot replace, nor

can be derived from, the other) but necessary for a complete description of motions of material objects, as illustrated below using DNA. Type II complementarity will be referred to as the *Bohrian* or *physical complementarity*.

Type III complementary pairs satisfy all of the three logical criteria of complementarity. As evident in the last row of Table 2.12, all of the examples given for Type III complementarity derive from philosophy because of the transcendentality criterion playing an important role. The transcendentality criterion entails invoking the two levels of reality that transcends each other – for example, the *epistemological* level where the complementary pair, A and B, has meanings and the *ontological* level, C, that transcends the epistemological level. In some cases, C may exist in the same level as A and B, for example, the triad of father (A), mother (B), and a child (C). We may refer to such cases as representing the Type III′ complementarity as compared to Type III.

The complementarity between the Watson–Crick base pairs (i.e., AT and GC) has been known since the helical structure of DNA duplex was discovered by Watson and Crick in 1953. About a decade later, it was discovered that the linear arrangements of three nucleotides along the long axis of a DNA strand encoded amino acids and the strings of nucleotide triplets in turn encoded genetic information specifying the structure of proteins.

The natural question that now arises is to which type of *complementarity* does the Watson–Crick base pairs belong? To answer this question, we must ask three related questions. (1) Do Watson–Crick base pairs satisfy the Exclusivity criterion? In other words, are the Watson–Crick base pairs mutually exclusive? The answer must be Yes, since these molecular pairs are distinct and mutually irreplaceable. (2) Do the Watson–Crick base pairs satisfy the Essentiality criterion? In other words, is there a third term C for which the Watson–Crick pairs are essential? Again the answer seems to be Yes, since without these base pairs, molecular copying (i.e., information transfer from one nucleic acid to another) would be impossible. (3) What is the third term that transcends the level of Watson–Crick base pairs and yet serves as their ground or source? One plausible answer seems to that the C term is the living cell, for the replication of which the Watson–Crick base pairs are essential and without which no Watson–Crick base pair can exists. Based on these answers, it may be concluded that the *Watson–Crick base pairs exhibit Type III complementarity*.

The above considerations are almost exclusively focused on the *information* aspects of life – complementary shapes of base pairs, nucleotide triplets, nucleotide sequences encoding genetic information, etc. Important as these aspects of life are, they alone are incomplete to account for the dynamics of life, since the utilization of genetic information encoded in DNA requires expending requisite free energy derived from chemical reactions catalyzed by enzymes. In other words, the *energy* aspect of DNA must be explicated along with the information aspect. Indeed, it can be stated that DNA carries not only genetic information but also mechanical energy, as evident in the formation of DNA supercoils catalyzed by ATP-driven topoisomerases and DNA gyrases (Sect. 8.3). Therefore, it can be asserted that the DNA duplex molecule embodies the *information–energy complementarity* that satisfies (1) Exclusivity (genetic information and mechanical energy are mutually exclusive), (2) Essentiality (genetic information and mechanical energy are both

needed for DNA replication and transcription), and (3) Transcendentality (self-replication is possible because of the existence of organisms which transcend the epistemological level of information and energy).

The two seemingly unrelated descriptions of DNA given above, one in terms of *information*, and the other in terms of *energy*, appear to be related to *kinematics* and *dynamics*, respectively (see Sect. 2.3.5 for the complementary relation between kinematics and dynamics, as first recognized by Bohr [Murdoch 1987]). If these analyses are valid, we can conclude that the DNA molecule embodies three different complementarities – (1) the Watson–Crick base pair complementarity, (2) the information–energy complementarity, and (3) the kinematic–dynamic complementarity.

2.3.7 *The Wave–Particle Complementarity in Physics, Biology, and Philosophy*

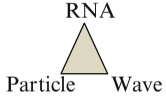
The wave–particle duality refers to the fact that quantum objects (or quons) exhibit both wave and particle properties. The particle property of light was demonstrated by the phenomenon of photoelectric effect which was quantitatively accounted for by Einstein in 1905 by assuming that light was a stream of particles. This idea may be denoted as Einstein's "wave → particle" postulate (see the upper portion of Table 2.13) (Herbert 1987). Inspired by the success of Einstein's "wave → particle" postulate, de Broglie hypothesized in his 1923 Ph.D. thesis the reverse, namely, that quantum particles exhibit wave properties (see "particle → wave" in Table 2.13), which was experimentally proven to be true a few years later by two American physicists, Davisson and Germer (Herbert 1987).

Although the wave–particle duality of quons is an experimental fact beyond any doubt, the question is still unsettled as to whether quons possess wave and particle properties intrinsically regardless of measurement (as asserted by de Broglie, Einstein, and Bohm) or they exhibit wave or particle properties only upon measurements, depending on the measuring apparatus employed (as maintained by Bohr, Heisenberg, and other "Copenhagenists") (Herbert 1987; Mermin 1990; Bacciagaluppi and Valenti 2009). It is truly astounding to me that, even after over a century's experimental work and mathematical theorizing, quantum physicists have yet to reach a consensus on the real nature of quons with respect to wave and particle properties (see the last column of the first row in Table 2.13).

The terms "wave–particle duality" and "wave–particle complementarity" differ in an important way – the former refers to an empirical fact, and the latter represents the interpretation of this fact according to Bohr and his school which contrasts with the interpretation offered by de Broglie and Bohm (Herbert 1987). That is, the wave–particle complementarity signifies that:

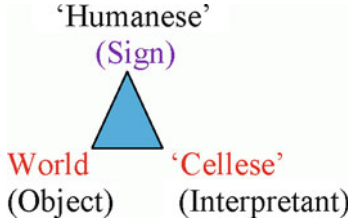
> Quons are neither waves nor particles but exhibit either of these two properties only upon their interactions with the measuring apparatus. (2.52)

Table 2.13 The universality of the principle of wave–particle duality (or complementarity) in physics, biology, and philosophy

Fields	Observations/facts	Theory	Reality question
Physics	1. Photoelectric effect	Wave → particle (Einstein 1905)	1. *The Copenhagen interpretation* (Herbert 1987): quons are neither particles nor waves but exhibit particle or wave properties upon measurement
	2. Electron diffraction	Particle → wave (de Broglie 1923)	2. *The de Broglie–Bohm interpretation* (Herbert 1987): quons possess wave and particle properties simultaneously and inherently even before measurement
Biology	3. Single-enzyme molecules show wave properties since they obey a Planck radiation law-like equation (Ji 2008b)		3. Enzymes and biochemicals inside the cell obey the principle of wave–particle duality: i.e., biomolecules are *wave–particle-dual*[a] as are quons in physics
	4. Microarray data on RNA levels in yeast cells also obey the Planck radiation law-like equation (Ji and So 2009d)		
Philosophy	5. Memory is not localized in any specific regions of the brain (Pribram 2010)	Memories are interference patterns of brain waves (Pribram 2010)	4. We think in waves 5. Thoughts are wave-like processes 6. Thoughts are waves 7. Thoughts are dissipatons[b] 8. Dissipatons are wave–particle-dual[a]
	6. We think in signs	Semiotics or the theory of signs (C. S. Peirce late nineteenth and early twentieth centuries) (Short 2007) Quantum physics (Herbert 1987; Pribram 2010)	9. Thoughts are wave–particle dual[a] 10. Thoughts as waves are constrained by the spectral area code, $\Delta W \, \Delta M > 1$ (Herbert 1987), which provides the mathematical basis for the *Knowledge Uncertainty Principle* (see Sect. 5.2.8)

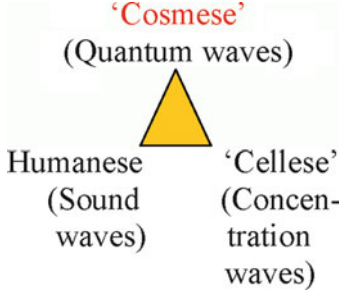
7. All objects, including signs, obey the principle of wave–particle duality

Isomorphism between human and cell languages (Ji 1997a, 1999b)



11. Peirce's theory of signs is based on the triad of *sign*, *object*, and *interpretant* (Short 2007). Based on quantum physics and cell biology, we can now identify Peirce's "interpretant" with *cell language* or *cellese* (Ji 1999b) that living cells use to represent the world internally

8. Both humans and living cells use languages as means to communicate. Human language (*humanese*) utilizes sound waves and electromagnetic waves; cell language (*cellese*) utilizes chemical concentration waves



12. *Humanese* and *cellese* may be the complementary aspects of the cosmological language (or *cosmese*) which can be identified with quantum mechanics in agreement with Pagels (1982)

[a] The term "wave–particle dual" is used to indicate that some physical objects or entities exhibit both wave- and particle-like properties such as light and electrons

[b] *Dissipatons* are synonymous with "dissipative structures," the structures that require the dissipation of free energy to exist and hence disappear upon the cessation of free energy supply (see Sect. 3.1). Examples of dissipatons include the flame of a candle, EEG (electroencephalogram), and life itself

Statement 2.52 is often synonymously expressed as follows:

Quons are complementary union of waves and particles. (2.53)

Waves and particles are the complementary aspects of quons. (2.54)

Statements 2.53 and 2.54 clearly satisfy the three criteria of the complementarian *logic* presented in Sect. 2.3.3, if quons are identified with the C term, and waves and particles with A and B terms. According to complementarism (Sect. 2.3.4), C transcends the level where A and B have meanings. Perhaps this provides one possible reason for the endless debates among quantum physicists over the real nature of C, i.e., light, electrons, and other quons.

There are two kinds of waves discussed in physics – (1) what may be called "physical waves" whose amplitude squared is proportional to the energy carried by waves, and (2) "nonphysical" or "information waves" (also called "proxy waves," "quantum waves," or "probability waves" in quantum mechanics) whose amplitude squared is proportional to the probability of observing certain events occurring. According to the Fourier theorem, any wave can be expressed as a sum of *sine waves*, each characterized by three numbers – (a) *amplitude*, (b) *frequency*, and (c) *phase*. A generalization of the Fourier theorem known as the "synthesizer theorem" (Herbert 1987) states that any wave, say X, can be decomposed into (or analyzed in terms of) a sum of waveforms belonging to any waveform family, say W, the sine waveform family being just one such example. The waveform family W whose members resemble X the closest is referred to as the *kin waveform family*, and the waveform family M whose members resemble X the least is called the "conjugate" waveform family of W. That is, the waveform family W is the conjugate of the waveform family M. When X is expressed as a sum of W waveforms, the number of W waveforms required to synthesize (or describe) wave X is smaller than the number of M waveforms needed to reconstruct X wave. The numbers of waveforms essential for reconstructing wave X in terms of W and M waveforms are called, respectively, the "spectral width" (also called "bandwidth") of W and M waveform families, denoted as ΔW and ΔM. The *synthesizer theorem* states that the product of these two bandwidths cannot be less than 1.

$$\Delta W \Delta M > 1 \tag{2.55}$$

Inequality 2.55 is called the *spectral area code* (Herbert 1987) and can be used to derive the Heisenberg Uncertainty Relation, since the momentum attribute of quons is associated with the sine waveform family (with spatial frequency, k, which is the inverse of the more familiar temporal frequency, f) and the position attribute is associated with the impulse waveform family; these two waveform families are conjugates of each other.

Most biologists, including myself until recently, assume that the wave–particle duality is confined to physics where microscopic objects (e.g., electrons, protons, neutrons) are studied but has little to do with biology since biological objects are much too large to exhibit any wave–particle-dual properties. I present below three pieces of evidence to refute this assumption.

1. *DNA level*. In Sect. 2.3.6, I have presented detailed analysis of the structure and function of the DNA molecule, leading to the conclusion that DNA embodies three kinds of complementarities – (a) the *Watson–Crick base pair complementarity*, (b) the *information–energy complementarity*, and (c) the *kinematics–dynamics complementarity* which includes the *wave–particle complementarity* (Sect. 2.3.5) (Murdoch 1987). Of these three kinds of complementarities, the information–energy complementarity and kinematics–dynamics complementarity may be viewed as belonging to the same family of what I often call the *global–local or (forest–tree) complementarity* which may be considered as the generalization of the wave–particle complementarity, wave being global and particle being local.
2. *Catalysis Level*. Single-molecule enzymic activity data (i.e., waiting time distribution) of cholesterol oxidase measured by Lu et al. (1998) fit the equation, $y = a(Ax + B)^{-5}/(\exp(b/(Ax + B)) - 1)$, where a, b, A and B are constants (see Sect. 11.3.3) (Ji 2008b). This equation reduces to the blackbody radiation equation discovered by M. Planck in 1900 when x = wavelength λ, y = the spectral energy density (i.e., the intensity of radiation emitted or absorbed at wavelength λ by the blackbody wall when heated to T K), $a = 8\pi hc$, $b = hc/kT$ (where h is the Planck constant, c is the speed of light, and k is the Boltzmann constant), $A = 1$, and $B = 0$. This unexpected finding strongly indicates that enzyme molecules exhibit both particle (e.g., their *nucleotide sequences*) and wave properties (e.g., the electromagnetic waves generated by the *vibrational motions* of covalent bonds within proteins) as symbolized by the first triangle appearing in Table 2.13. *It appears possible that the enzymic activity of a protein is the result of the electronic transitions (or quantum jumps) triggered by the coincidence of the phase angles of a set of vibrating bonds within an enzyme–substrate complex*.
3. *Control Level*. The Planck radiation law-like equation described above also fit the microarray data measured in budding yeast undergoing glucose–galactose shift (Ji and So 2009d). Garcia-Martinez et al. (2004) measured the genome-wide RNA levels of budding yeast at six time points (0, 5, 120, 360, 450, and 850 min after the nutritional shift) which showed pathway-specific trajectories (see Fig. 12.1). It is well known that the RNA levels inside the cell are determined by the balance between two opposing processes, i.e., *transcription* and *transcript degradation* (Ji et al. 2009a) (see Steps 4 and 5 in Fig. 12.22, Sect. 12.11). When these RNA level data are mapped onto a six-dimensional mathematical space (called the "concentration space"), each RNA trajectory (also called an "RNA expression profile") is represented as a single point and the whole budding yeast genome appears as a cluster of approximately 6,000 points. There are about 200 metabolic pathways in budding yeast, and each one of these pathways occupies a more or less distinct region in the 6-D concentration space. If a metabolic pathway contains n genes, n being typically 10–50, it is possible to calculate the distances between all possible RNA pairs belonging to a given metabolic pathway as $n(n - 1)/2$. When these distances are "binned" (i.e., grouped into different "bins" based on the different classes of distance values,

e.g., 1–10, 11–20, 21–30, etc.), a *histogram* or *distribution curve* is obtained (see Figs. 12.24 and 12.25) that fits the Planck radiation law-like equation (Ji and So 2009d). Again this unexpected finding indicates that the enzyme systems (i.e., transcriptosomes and transcript degrading enzymes to be called "degradosomes," a term imported from bacteriology) that regulate the RNA levels inside the budding yeast exhibit wave–particle duality as symbolized by the second triangle in Table 2.13 (see Sect. 12.12 for more details). One possible mechanism of coupling *transcriptosomes* and *degradosomes* involves the transformation of the complex vibrational motions of the combined *transcriptosomes* and *degradosomes* into the *concentration waves* of RNA molecules in the cytosol through the electronic transitions (also called chemical reactions or quantum jumps) coincident on the phase synchronization among relevant waves of protein vibrations. This idea may be referred to as the "bond vibration/quantum jump/chemical concentration" coupling hypothesis. The same coupling mechanism is most likely implicated in the single-molecule enzyme catalysis (see the last column in the second row of Table 2.13).

The evidence that the human brain obeys the wave–particle duality is more direct – the existence of electroencephalograms (EEG) resulting from neuronal firings or action potentials, the producers of the electromagnetic waves in the brain. Pribram (2010) proposed a wave-based model of memory, according to which the brain stores information as *holograms* resulting from phase-sensitive interactions among brain waves. A hologram (from Greek *holo* meaning whole and *gram* meaning drawing), unlike photography which records an image as seen from a single viewpoint, is a record of an object as seen from many viewpoints using coherent laser beams. Thus, it is here postulated that the brain obeys the wave–particle duality – the particle aspect of thoughts being identified with the local biochemical components of the chemical reactions supplying the free energy needed for thinking processes, and the wave aspect with the global biochemical network property of the brain as a whole (see the last row in Table 2.13).

According to C. S. Peirce (1839–1914), *we think in signs. Signs are defined as* any physical or symbolic entities that stand for things other than themselves (see Sect. 6.2.1). Based on the principles of physics, it can be maintained that all signs possess wave properties (e.g., electromagnetic waves of visible objects, sound waves of music or speeches). Since all thoughts are accompanied by electromagnetic waves, it follows that we think in waves which are in turn signs. Therefore, it may be concluded that modern brain science has amply demonstrated the validity of Peirce's thesis that we think in signs. Furthermore, signs being waves, human thoughts must obey the *spectral area code*, i.e., Eq. 2.55, which may underlie the Knowledge Uncertainty Principle to be described in Sect. 5.2.7.

It was found that the human language ("humanese") and the cell language ("cellese") obey a common set of linguistic (or semiotic) principles (Ji 1997a, 1999b) (see Sect. 6.1.2). This finding led me to conjecture that there exists a third language for which *humanese* and *cellese* may be complementary aspects. The conjectured third language was named the "cosmological language" or "cosmese"

(Ji 2004b), and the *cosmese* may be identified with quantum mechanics in agreement with Pagels (1982) (see the last row in Table 2.13). It is here suggested that the *cellese* can be identified with the *interpretant* of Peirce who defined it as *the effects that a sign has on the mind of the interpreter* (see the third triangle in Table 2.13). According to this view, humanese can refer to objects in the world if and only if mediated by cellese, *the molecular language of brain cells*.

What is common to all these different classes of languages is the *waving process*, either physical or nonphysical (as in the probability wave) and hence these languages may obey the principle of *nonlocality* in addition to that of *spectral area code*, Eq. 2.55, the two consequences of the wave–particle duality or complementarity (Herbert 1987). The *principle of nonlocality* states that the influence of an event occurring at one region in space can be instantly correlated with another event occurring elsewhere, no matter how distant, without any exchange of signals between the two correlated events, in apparent violation of the predictions made by the special relativity theory. In the 1970s and 1980s, it was experimentally demonstrated that the principle of nonlocality is obeyed by quantum objects (Herbert 1987; Mermin 1990). I here postulate that all biological processes such as enzymic catalysis (Sect. 7.2) and morphogenesis (Sect. 15.1) embody *nonlocal phenomena* that may be identified with all the physicochemical processes of living systems which cannot be completely accounted for in terms of the laws of classical physics and chemistry. Biological evolution itself (Chap. 14) may embody nonlocality, both in space and time. Most nonlocal phenomena discussed in physics (e.g., the Eistein–Podolsky–Rosen [EPR] experiments) deals with nonlocality in the spatial dimension, but the nonlocality of biological evolution may involve both the spatial and temporal dimensions. Thus, we can recognize two kinds of nonlocalities – the spatial and temporal nonlocalities. By "temporal nonlocality," I have in mind those situations in nature where an event occurring at one time point is correlated with another event occurring at the same or different time points, without any exchange of signals between the two events. Karl Jung's synchronicity (Jung 1972), for example, precognition, and coincidences of dreams, may be the best documented example of what is here called the *temporal nonlocality*. *Synchronicity* is defined as *"the experience of two or more events that are apparently causally unrelated occurring together in a meaningful manner. To count as synchronicity, the events should be unlikely to occur together by chance"* (http://en.wikipedia.org/wiki/Synchronicity).

In conclusion, the *wave–particle duality* that was first demonstrated by Einstein (1905) in connection with the photoelectric effect was found to apply to electrons by de Broglie in 1923 (de Broglie 1924; Bacciagaluppi and Valenti 2009), to molecular biology (Ji 2008b), to cell biology (Ji and So 2009d), and to the human brain, a system of neurons (Pribram 2010) (see Step 1 in Fig. 2.6). If these developments can be substantiated by future investigations, it would be possible to conclude that quantum physics plays a pivotal role in unraveling the mysteries of life (see Step 2 in Fig. 2.6). It is hoped that the enlightening influence of physics on biology is not a one-way street but a two-way one in the sense that a deep understanding of living processes (including human thinking) will eventually aid physicists in solving their challenging problems such as the ultimate nature of quons and the origin of the Universe (see Step 3 in Fig. 2.6).

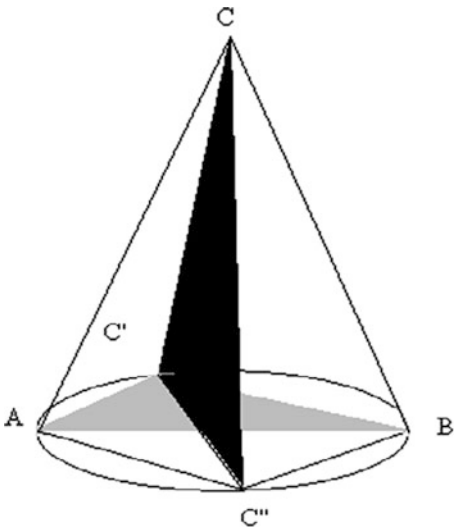


Fig. 2.7 A circular cone treated as a combination of the two sets of triangles or triads – the horizontal (or "in-plane") triads (e.g., AC′B and AC″B) and the vertical (or "out-of-plane") triads (e.g., ACB and C′CC″)

2.3.8 The Conic Theory of Everything (CTE)

Complementarity began its philosophical career as Bohr's interpretation of quantum mechanics (Murdoch 1987; Plotnitsky 2006; Lindley 2008), but the complementarism (see Sect. 2.3.4) that was formulated in the mid-1990s (Ji 1993, 1995), although inspired by Bohr's complementarity initially, is now based on the complementarian logic (see Sect. 2.3.3) whose validity is no longer critically dependent upon the validity of Bohr's complementarity as a philosophy of quantum mechanics (Murdoch 1987; Plotnitsky 2006; Lindley 2008) and can stand on its own feet. The wave–particle duality, which served as the model for the complementarian logic, may or may not obey all the three logical criteria of complementarism (especially the exclusivity criterion), depending on how one interprets experimental data such as the Airy patterns (Herbert 1987) and de Broglie equation, Eq. 2.37.

In July, 2000 (see Appendix A), I proposed to divide all complementary triads into two classes – one residing on the base of a circular cone (called "in-plane" or "horizontal triads") and the other standing on the circular base (called "out-of-plane" or "vertical triads") (see Fig. 2.7). One interesting consequence of dividing all triads into these two classes is that only the vertical triads possess a common apex (i.e., C), the horizontal triads have an infinite number of the apexes (i.e., C′, C″, A, B, etc.). This geometric feature of the circular cone may be useful in representing some of the profound philosophical ideas such as the Tao (viewed as C in Fig. 2.7) as the source of everything (A, B, C′, C″, etc. on the base of the circular cone) in the Universe.

The Conic theory of Everything (CTOE) consists of the following elements.

All the regularities of objects in this Universe, both living and nonliving, can be represented in terms of triads, each consisting of a pair of opposites (A & B) and a third term, C. All these triads form a circular cone, some constituting the base of the cone and others the body of the cone erected on it.

These triads, A-C-B, can be divided into two groups – the epistemological triads (E-triads) identified with the horizontal triads (e.g., AC′B, AC″B in Fig. 2.7), and the ontological triads (O-triads) identified with the vertical ones (e.g., ACB, C′CC″). One example of the E-triad is the well-known complementary relation between the wave (A) and particle (B) behaviors of light (C). An example of the O-triad is the triadic relation among Spinoza's Extension (A), Thought (B), and Substance (also called God or Nature) (C); or the recently postulated complementary relation among energy/matter (A), information (B), and gnergy (C) (Ji 1991, 1995). The main difference between E- and O-triads is that the validity of the relations embodied in the former can in principle be tested by scientific/experimental means, while the validity of the relations represented by the latter cannot be so tested and must be judged on the basis of its utility in organizing data into coherent models or pictures.

The Universe consists of two worlds – the Visible consisting of E-triads, and the Invisible, converging on the Apex of the O-triads. The Visible World is characterized by multiplicity and diversity as represented by the large number of points on the periphery of the base of the cone, whereas the Invisible World is characterized by a unity as symbolized by the Apex of the cone.

It is beyond the scope of the present book to discuss the possibility of classifying all the triads (numbering close to a hundred or more) that I have formulated during the past decade or so (e.g., see Table 2.7 and Appendix B) and probably equally numerous triads that C. S Pierce described in the late nineteenth century, but it appears feasible to utilize the geometric properties of the circular cone depicted in Fig. 2.7 to divide them into the E- and O-triads as defined in the conic theory of everything.

2.3.9 The Cookie-Cutter Paradigm and Complementarity

The cookie-cutter paradigm (CCP) of quantum physics has been described by Mohrhoff (2002). Although CCP may have some shortcomings in representing quantum physics, it may serve as a convenient metaphor for complementarity or complementarism (Sect. 2.3). It is interesting to note that CCP can also accommodate the "model-dependent realism: the idea that a physical theory or world picture is a model (generally of a mathematical nature) and a set of rules that connect the elements of the model to observations" that was recently proposed by Hawking and Mlodinow (2010). The CCP model of complementarity consists of the following identities:

1. Dough = reality (C term)
2. Cookie cutters = models

3. Cookie = A piece of reality captured by (or that fits) the model or theory (A term)
4. Empty space left behind = Anti-cookie, or the anti-model, that opposes the reality captured by a model (B term)
5. The dough left behind = the reality that is beyond (or untouched by) the model
6. Different kinds of dough = There are more than one kind of reality that can be captured by models. Some reality (e.g., music, spirituality) is more difficult to model (i.e., to cut out with the "music" cookie cutter) than others (e.g., biology, with the "biology" cookie cutter, physics with the "physics" cookie cutter, etc.)

Evidently the CCP model of complementarity contains three elements (b, e and f) that are not specified by the complementarian logic (A, B, and C) (Sect. 2.3.3), which are valuable new features. Just as there are many different cookie cutters (for a star, a circle, a bear, a gingerbread man, an airplane, an elephant, etc.) so, there can be many different models of reality cut out by different "types" of cookie cutters known as physics, biology, philosophy, art, and religion, each type having almost an infinite number of tokens called relativity theory, quantum theory, statistical mechanics in physics, or molecular biology, cell biology, physiology, psychology, cardiology, cancer biology, neurobiology, etc. in biology. This visual way of representing complementarity may be referred to as the "cookie-cutter paradigm" of complementarity (CCPC). The cookie-cutter paradigm of complementarity is applied to Wolfram's New Kind of Science in Sect. 5.2.1.

2.4 Renormalizable Networks and SOWAWN Machines

2.4.1 Definition of Bionetworks

A bionetwork (BN), i.e., the networks representing the structure of biological systems, can be defined as a system of nodes connected by edges that exhibits some biological functions or emergent properties not found in individual nodes. Thus, a bionetwork can be represented as a 3-tuple:

$$\mathrm{BN} = (\mathrm{n}, \mathrm{e}, \mathrm{f}) \tag{2.56}$$

where n is the *node*, e is the *edge,* and f is the function or the emergent property of BN.

The term "renormalization" originated in quantum field theory and condensed matter physics. In the latter field, the term is employed to refer to the fact that, under some unusual conditions known as the critical points, a group of microscopic entities (e.g., atoms, molecules) can form (or act as) a unit to exhibit novel properties (e.g., convection, rigidity, superconductivity, and superfluidity) that are beyond (and hence unobservable in) individual component entities (Anderson 1972; Cao and Schweber 1993; Huggett and Weingard 1995; Domb 1996; Laughlin 2005). The essential idea of "renormalization" is captured by Barabasi (2002, p. 75) thus:

$$\text{Interacton 1} + \text{Interaction 2} \xrightarrow[\text{'Chunking'}]{\text{Renormalization}} \text{Emergenton}$$

Fig. 2.8 A schematic representation of the definition of renormalization. *Interactons* are defined as material entities or processes that interact with one another physically or chemically to produce new entities or processes called *emergentons*. The process of interaction between *interactons* leading to the production of an *emergenton* is here defined as "renormalization," which is deemed equivalent to the concept of "chunking" used in computer science (Hofstadter 1980)

> In the vicinity of the critical point we need to stop viewing atoms separately. Rather, they should be considered communities that act in unison. Atoms must be replaced by boxes of atoms such that within each box all atoms behave as one.

For the purpose of biological applications, we will define "renormalization" as the process of grouping or "chunking" (Hofstadter 1980, pp. 285–309) two or more entities or processes (to be called *interactons*) into one unit of action (to be called *emergentons*), leading to the emergence of new properties not possessed by individual *interactons*. We may represent this idea schematically as shown in Fig. 2.8.

One of the simplest examples of renormalization as defined in Fig. 2.8 is provided by the chemical reaction occurring in a test tube between two reactants, A and B, to form product C:

$$\text{A} + \text{B} \rightarrow \text{C} \tag{2.57}$$

Using the language of "renormalization," Reaction 2.57 can be described as "A and B combining to form a new unit called C which exhibits some emergent properties."

The speed of Reaction 2.57 is determined by the concentrations of A and B, the properties of the agents mediating the reactions (e.g., enzymes), and the physical conditions of the reactor (e.g., pressure, temperature, surface characteristics of reactor walls).

Most chemical reactions essential for maintaining the living state of the cell do not occur without being catalyzed by enzymes. That is, they have too high activation energy barriers to be overcome through thermal collisions alone (Ji 1974b, 1991, 2004a). This can be represented schematically as:

$$\text{A} + \text{B} \xrightarrow{\text{E}} \text{C} \tag{2.58}$$

where E stands for the enzyme catalyzing the reaction. Since A and B combining to form C can be described as a *renormalization* (or *chunking*) process and since this process does not occur without E, we can refer to E as the *renormalizer* (or a *chunkase*). That is, all enzymes are *renormalizers* or *chunkases* consistent with the definition of renormalization or chunking given in Fig. 2.8. Also, since renormalization leads to the emergence of novel properties, we can state that:

> Enzymes provide the physical mechanisms for the emergence of new properties in the cell. (2.59)

Since one of the unique features of all networks is the emergence of a new property beyond the properties of individual nodes, it may be claimed that:

The *raison d'être* of a network is its *emergent* property. (2.60)

That is, there is an inseparable connection between *networks* and *emergences* in the sense that no emergence is possible without a network. Therefore, we may refer to Statement 2.60 as the Emergent Definition of Networks (EDN).

Emergence has become a topic of great theoretical and philosophical interests in recent years (Laughlin 2005; Clayton and Davies 2006; Reid 2007), and the concept of network is even more widely discussed in natural, computer, and human sciences (Barabasi 2002; Sporns 2011). However, to the best of my knowledge, not much attention has been given so far to formulating possible *mechanisms* connecting networks to their emergent properties. One of the major aims of this book is to suggest that "renormalization" as defined in Fig. 2.8 can serve as a universal mechanism of emergence in all networks in physics, chemistry, biology, and beyond. For a related discussion, readers are referred to Cao and Schweber (1993).

2.4.2 "Chunk-and-Control" (C & C) Principle

As indicated in Fig. 2.8, the concepts of renormalization and chunking can be viewed as essentially equivalent in content, the only difference being that the former emerged in physics and the latter in computer science independently. The main point of this section is to suggest that the principle of renormalization or chunking has also been in operation in the living cell since eukaryotes emerged on this planet over 1.5 billion years ago.

Computer scientists have discovered the utility of the *divide and conquer* (D & C) strategy in software programming in which they break down a large and complex problem into two or more smaller sub-problems repeatedly until the sub-problems become easy enough to be solved directly. Cells apparently utilize a similar strategy on the molecular level. For example, when cells divide they must control the behaviors of all the DNA molecules (46 of them in the human genome, each 10^7 base-pair long) in the nucleus so that they are reproduced and divided into two identical sets. To accomplish this gigantuan task, cells appear to chunk the DNA components into increasingly larger units as shown in Fig. 2.9, first into nucleosmes which are "strung" together into 11 nm-diameter "beads-on-a-string" form. This is wound into a 30 nm chromatin fiber (also known as solenoid) with six nucleosomes per turn, which is further condensed into 300 nm looped domain, 50 turns per loop. The next stage of condensation or chunking is "miniband," each containing 18 loops. Finally these minibands are stacked together to form the metaphase chromosomes with the cross-sectional diameter of about 1.4×10^{-6} m. Thus, the cross-section diameter of a DNA double helix (or DNA duplex) (2×10^{-9} m) has increased by a factor of about 10^3, resulting in a 10^9-fold compaction of DNA volume. Since this compaction has taken place in five steps,

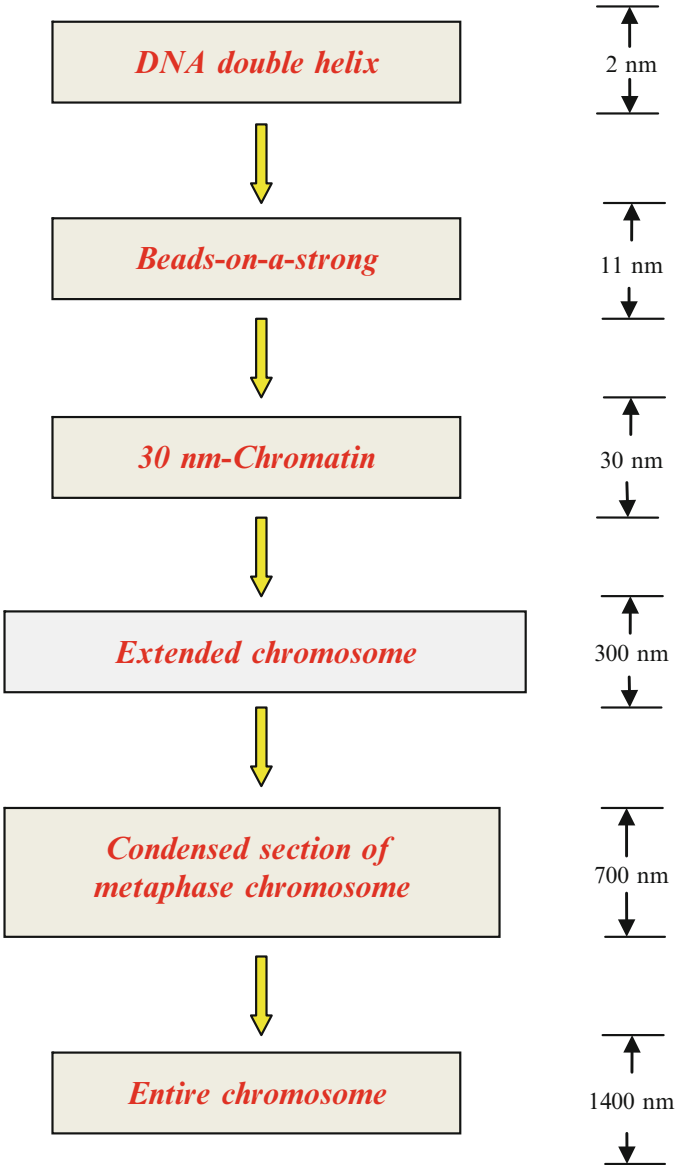


Fig. 2.9 The step-wise packaging of a single-strand DNA double helices into a chromosome in the metaphase. The "chunking" of the single-strand DNA duplexes into chromosomes facilitates DNA replication and sorting during cell division (Downloaded from http://library.thinkquest.org/C004535/media/chromosome_packing.gif, May 2009)

the average rate of compaction per step is about 10^2. This would mean that on average, each chunking process reduces the motional degree of freedom of DNA components by a factor of about 10^2. Thus, we can conclude that "chunking" is synonymous with "constraining" and hence the acronym, C & C, can be interpreted to mean either "chunking-and-constrain" or "chunking-and-control."

The "chunking" phenomenon depicted in Fig. 2.9 is a highly organized process and thus requires dissipating free energy catalyzed by enzymes. Therefore, it would be reasonable to predict that five different classes of enzyme complexes catalyzing each of the five chunking (or coding, or renormalizing) operations shown in the figure will be discovered. I coined the term "chunkase" around 2005 while teaching "Theoretical Aspects of Pharmacology" to Pharm D students at Rutgers. Each chunkase is probably as large as ribosomes or spliceosomes, whose orderly motions would be driven by conformons derived from chemical reactions (Sect. 8.4).

As already alluded to, one of the main reasons for the "chunking operations" found in the eukaryotes is most likely to facilitate self-replication of the cell which entails replicating DNA. In principle, DNA replication can be achieved in two ways

1. *Replication without chunking* – First replicate n DNA molecules into 2n DNA molecules, separating them into two identical groups by transporting only one of the sets across a membrane through an active transport mechanism.
2. *Replication with chunking* – Replicate n DNA molecules into 2n molecules, each chunked into smaller, more compact particles, which can be more easily *counted* and *sorted* than the original, unchunked DNA double helices.

It is intuitively clear that Mechanism (1) would be much more difficult to implement than Mechanism (2) in agreement with von Neumann who also considered similar mechanisms of cell divisions (von Neumann 1966). In fact it should be possible to compute the two different efficiencies of cell divisions (or mitosis) based on the two mechanisms of DNA replications described above. Such chunking-based cell division may not be necessary for prokaryotes but becomes important as the number of chromosomes to be replicated increases in eukaryotes.

Chunking is reversible: What gets chunked must get "de-chunked" at some point during a cell cycle, catalyzed by enzyme complexes distinct from associated chunkases. The enzyme complexes postulated to catalyze de-chunking operations may be referred to as "i- $>$ j de-chunkase," where i and j refer to the adjacent levels of chunking with i $>$ j.

The purpose of chunking the (n $-$ 1)th level components of a network into a node at the nth level may be construed as producing a new function at the nth level that is not available on the (n $-$ 1)th level (see Fig. 2.10). The function at the nth level may be viewed as a chunked version of (structure, processes, and mechanisms) at the (n $-$ 1)th level.

Since the Peircen sign (Sect. 6.2.1) can also be defined in a traidic manner as shown in Fig. 6.2, we can conclude that chunking and de-chunking operations can

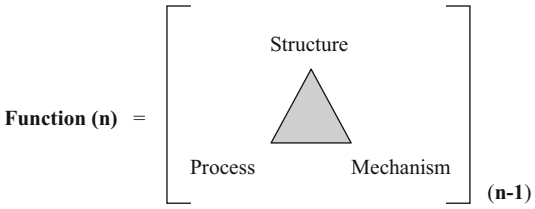


Fig. 2.10 The function viewed as a node (or sign) on the nth level of organization "encoding" (or "chunking") a network on the (n − 1)th level. Conversely, a function on the nth level of organization can be decoded (de-chunked) into a network of structures, processes and mechanisms on the (n − 1)th level (See Sect. 6.2.11 for a triadic model of function)

be viewed as sign processes (or coding and decoding processes, i.e., semiosis). In other words:

> Chunking and de-chunking operations are the molecular equivalents of coding and decoding processes in semiotics. (2.61)

The chunking and de-chunking operations shown in Fig. 2.9 occur within one language, namely, DNA language. It is interesting to note that chunking and de-chunking processes can occur involving two or more different languages, for example, from *DNese* to *RNese* (during transcription), from *RNese* to *proteinese* (during translation), and *proteinese* to *biochemicalese* (during catalysis) (see Table 11.3 and Footnote d for the background behind the various "-eses").

The suggestion seems reasonable that the chunking and de-chunking operations occurring within DNese may be mainly to facilitate cell *replication* (or *mitosis*). An equally reasonable suggestion may be made concerning the role of the chunking and de-chunking operations occurring between different languages: The chunking and de-chunking operations involving two or more different languages may be mainly for facilitating cell *differentiation* in space and time.

Since *cell divisions* and *cell differentiations* are essential for both development and evolution, it may be concluded that chunking and de-chunking operations involving DNese, RNese, proteinese, and biochemicalese taking place in cells are necessary and sufficient for ontogeny (under the synchronic environment; see Sect. 15.4) and phylogeny (under the diachronic environment). Individual cells can only experience synchronic environment, not the diachronic one, while populations of cells as a group can experience both the diachronic and synchronic environments.

If the above analysis is correct, chunking and de-chunking (or "renormalization") operations may turn out to be fundamental to life, and the reason for this may well lie in the fact that when complex processes or structures are chunked into simpler processes or structures, it becomes easier to control or regulate them. For this reason, we may refer to this idea as the "chunk-and-regulate" (C & C) principle, which may be isomorphic with the "divide-and-conquer" (D & C) principle in computer science.

Table 2.14 Three major classes of renormalizable networks in biology

Renormalizable network	Node	Network	Network of networks	Emergent properties
1. Cells	Atoms	Molecules	System of molecules	Self-reproduction (cell cycle)
2. Organisms[a]	Molecules	Cells	System of cells	Development (ontogeny)
3. Populations	Cells	Organisms	System of organisms	Evolution (phylogeny)

[a] Organisms can be either multicellular or unicellular. In other words, the term "organism" can signify either an independent organism or a part of an organism, depending on the context of the discourse

2.4.3 *Living Systems as Renormalizable Networks of SOWAWN Machines*

It has been known for over one and a half centuries that all living systems are composed of networks (i.e., systems) of cells. Since the development of biochemistry in the early decades of the twentieth century, cells have in turn been known to be composed of networks of biopolymers (e.g., DNA, RNA, proteins, carbohydrates) and small molecular and submolecular entities (e.g., ATP, glucose, metal ions) that are transformed and organized in space and time. Based on these observations alone, it appears logical to conclude that living systems are examples of *networks of networks* – i.e., networks in which individual nodes can in turn act as networks at a lower level of organization (or a higher level of resolution). The phenomenon of a network acting as a unit to constitute a node in a higher-order (or higher-level) network represents "renormalization" as defined in Fig. 2.8. In addition, networks are renormalizable in that a network can act as a node of a larger network or accept as its node's smaller networks. Therefore, a renormalizable network can act as any one of the following – (a) a network, (b), a node, and (c) a network of networks – depending on the level of resolution at which it is viewed. The concept of a *renormalizable network* can be applied to at least three distinct levels in biology, as shown in Table 2.14. It is here postulated that, at each level of the networks, a new property emerges that is unique to that level (see the last column in Table 2.14). The emergent property of a renormalizable network is in turn thought to result from a unique set of mechanisms of interactions operating among its component nodes (or *interactons*) and it is such mechanisms that implement renormalization.

As evident in Table 2.14, the *renormalizable network theory* (RNT) described here is a general molecular theory that can be applied to all living systems, ranging from unicellular to multicellular organisms and their populations. The RNT described in this book combines the molecular theories of enzymic catalysis formulated in 1974 (Ji 1974a, 1979), the concept of renormalization imported from condensed matter physics (Cao and Schweber 1993; Stauffer and Aharony

1994; Huggett and Weingard 1995; Domb 1996; Fisher 1998; Stanley 1999), and the language of networks that has emerged in recent years as a powerful new tool in science (Barabasi 2002).

Renormalizable networks as defined above are synonymous with *S*elf-*O*rganizing-*W*henever-*A*nd-*W*herever-*N*eeded (SOWAWN) machines (Ji 2006b, 2007b). The concept of machines (or systems) is indispensable in understanding living structures and processes at all levels of organization – from molecules, to cells, to the blood coagulation cascade, to the human body, and to societies. One of the reasons for the universal usefulness of the machine concept in living systems appears to be the possibility of applying to biosystems the Law of Requisite Variety (LRV; see Sect. 5.3.2), which provides the principles underlying the complexity of the internal structures of machines or systems.

In the course of teaching Theoretical Aspects of Pharmacology to Pharm D students at Rutgers University in 2005, it occurred to me that there may be a new kind of machine operating in cells and the human body, which the author elected to call "self-organizing-whenever-and-wherever-needed" (SOWAWN) machine, for the lack of a better term. The idea of SOWAWN (pronounced "sow-on") machine came as I was discussing the blood coagulation system with students, one of the most complicated biochemical, biophysical, and cellular processes that go on in our body. At least a dozen proteins (called blood coagulation factors) and two cell types (platelets and red blood cells) and several biochemical entities (e.g., thromboxane) participate in a dynamic process triggered by signals released from ruptured blood vessels whose purpose is to stop bleeding by forming insoluble clots around the damaged vessel (and not anywhere else). The blood coagulation cascade is a good example of SOWAWN machines, because:

1. It is activated (or assembled) only when and where needed in order to prevent interfering with normal blood flow in body compartments without any damaged vessels.
2. It does not exist pre-assembled, because any pre-assembled components of the blood cascade system may plug up capillaries due to their bulky molecular dimensions.
3. The necessary components of the blood coagulation cascade are randomly distributed in the blood compartment and are constantly available anywhere in our vascular system so that they can be signaled to carry out pre-programmed actions at moment's notice.
4. The free energy needed to drive the self-assembling processes may be derived from the hydrolysis of proteins which provides about ¼ of the Gibbs free energy of ATP hydrolysis (In other words, peptide bonds may serve as the extracellular analogs of ATP).

Another example of SOWAWN machines is the so-called signal transduction cascades or pathways inside the cell. A signal transduction pathway (comprising, again, about a dozen proteins) in cells are activated by signals (e.g., hormones) binding to cell membrane receptors (Table 12.14 and Fig. 12.34). A signal-bound cell membrane receptor undergoes a shape (or conformational) change which

triggers a self-assembling process of about a dozen proteins (called signal transducing proteins known as MAPKKK, MAPKK, MAPK, STAT, JAK, etc.) (Fig. 12.35), driven by free-energy releasing phosphorylation–dephosphorylation reactions catalyzed by ubiquitous (about 100 different kinds!) proteins called kinases and phosphoprotein phosphatases present inside the cell. The biological function of a signal transduction cascade, viewed as a SOWAWN machine, is to turn on or off a target gene (related to V_O in Eq. 5.63) under complex intracellular environmental conditions (related to V_E) by increasing the complexity of the internal state of the cascade (indicated by V_M).

As was suggested for the blood coagulation system, the components of a signal transduction cascade do not exist inside the cell pre-assembled (most likely to prevent cellular jam up) but are distributed randomly throughout the cell volume and are programmed to assemble wherever and whenever needs arise inside the cell.

It is clear that SOWAWN machines are examples of what Prigogine called "dissipative structures" (Prigogine 1977, 1980) and share common characteristics with what Norris et al. refer to as "hyperstructures" (Norris et al 1999), what Hartwell et al. (1999) called "modules," and what I referred to as "IDSs" (intracellular dissipative structures) (Ji 1991, pp. 69–73) (see Chap. 9).

Machines and tools have been used by *Homo sapiens* probably for 2–3 millions years. The concept of machines was generalized to include dynamic and transient assemblies of interacting components (i.e., *interactons*) only in the mid- to the late-twentieth century, here called SOWAWN machines. And yet we now realize that living systems may have been utilizing SOWAWN machines from their very inception, i.e., for over 3.5 billion years!

Organisms can be viewed as networks of SOWAWN machines made out of smaller SOWAWN machines. As already indicated, SOWAWN machines are dissipative structures carrying both *free energy* and *genetic information* that are essential for self-organizing into dynamic and transient systems to effectuate specific functions including self-replication (see Eq. 2.56). It should be pointed out that, although SOWAWN machines are dissipative structures, not all dissipative structures are SOWAWN machines. As accurately reflected in their acronym, SOWAWN machines are dynamic material systems that have evolved to possess the following characteristics:

1. Ability to self-organize (SO)
2. Ability to move/change in space and time (WAW) and
3. Ability to sense and meet the need (N) of themselves and others

2.4.4 Hyperstructures and SOWAWN Machines

There are concepts and theories published in the literature that are closely related to SOWAWN machines, including *metabolons* (Srere 1987), *metabolic machines* (Holcome 1982; Ji 1991, pp. 44–49), *cytosociology* (Smith and Welch 1991), *modules* (Hartwell et al. 1999), *IDSs*, or *intracellular dissipative structures* (see Sect. 3.1.2 and

Table 2.15 A classification of *hyperstructures* based on the dissipative structure theory of Prigogine

	Hyperstructures	
	Active	Passive
1. Alternative names	SOWAWN machines	SAWAWN machines
2. Self-organizing	Yes	No
3. Self-assembling	Yes	Yes
4. Equilibrium structure	No	Yes
5. Dissipative structure	Yes	No
6. Kinetics of the formation – degradation cycle ($t_{1/2}$)	Rapid (ms?)	Slow (min ~ h?)

SOWAWN self-organzing-whenever-and-wherever-needed, *SAWAWN* self-assembling-whenever-and-wherever-needed

Table 2.16 The three levels of characteristic spatiotemporal scales of organisms (or living systems)

	Microscopic	Mesoscopic	Macroscopic
Examples	Enzymes	Cells	Animals and plants
Distance scale (nm)	$1 - 10$	$10 - 10^4$	$10^4 - 10^{10}$
Volume scale (nm^3)	$1 - 10^3$	$10^3 - 10^{12}$	$10^{12} - 10^{30}$
Time scale (s)	$10^{-12} - 1$	$1 - 10^6$	$10^6 - 10^{10}$
Order parameter	Degree of coincidence of (or correlation between) amino acid residues at the active site	Degree of coincidence of (or correlation between) intracellular events	Degree of coincidence of (or correlation between) intercellular events

Chap. 9) (Ji 1991), and *hyperstructures* (Norris et al. 1999, 2007a,b). The last concept is especially interesting because it is highly detailed and supported by strong experimental data originating from microbiology. Therefore, it may be instructive to compare SOWAWN machines and hyperstructures as shown in Table 2.15. In constructing Table 2.15, it became necessary to make a distinction between "self-organization" and "self-assembly," the former implicating dynamic steady states far from equilibrium and the latter implicating "an approach-to-equilibrium." Norris et al. (1999) also distinguish "nonequilibrium" or "dissipative" and "equilibrium" forms of hyperstructures. It should be noted that Table 2.15 lists both the similarities and differences between hyperstructures and SOWAWN/SAWAWN machines. The most important difference may be the differential kinetic behaviors specified for SOWAWN vs. SAWAWN machines (see Row 6) whereas no such differential behaviors were specified for active and passive hyperstructures.

2.4.5 *Micro–Macro Correlations in Bionetworks*

Organisms, from the unicellular to multicellular levels, cover a wide range of sizes and temporal scales, which may be conveniently divided into three levels as shown in Table 2.16. What is common to these three levels of organization is the

phenomenon of *long-range correlations*, namely, the influence of molecules on the behaviors of cells and multicellular systems exerted over distance scales varying by 10, time scales by 22, and volume ratios by 30 orders of magnitude as indicated in the second, third, and fourth rows, respectively.

The spatiotemporal correlations over these scales may be expressed quantitatively in terms of "order parameter," the concept borrowed from condensed matter physics (Domb 1996), unique to living systems, which may be defined as the *degree of correlation* (e.g., *coincidence* or *synchrony* in the time dimension) *among critical structures or events* (see the last row in Table 2.16). In physics and chemistry, the adjective, "critical," refers to the value of a measurement, such as temperature, pressure, or density, at which a physical system undergoes an abrupt change in quality, property, or state. For example, at the *critical* temperature of 0°C, water changes from the liquid (disordered) to solid (ordered) state, passing through the *critical state* or *phase* where both ordered and disordered states of water coexist. The biological systems may exist in states resembling such a *critical state*, in that ordered and nonordered processes can coexist in cells and multicellular systems.

It may be necessary to distinguish between two levels of order–disorder transitions – at the molecular and organismic levels. At the molecular level, biologists can employ the same opposite pairs, *order* vs. *disorder*, to describe, say, protein structures, just as physicists use such an opposite pair to describe physical states on either side of a critical point. At the organismic (i.e., cellular or higher) levels, it may be necessary to adopt another opposite pair such as *life* vs. *nonlife* (or *live* vs. *dead)*. Thus, in biology, we may have a duality of opposite pairs: (1) *order* vs. *disorder* on the molecular and subcellular levels, and (2) *life* vs. *nonlife* that is applicable to cells and multicellular systems.

It may well turn out that cells are constantly at a critical point in the sense that both ordered and disordered states of subcellular constituents coexist as a means to effectuate long-range interactions over micro- and meso-scopic scales, and such interactions may be an essential condition for the *living state* of the cell (see Sect. 16.7 for a related discussion). If this view turns out to be correct, what is unique about the phenomenon of life would be micro–macro correlation (e.g., the body movement driven by molecular motors utilizing the free energy of ATP hydrolysis) mediated by cells to couple micro- to meso-scale structures and processes. In this sense, we may view cells as the effector or the agent of micro–macro correlations (or coupling) under varied environmental conditions conducive to life, which conditions may be referred to as "bio-critical points" (see Sect. 15.12 for a related discussion).

Micro–meso correlations/interactions/couplings are evident in the theoretical model of the cell known as the Bhopalator proposed in Ji (1985a). This model is reproduced in Fig. 2.11. The Bhopalator model appears to be the first comprehensive molecular model of the living cell proposed in the literature. Two novel concepts are embedded in the Bhopalator: (1) The ultimate form of the expression of a gene is a dynamic structure called "dissipative structure" (or *dissipation*) defined as any spatiotemporal distribution of matter produced and maintained by dissipation of free energy (Sect. 3.1, Chap. 9), and (2) enzymes are molecular

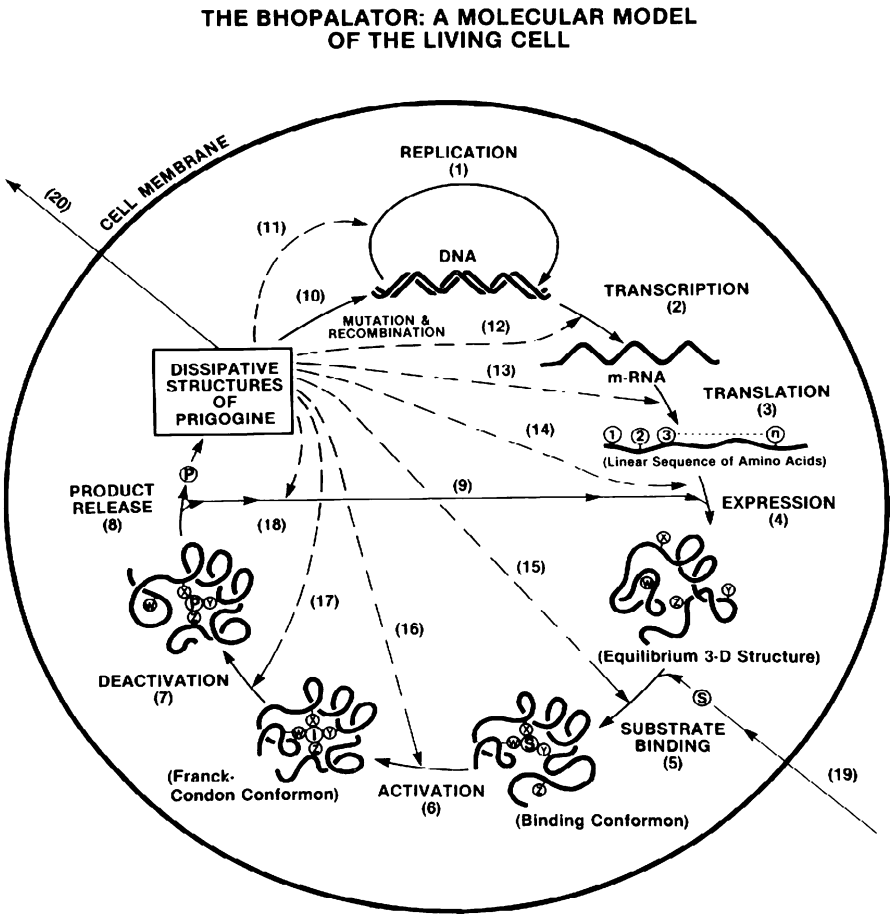


Fig. 2.11 The Bhopalator – a molecular model of the living cell (Reproduced from Ji 1985a, b). The cell can be treated as the physical system wherein micro-meso correlations occur under a wide variety of environmental conditions supported by free energy utilizing enzymes acting as *coincidence detectors* (see Sect. 7.2.2). The Bhopalator consists of a total of 20 major steps: 1 = DNA replication; 2 = transcription; 3 = translation; 4 = protein folding; 5 = substrate binding; 6 = activation of the enzyme–substrate complex; 7 = equilibration between the substrate and the product at the metastable transition state; 8 = product release contributing to the formation of the intracellular dissipative structure (IDS); 9 = recycling of the enzyme; 10 = IDS-induced changes in DNA structure; 11–18 = feedback interactions mediated by IDS; 19 = input of substrate into the cell; and 20 = the output of the cell effected by IDSs, which makes cell function and IDSs synonymous (see Sect. 10.1 for more details)

machines driven by conformational strains (i.e., conformons) generated from chemical reactions and localized in sequence-specific sites. The arrows, both solid and dotted, represent molecular processes mostly catalyzed by enzymes (which are viewed as elementary coincidence detectors (see Sect. 7.2.2)) that are organized in space and time to produce coherent behaviors of cells at the meso-

scopic level. For example, the binding of a ligand to a cell surface receptor can influence what happens in the center of the nucleus 5–10 μm away, suggesting that *correlation lengths* in cells at critical points can be 5–10 μm, which is much longer than the persistence length (i.e., the length over which mechanical forces can be transmitted owing to stiffness) of biopolymers, typically less than 0.1 μm (Bednar et al. 1995). The Bhopalator model of the cell suggests that there are three possible mechanisms for effectuating the micro–meso correlations or couplings:

1. Mechanical mechanisms mediated by the cytoskeleton as has long been advocated by Ingber and his group (1998)
2. Chemical mechanisms mediated by diffusible molecules and ions as are well established in signal transduction pathways (Kyriakis and Avruch 2001) and the actions of transcription factors and
3. Electromagnetic field mechanisms as evident in various membrane potential-dependent processes such as voltage-gated ion-channel openings and closings

Unlike in condensed matter physics where long-range correlations (e.g., snow crystal formation [Libbrecht 2008]) are driven solely by the free energy of interactions among molecular components, the long-range correlations seen in cells are driven by both *free energy* and *genetic information*, because both of these factors are essential in the operation of enzymes as catalysts (see information–energy complementarity in Ji (2002b, 2004a, b)). Thus, it may be concluded that the role of enzymes are what distinguishes biotic and abiotic critical phenomena exhibited, for example, by living cells.

2.5 The Theory of Finite Classes

Bohr thought that biologists should accept the *functions of living systems* as given, just as physicists accept *quantum of action* as an irreducible unit of physical reality at the microscopic level. This is the essence of the *holism* in biology that Bohr suggested seven decades ago. This seminal idea was further developed and elaborated on by W. Elsasser from the 1960s through the 1990s, laying the logical foundation for Bohr's intuitive grasp of the essence of the phenomenon of life. Hence, we may well consider Bohr and Elsasser as the originators of *holistic* or *systems biology* that has been gaining momentum in recent years (Hartwell et al. 1999; Bechtel 2010).

Elsasser dedicated the last three decades of his life to the theoretical research aimed at defining the basic difference between physics and biology. He maintains that the class of the objects studied in physics is *homogeneous* in kind and *infinite* in size (in the order of Avogadro's number, $\sim 10^{23}$), whereas the class of objects studied in biology is *heterogeneous* in kind (the number of different kinds in this case being in the order of $10^{10\wedge 9}$, the number of all possible strings that can be constructed out of the different kinds of deoxyribonucleotides, one billion units

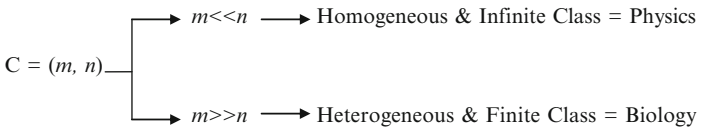


Fig. 2.12 A diagrammatic representation of the homogenous and heterogeneous classes, the former being the primary object of study in physics and the latter in biology, according to Elsasser (1998)

long, as found in the human genome) and *finite* in size (less than ~10^6 molecules) (see Fig. 2.12). According to Elsasser, the traditional mathematical equations used in physics and chemistry cannot be applied to biology because they do not converge when applied to finite classes (Elsasser 1998). Wolfram (2002) reached a similar conclusion from a different direction.

To distinguish between *homogeneous* and *heterogeneous* classes, it may be useful to represent a class, C, as a 2-tuple:

$$\mathrm{C} = (m, n) \tag{2.62}$$

where m is the number of different kinds of the elements of a class, and n is the number of copies of each kind in a class. It should be noted here that m in Eq. 2.62 can be characterized further in terms of M, the number of components of a living system, and N, the number of particles in each component as done by Mamontov et al. (2006). Variables m and n can have two ranges of values – large and small. When m is small we can refer to the class as homogeneous; when m is large, heterogeneous. Likewise, when n is large, the class can be referred to as infinite; when small, finite:

One important conclusion that Elsasser arrived at, based on the recognition of the two classes of objects, is that *reductionist scheme works only for homogeneous classes but not for heterogeneous ones*. For the latter, the principle of holism is essential. This conclusion, when applied to the cell, a prototypical example of the objects belonging to the heterogeneous class, is that *the property or phenomenon we call life belongs to the class as a whole and not to any members of the class*. This is the same conclusion that Bohr arrived at based on the analogy between the cell and the atom (Bohr 1933) and is consonant also with the concept of the bionetwork in the sense that life belongs to the cell (a network), not to component molecules (i.e., nodes) such as enzymes and DNA.

The author found the following quotations from (Elsasser 1998) helpful in understanding Elsasser's theory of holistic biology:

> There has been in the past a tendency to apply the successful methods of physical science more or less blindly to the description of organism; reductionist reasoning being one of the results of this tendency. Here, we shall try to deal with the difference between living and dead material in terms of a closer analysis that consists, as already indicated, in suitable generalizations of the logical concept of classes. This gets one away from the exclusive use of purely quantitative criteria, which use is a remnant of the uncritical transfer of the

> methods of physical sciences to biology. Instead of this we shall find a more subtle use of the class concept. (pp. 22–23)
>
> The basic assumption to be made in our interpretation of holism is that an organism is a source (or sometimes a sink) of causal chains which cannot be traced beyond a terminal point because they are lost in the unfathomable complexity of the organism. (p. 37)
>
> Drawing on the idea of generalized complementarity interpreted here as mechanistic vs. holistic properties, we have strongly emphasized the holistic aspects . . .. (p. 148)

Consistent with the holism advocated by Bohr (1933) and Elsasser (1998), I concluded (Ji 1991) that, to account for the functional stability (or robustness) of the metabolic networks in cells in the face of the randomizing influence of thermal fluctuations of molecules, it was necessary to postulate the existence of a new kind of force holding molecules together in functional relations within the cell (and hence called the *cell force* mediated by "cytons"), just as physicists were forced to invoke the concept of the strong force (mediated by gluons) as the agent that holds together nucleons to form stable nuclei against electrostatic repulsion (Ji 1991, pp. 110–113).

2.6 Synchronic vs. Diachronic Causes

It appears to be the Swiss linguist Ferdinand de Saussure (1857–1913) who first distinguished between the *synchronic* study of language (i.e., the study of language as it is practiced *here* and *now*, without reference to *history*) and the *diachronic* study (i.e., the study of language *evolution*) (Culler 1991). (This distinction may be analogous to the distinction between *space* and *time* in nonrelativistic physics.)

Table 2.17 Two kinds of causalities are operative in the material universe. When two objects or events, A and B, are correlated, A and B may interact directly (i.e., synchronically) by exchanging material entities, C (e.g., photons, gravitons, gluons, etc. [Han 1999]), or indirectly (i.e., diachronically) through the historical sharing of a common entity, C, which preceded A and B in time

	Causality	
	Synchronic	Diachronic
1. Interaction mediated by	Synchronic agent (e.g., photons, gravitons, gluons)	Diachronic agent (e.g., entangled phases of wave functions, DNA)
2. Interaction speed limited by the speed of light	Yes (i.e., local)	No (i.e., nonlocal)
3. Mathematics needed for description	Analytical functions (e.g., differential equations, probability wave functions)	Algorithms (e.g., cellular automata)
4. Phenomena explained	A-historic phenomena	Historic phenomena (e.g., cosmogenesis, origin of life, biological evolution, EPR paradox [Herbert 1987])
5. Alternative names	Energy-based causality	History-based causality
	Local causality	Nonlocal causality
	Luminal causality	Superluminal causality

The main purpose of this section is to suggest that the linguistic concepts of *synchronicity* and *diachronicity* can be extended to all of the sciences, both natural and human, including biology. It is possible that linguistic principles in general are as important as the principles of physics (and chemistry) in helping us understand the Universe, including the phenomenon of life and the workings of organisms at the fundamental levels (Pattee 1969, 2001; Ji 1997a, b, 1999b, 2001, 2002b). So it seems logical to suggest that there are two kinds of causalities – here called the "synchronic causality" widely discussed in physics (which dominates the thinking of most contemporary molecular biologists) and the "diachronic causality" derived from linguistics and other historical sciences, including sociology. Table 2.17 summarizes the characteristics of these two kinds of causalities.

If the content of the above table is right, we will have access to two (rather than just one) kind of causalities with which to explain and understand what is going on around us – including cosmogenesis, the origin of life, biological evolution, the working of the living cell, and the relation between the mind and the brain (Amoroso 2010).

Chapter 3
Chemistry

3.1 Principle of Self-Organization and Dissipative Structures

The phenomenon of spontaneous generation of spatial patterns of chemical concentration gradients was first observed in a purely chemical system in 1958 (see Fig. 3.1) (Babloyantz 1986; Kondepudi and Prigogine 1998; Kondepudi 2008) and inside the living cell in 1985 (see Fig. 3.2) (Sawyer et al. 1985). These observations demonstrate that, under appropriate experimental conditions, it is possible for chemical reactions to be organized in space and time to produce *oscillating chemical concentrations*, *metastable states*, *multiple steady states, fixed points* (also called *attractors*), etc., all driven by the free energy released from exergonic (i.e., $\Delta G < 0$) chemical reactions themselves. Such phenomena are referred to as *self-organization,* and physicochemical systems exhibiting self-organization are called *dissipative structures* (Prigogine 1977; Babloyantz 1986; Kondepudi and Prigogine 1998; Kondepudi 2008). It has been found convenient to refer to *dissipative structures* also as *X-dissipatons*, X referring to the function associated with or mediated by the dissipative structure. For example, there is some evidence (Lesne 2008; Stockholm et al. 2007) that cells execute a set of *gene expression pathways* (GEPs) more or less randomly in the absence of any extracellular signals until environmental signals arrive and bind to their cognate receptors, stabilizing a subset of these GEPs. Such mechanisms would account for the phenomenon of the *phenotypic heterogeneity* among cells with identical genomes (Lesne 2008; Stockholm et al. 2007). Randomly expressed GEPs are good examples of *dissipatons*, since they are dynamic, transient, and driven by dissipation of metabolic energy. Ligand-selected GEPs are also dissipatons. All living systems, from cells to multicellular organisms, to societies of organisms and to the biosphere, can be viewed as evolutionarily selected *dissipatons*. As indicated above, attractors, fixed points, metastable states, steady states, oscillators, etc., that are widely discussed in the nonlinear dynamical systems theory (Scott 2005) can be identified as the mathematical representations of *dissipatons*.

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_3,

Fig. 3.1 The Belousov–Zhabotinsky (BZ) reaction. The most intensely studied chemical reaction–diffusion system (or dissipative structure) known. Reproduced from Prigogine (1980)

The theory of dissipative structures developed by Prigogine and his coworkers (Prigogine 1977; Nicolis and Prigogine 1977; Prigogine 1980; Kondepudi and Prigogine 1998; Kondepudi 2008) can be viewed as a thermodynamic generalization of previously known phenomena of *self-organizing chemical reaction–diffusion processes* discovered independently by B. Belousov in Russia (and by others) working in the field of chemistry and by A. Turing in England working in mathematics (Gribbins 2004, pp. 128–134). That certain chemical reactions, coupled with appropriate diffusion characteristics of their reactants and products, can lead to symmetry breakings in molecular distributions in space (e.g., the emergence of concentration gradients from a homogeneous chemical reaction medium; see Fig. 3.2) was first demonstrated mathematically by A. Turing (1952; Gribbins 2004, pp. 125–140). Murray (1988) has shown that the Turing reaction-diffusing

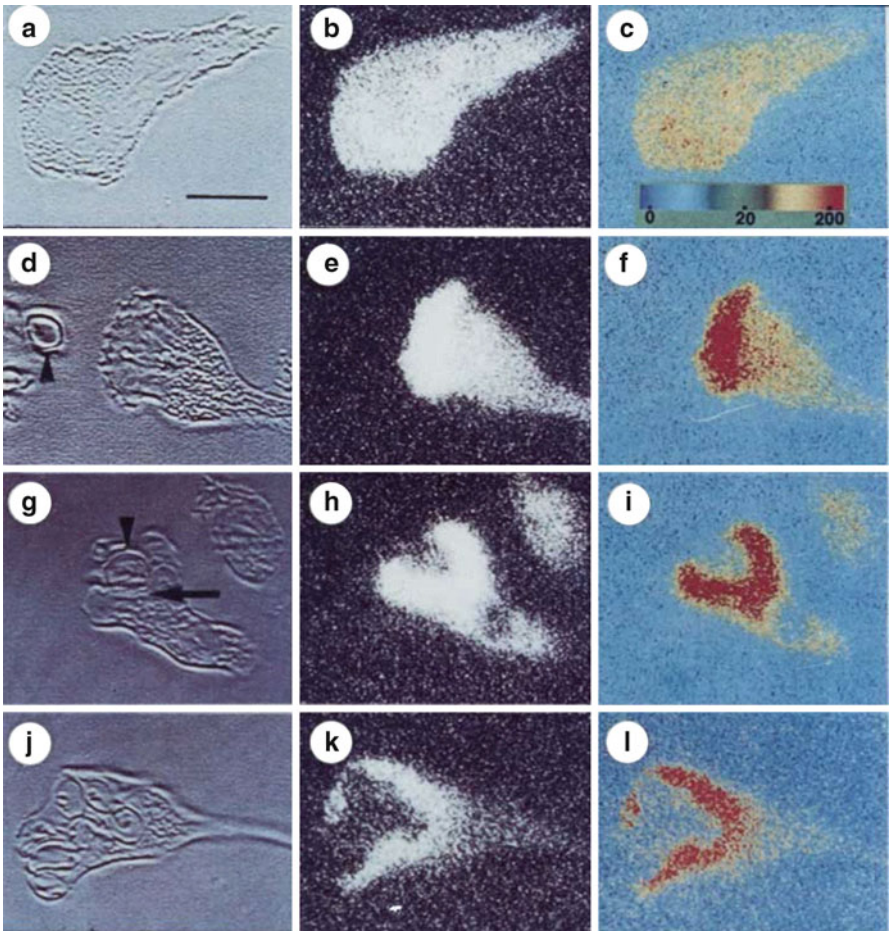


Fig. 3.2 Intracellular Ca^{++} ion gradients generated in the cytosol of a migrating human neutrophil. The intracellular Ca^{++} ion concentration was visualized using the Ca^{++}-sensitive fluorescent dye, Quin2. The pictures in the first column are bright-field images of a human neutrophil, and those in the second column are fluorescent images showing intracellular calcium ion distributions (*white* = high calcium; *gray* = low calcium). The pictures in the third column represent the color-coded ratio images of the same cell as in the second column. Images on the first row = unstimulated neutrophil. Images on the second row = the neutrophil migrating toward an opsonized particles, "opsonized" meaning "being treated with certain proteins that enhance engulfing" by neutrophils. Images on the third row = the neutrophil with pseudopods surrounding an opsonized particle. Images on the fourth row = the neutrophil after having ingested several opsonized particles. Before migrating toward the opsonized particle (indicated by the *arrows* in *Panels D* and *G*), the intracellular Ca^{++} ion concentration in the cytosol was about 100 nM (see *Panel C*), which increased to several hundred nM toward the advancing edge of the cell (see *Panel F*) (Reproduced from Sawyer et al. (1985)

models can account for the colored patterns over the surface of animals such as leopards, zebra, and cats.

Prigogine suggested that the so-called far-from-equilibrium condition is both necessary and sufficient for *self-organization*, but the general proof of this claim may be lacking as already pointed out. Nevertheless, Prigogine and his group have made important contributions to theoretical biology by establishing the concept that structures in nature can be divided into two distinct classes – *equilibrium* and *dissipative structures* and that organisms are examples of the latter. It should be noted that these two types of structures are not mutually exclusive, since many dissipative structures (e.g., the living cell) require equilibrium structures as a part of their components such as phospholipid bilayers of biomembranes (which last much longer than, say, action potentials upon removing free energy supply).

One of the characteristic properties of all *self-organizing systems* is that the free energy driving them is generated or produced within the system (concomitant to self-organization), most often in the form of exergonic chemical reactions, either catalyzed by enzymes (e.g., see Fig. 3.2) or uncatalyzed (Fig. 3.1). In contrast, there are many organized systems that are driven by forces generated externally, such as the Bernard instability (Prigogine 1980), which is driven by externally imposed temperature gradients and paintings drawn by an artist's brush. To describe such systems, it is necessary to have an antonym to "self-organization," one possibility of which being "other organization." It is unfortunate that, most likely due to the lack of the appropriate antonym, both self-organized (e.g., the flame of a candle) and *other-organized* entities (e.g., a painting, or the Bernard instability) are lumped together under the same name, that is, *self-organization*.

Dissipative structures are material systems that exhibit nonrandom behaviors in space and/or time driven by irreversible processes. Living processes require both *equilibrium* and *dissipative structures*. Operationally, we may define the *equilibrium structures* of living systems as those structures that remain, and *dissipative structures* as those that disappear, upon removing free energy input. Some *dissipative structures* can be generated from *equilibrium structures* through expenditure of free energy, as exemplified by an acorn and a cold candle, both *equilibrium structures*, turning into an oak and a flaming candle, *dissipative structures*, respectively, upon input of free energy:

$$\text{Equilibrium Structures} \xrightarrow{\text{Free Energy}} \text{Dissipative Structures} \qquad (3.1)$$

The flame of a candle is a prototypical example of dissipative structures. The pattern of colors characteristic of a candle flame reflects the space- and time-organized oxidation-reduction reactions of hydrocarbons constituting the candle that produce transient chemical intermediates, some of which emit photons as they undergo electronic transitions from excited states to ground states. From a mechanistic point of view, the flame of a candle can be viewed as high-temperature self-organizing *chemical reaction–diffusion systems* in contrast to the Belousov–Zhabotinsky reaction (Fig. 3.1) which is a low-temperature self-organizing *chemical reaction–diffusion system.*

3.1.1 Belousov–Zhabotinsky Reaction–Diffusion System

The Belousov–Zhabotinsky (BZ) reaction was discovered by Russian chemist, B. P. Belousov, in 1958 and later confirmed and extended by A. M. Zhabotinski (Babloyantz 1986; Gribbins 2004, pp. 131–34). The spatial pattern of chemical concentrations exhibited by the BZ reaction results from the chemical intermediates formed during the oxidation of citrate or malonate by potassium bromate in acidic medium in the presence of the redox pair, Ce^{+3}/Ce^{+4}, which acts as both a catalyst and an indicator dye. Ce^{+4} is yellow and Ce^{+3} is colorless. The BZ reaction is characterized by the organization of chemical concentrations in space and time (e.g., oscillating concentrations). The spatial patterns of chemical concentrations can evolve with time. "Patterns of chemical concentrations" is synonymous with "chemical concentration gradients." The organization of chemical concentration gradients in space and time in the BZ reaction is driven by free energy-releasing (or exergonic) chemical reactions. The BZ reaction belongs to the family of oxidation-reduction reactions of organic molecules catalyzed by metal ions. The mechanism of the BZ reaction has been worked out by R. Field, R. Noyes, and E. Koros in 1972 at the University of Oregon in Eugene. The so-called FNK (Field, Noyes, and Koroso) mechanism of the BZ reaction involves 15 chemical species and 10 reaction steps (Leigh 2007). A condensed form of the FNK mechanism still capable of exhibiting spatiotemporally organized chemical concentrations is known as the *Oregonato*r. A simplified mathematical model of the BZ reaction was formulated in 1968 and is known as the *Brusselator* (Babloyantz 1986; Gribbins 2004, pp. 132–34).

3.1.2 Intracellular Dissipative Structures (IDSs)

Living cells are formed from two classes of material entities that can be identified with Prigogine's *equilibrium structures* (or *equilibrons* for brevity) and dissipative structures (or *dissipatons*) (Sect. 3.1). What distinguishes these two classes of structures is that *equilibrons* remain and *dissipatons* disappear when cells run out of free energy. Dissipatons are also theoretically related to the concept of "attractors" of nonlinear dynamical systems (Scott 2005).

All of the cellular components that are *controlled* and *regulated* are dissipatons referred to as intracellular dissipative structures (IDSs) (Ji 1985a, b, 2002b). One clear example of IDSs is provided by the RNA trajectories of budding yeast subjected to glucose-galactose shift that exhibit pathway- and function-dependent regularities (Panel a in Fig. 12.2), some of which were found to obey the blackbody radiation-like equation (see Panels a through d in Fig. 12.25). The main idea to be suggested here is that IDSs constitute the immediate causes for all cell functions (Ji 1985a, b, 2002b). In other words, *IDSs* and *cell functions* are synonymous:

> IDSs constitute the internal (or endo) aspects and cell functions constitute the external (or exo) aspects of the living cell. (3.2)

The concepts of *dissipative structures* or *self-organizing chemical reaction–-diffusion systems* are not confined to abiotic (or inanimate) systems, but can be extended to biotic (or animate) systems such as intracellular chemical reaction–-diffusion processes, which were first demonstrated experimentally in chemotaxing human neutrophils by Sawyer, Sullivan, and Mendel (1985) (see Fig. 3.2). What is interesting about the findings of these investigators is that the direction of the intracellular calcium ion gradient determines the direction of the chemotactic movement of the cell as a whole. This is one of the first examples of *intracellular dissipative structures* (IDSs), that is, intracellular calcium gradients, in this case, that are observed to be linked to cell *functions*. Figure 3.2 offers two important take-home messages – (1) *dissipative structures* in the form of ion gradients can be generated inside a cell without any membranes (see Panels F, I, and L), and (2) IDSs determine cell functions.

There are three major differences to be noted between the dissipative structures in the Belousov–Zhabotinsky (BZ) reaction shown in Fig. 3.1 and the dissipative structures shown in Fig. 3.2: (1) The boundary (i.e., the reaction vessel wall) of the BZ reaction is fixed, and (2) The boundary of IDSs (such as the intracellular calcium ion gradients) is mobile, and (3) The BZ reaction is a purely chemical reaction–diffusion system, while the intracellular dissipative structures in Fig. 3.2 are chemical reactions catalyzed by enzymes which encode genetic information. Hence, the cell can be viewed as dissipative structure regulated by genetic information or as a "genetically informed dissipatons (GIDs)."

3.1.3 Pericellular Ion Gradients and Action Potentials

The action potential is another example of dissipative structures with a well-defined biological function, for example, the transmission of information along the axon. Action potentials (APs) differ from intracellular calcium ion gradients as shown in Fig. 3.2, in that they implicate a movement of ions across the cell membrane. For this reason, it may be more accurate to refer to action potentials as "transmembrane" or "pericellular dissipative structures" (TDSs or PDSs) in contrast to cytosolic calcium ion gradients which are "intracellular dissipative structures" (IDSs). APs can be viewed as a network of transmembrane transport processes of four key ions, namely, K^+, Na^+, Ca^{++}, and Cl^- that are precisely coordinated in time and space with respect to the direction and speed of ion movements.

According to the Bhopalator model of the cell (Ji 1985a, b, 2002b), the final form of gene expression is not proteins as is widely believed but a set of *intracellular dissipative structures* (IDSs) or *dissipatons*, including transmembrane dissipative structures and mechanical stress gradients of the cytoskeleton (Ingber 1998; Chicurel et al. 1998). Since IDSs and cell functions are determined by genes to a

large extent, to that extent it would follow logically that cell functions and IDSs are equivalent or synonymous. We may express this idea in the form of a syllogism:

$$\begin{aligned} &(1)\ \text{Premise 1}: \ \text{Genes} && \Rightarrow\ \text{Dissipative Structures} \\ &(2)\ \text{Premise 2}: \ \text{Genes} && \Rightarrow\ \text{Functions} \\ &(3)\ \text{Conclusion}: \ \text{Dissipative Structures} && \Rightarrow\ \text{Functions} \end{aligned} \tag{3.3}$$

where the ⇒ reads "determine" or "cause." Or we may regard *functions* as the external (or exo) aspect or view and *dissipative structures* as the internal (or endo) aspect or view of the same phenomenon called life on the cellular level (see Statement 3.2).

3.1.4 Three Classes of Dissipative Structures in Nature

Although organisms are dissipative structures, not all dissipative structures are organisms. I agree with Pattee (1995) who stated that

> a productive approach to the theories of life, evolution, and cognition must focus on the complementary contributions of nonselective law-based material self-organization and natural selection-based symbolic organization (meaning the genetic mechanisms; my addition). (3.4)

According to this so-called *matter-symbol complementarity* view, dissipative structures alone, as exemplified by the Belousov–Zhabotinsky (BZ) reaction, is not sufficient to give rise to life, because they are devoid of any *symbolic elements* that encode evolutionary history/record. There is a great similarity between Pattee's emphasis on a *symbolic aspect* of organisms and my emphasis on the role of genetic *information* in life (see "liformation" in Table 2.6). Thus, we can recognize three distinct classes of *dissipative structures*, depending on the physicochemical nature of the *boundaries* delimiting dissipative structures as shown in Table 3.1.

The main difference between *moving boundaries* and *informed moving boundaries* is that the latter is not only mobile (e.g., the intracellular calcium ion gradient or the action potentials) but also "communicates" with the chemical reactions that they catalyze through exchanging energies with both the chemical reactions and thermal environment (see Sect. 2.1.2). The conformon-based mechanisms of enzymic catalysis are consistent with Circe effect of Jencks (1975), the essence of which is that a part of the substrate-binding energy is stored in enzyme-substrate complex as mechanical energy to be later utilized to lower (or, more accurately, to regulate) the activation free energy barrier for the enzyme-catalyzed reaction. The evidence for enzymes regulating their own catalytic rates (and activation energy barriers) came from the fact that the waiting times of single-molecule enzymes are distributed not randomly but in accordance with Planck's radiation law-like manner (see Sect. 11.3.3).

Table 3.1 Three classes of dissipative structures: (1) dissipative structures with *fixed* boundaries, (2) dissipative structures with *moving* boundaries, and (3) dissipative structures with *informed* boundaries

	Dissipative structures with		
	Fixed boundaries	Moving boundaries	"Informed" moving boundaries
Boundaries	Walls of reaction vessels	Surface of the object moving in fluid	Catalytic residues of enzymes at their active sites whose spatiotemporal arrangements are determined by genetic information (see Sects. 11.3.2 and 11.3.3)
Examples	Belousov–Zhabotinsky reaction	Turbulent fluid flow patterns around moving objects	Enzymes utilizing binding energy to regulate the rates of chemical reactions (also called the *Circe effect* [Jencks 1975])
Theoretical models	Brusselator (Prigogine and Lefever 1968)	Navier–Stokes equation (Moin and Kim 1997)	Conformon model of enzymic catalysis (Ji 1974a, b, 2004a)

If the classification scheme in Table 3.1 is valid, we can identify all molecular machines and motors *in action* driven by chemical reactions as "dissipative structures with informed moving boundaries." Because of the *informed* nature of the molecular structures of enzymes, enzymes can search out their target molecules to bind or target reactions to *catalyze* and execute *motions* in the direction of achieving informed/instructed functions. When a right set of such informed molecular machines are put in a confined space such as the interior of the cell, the molecular machines (Alberts 1998) can find their correct targets to interact with, forming a *molecular machine network,* which executes collective nonrandom molecular motions that we recognize as life. Therefore, we are entitled to view the living cell as a "super-dissipative structure with informed boundaries" or "SDSIMB." I suggest that SDSIMBs are capable of any *computation, communication*, and *construction on the molecular level,* which may be regarded as the microscopic realization of the Turing machine and the von Neumann's Universal Constructor (von Neumann 1966) combined.

3.1.5 *The Triadic Relation Between Dissipative Structures (Dissipatons) and Equilibrium Structures (Equilibrons)*

The living cell can be viewed as a prototypical example of *dissipative structures* or a *dissipaton*. We can recognize two kinds of structures in the cell – those that disappear within time τ upon the cessation of free energy input and those that remain unaltered for times longer than τ following the removal of the free energy from the cell. We will identify the former as *processes* (since all processes will stop without free energy dissipation) and the latter as *equilibrium structures* or

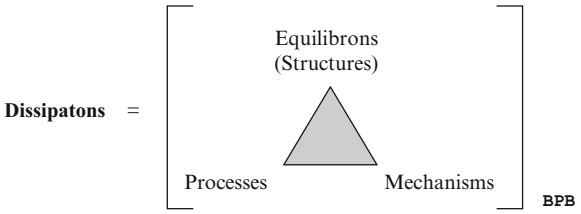


Fig. 3.3 The triadic relation between *dissipatons* (dissipative structures) and *equilibrons* (equilibrium structures)

equilibrons. Here I am distinguishing between *dissipative structures* and *processes*. *Dissipative structures are processes but not all processes are dissipative structures*. For example, unless meticulous experimental conditions are satisfied (such as the concentration ranges of the reactants, the surface condition of the reaction vessel, temperature, pressure, etc.) the same set of reactions (i.e., processes) giving rise to pattern formations in the Belousov–Zhabotinsky reaction under the right set of conditions may proceed without producing any patterns of chemical concentration gradients. Another more mundane example would be the combustion engine: Without the mechanical boundaries provided by the cylinder block and the mobile piston, the oxidation of gasoline in the combustion chamber would lead to an explosion without producing any directed motions of the crankshaft. Thus it is clear that the boundary conditions (and in some cases the initial conditions as well) of chemical reactions are of an utmost importance in successfully producing *dissipative structures*. The boundaries that constrain motions to produce coordinated motions leading to some functions will be referred to as the *Bernstein–Polanyi boundaries* to recognize the theoretical contributions made by Bernstein (1967) and Polanyi (1968) in the fields of structure–function correlations at the human-body and molecular levels (see Sect. 15.12). Thus, we can view a *dissipaton* or a *dissipative structure* as an irreducible triad as shown in Fig. 3.3.

Dissipatons are defined as those *processes*, selected by some goal-directed or *teleonomic* mechanisms because of their ability to accomplish some functions. For this reason, dissipatons carry "meanings" whereas processes do not. Goal-directed or teleonomic mechanisms include enzyme-catalyzed chemical reactions and the biological evolution itself. The subscript, BPB, on the right-hand side of the bracket in Fig. 3.3 stands for the *Bernstein–Polanyi boundaries*, the boundary conditions essential for *harnessing the laws of physics and chemistry to constrain motions to achieve functions*. Thus, the following dictum suggests itself:

Without Bernstein-Polanyi boundaries, no function. (3.5)

Figure 3.3 indicates that *equilibrons* are a necessary condition for *dissipatons* but not a sufficient one. The sufficient condition includes the mechanism that selects dissipatons out of all possible processes derived from a set of equilibrons and associated thermodynamic forces, the selection being based on functions. Since organisms are examples of dissipatons and since biology is the study of organisms, Fig. 3.3 suggests a novel way of defining *biology* in relation to *physics* and *chemistry* (which are widely acknowledged as the necessary conditions of life) as

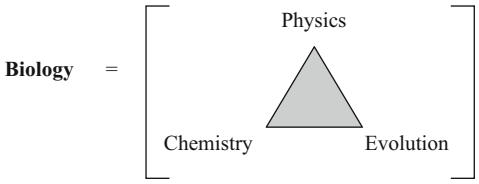


Fig. 3.4 Biology as the triadic science of *physics*, *chemistry*, and *evolution* (or *history*). Physics is viewed as the study primarily of material objects themselves (e.g., three-dimensional structures of matter), chemistry as the study of material transformations from one kind to another (i.e., chemical reactions), and biology as the study of those processes and structures that have been selected by the biological evolution (e.g., metabolic networks, the cell cycle, morphogenesis)

shown in Fig. 3.4. One unexpected consequence of Fig. 3.4 is the emergence of the fundamental role of biological *evolution* as the mechanism that selects those chemical reactions and physical processes that contribute to the phenomenon of life.

3.1.6 Four Classes of Structures in Nature

As discussed in Sect. 3.1, Prigogine (1917–2003) divides all structures in the Universe into *equilibrium* (e.g., rocks, three-dimensional structures of proteins, amino acid sequences of proteins, nucleotide sequences of DNA and RNA) and *dissipative* (e.g., flames, concentration gradients, DNA supercoils) structures. It appears that Prigogine's classification of structures into *equilibrium* and *dissipative* structures is based on *dynamics*, the study of the causes of motions, namely, the energies and forces causing motions. Since the science of mechanics comprises *dynamics* and *kinematics* that are complementary to each other (see Sect. 2.3.5) according to Bohr (Murdoch 1987; Plotnitsky 2006), it may be logical to classify structures into two groups based on *kinematics* as well. Kinematics is defined as the study of the space and time coordinations of moving objects without regarding their causes. In contrast to the classification of structures into equilibrium and dissipative structures based on dynamics, it is here suggested that the two divisions of structures based on kinematics are (1) *local* and (2) *global* motions, including the division into microscopic and macroscopic motions. Therefore, the structures of the Universe can be divided into four distinct classes based on the kinematics–dynamics complementarity – (1) *local equilibrons*, (2) *global equilibrons*, (3) *local dissipatons*, and (4) *global dissipatons* as summarized in Table 3.2 with specific examples given for each class. Several points emerge from Table 3.2. First, *equilibrons* (equilibrium structures) can be identified with "thermal motions" or "random motions," which entail no dissipation of free energy, while *dissipatons* (dissipative structures) can be identified with "directed motions" or "non-random motions," which entail free

Table 3.2 The classification of structures into four groups based on the *principle of the kinematics–dynamics complementarity* (Sect. 2.3.5). Equilibrons dissipate no free energy, that is, $dG/dt = 0$, while dissipatons do, that is, $dG/dt < 0$, where dG is Gibbs free energy change

Dynamics / Kinematics	Equilibrons (E) Random motions $dG/dt = 0$	Dissipatons (D) Directed motions $dG/dt < 0$
Local (L) motions	LE (**Local Equilibrons**) (e.g., *thermal fluctuations of bonds*)	LD (**Local Dissipatons**) (e.g., *DNA supercoils, molecular motors*)
Global (G) motions	GE (**Global Equilibrons**) (e.g., *Brownian motions of molecules*)	GD (**Global Dissipatons**) (e.g., *enzyme complexes, action potentials*)

energy dissipation. Second, *thermal motions* are divided into *local* and *global* thermal motions, the former being identified with "thermal fluctuations," essential for enzymic catalysis (see Sect. 7.1.1) (Welch and Kell 1986; Ji 1974a, 1991), and the latter with "Brownian motions," which may play an essential role in the regulation of cell metabolism and motility. Another example of *local* versus *global equilibrons* is provided by individual bond vibrations versus domain or segment motions of an enzyme involving hundreds and thousands of covalent bonds whose vibrational motions can be coupled into coherent modes.

The cell can be viewed as a dynamic system of molecules (biochemicals, proteins, nucleic acids, etc.) that are organized in space and time to form *local dissipatons* (e.g., enzyme turnovers driven by conformons; Chaps. 7 and 8) and *global dissipatons* (e.g., cell cycles, cell motility driven by local dissipatons). Since all organizations in the cell are driven by the free energy supplied by chemical reactions catalyzed by enzymes, which in turn are driven by *conformons,* examples of local dissipatons, it would follow that all *global dissiptons* of the cell are ultimately driven by *local dissipatons*, which may be a case of the local–global coupling. Local–global couplings are important in biology in general and cell biology in particular, and are likely controlled by the generalized Franck–Condon principle or the Principle of Slow and Fast Processes discussed in Sect. 2.2.

3.1.7 *Activities versus Levels (or Concentrations) of Bioploymers and Biochemicals in the Cell*

The molecular entities (or biomolecules) of the cell may exist in two distinct states – *active* and *inactive*. For example, genes are *inactive* when they are buried deep inside chromosomes and *active* only when they are unpacked and brought out onto the surface of chromatins so that they can interact with transcription factors and enzymes. Another example would be RNA molecules that are *free* versus *bound* to other molecules to affect their actions. Biomolecules need not be stable structures

but include dynamic, multisubunit complexes (e.g., hyperstructures of Norris et al. (1999, 2007a, b)) that are formed transiently to carry out needed metabolic functions and disassemble when their work is done. In analogy to the concept of *activity coefficients* in physical chemistry (Moore 1963, pp. 192–195; Wall 1958, pp. 341–344; Kondepudi and Prigogine 1998, pp. 199–203), we may define what may be called "*bioactivity coefficient*," β, as follows:

$$\beta_i = C_{a,i}/(C_{a,i} + C_{i,i}) = C_{a,i}/C_{t,i} \tag{3.6}$$

where β_i is the *bioactivity coefficient* of the ith component of the cell, $C_{a,i}$ is the concentration (i.e., the number of molecules in the cell) of the *active form* of the ith component, $C_{i,i}$ is the concentration of the ith component in its *inactive form*, and $C_{t,i}$ is the total concentration of the ith component. Therefore, the *active* or *effective concentration* of the ith cell component is given by

$$C_{a,i} = \beta_i C_{t,i} \tag{3.7}$$

The mechanisms by which a component of the cell is activated or inactivated include (1) covalent mechanisms (e.g., post-replicational and post-translational modifications such as phosphorylation, methylation, acetylation, formylation, protonation, reduction, oxidation, etc.), and (2) noncovalent mechanisms (e.g., conformation changes of biopolymers and their higher-order structures induced by pH, ionic strength, mechanical stresses, local electric field, and ligand binding).

The bioactivity coefficient as defined in Eq. 3.7 is synonymous with the "fractional activity of biomolecules," namely, the fraction of the total number of the ith biomolecule that is activated or active at any given time t at a given microenvironment located at coordinates x, y, and z. In other words, β_i in Eq. 3.7 is not a constant, as activity coefficients are in chemistry, but a function of space and time, leading to the following expression:

$$1 > \beta_i(x, y, z, t) \geq 0 \tag{3.8}$$

Inequality 3.8 states that the activity of the ith biomolecule inside the cell is dependent not only on the intrinsic physicochemical properties of the molecule itself but also on its microenvironment and time. We may refer to this statement as the Principle of the Space-Time Dependent Bioactivity Coefficient (PSTDBC). PSTDBC is consistent with the "metabolic field theory of cell metabolism," also known as "cytosociology," formulated by Welch and his colleagues (Welch and Keleti 1981; Welch and Smith 1990; Smith and Welch 1991). It is very likely that PSTDBC has provided important additional degrees of freedom for the living cell to complexify its internal states, thereby enhancing its survivability in the increasingly complexifying environment of the biosphere over the evolutionary time scale (see Sect. 5.2.3). The emerging importance of "crowding" effects on cell functions (see Fig. 12.28) (Minton 2001) is predictable from the perspective of PSTDBC.

3.2 Configurations versus Conformations; Covalent versus Noncovalent Interactions (or Bonds)

It is important to distinguish between *conformations* and *configurations* on the one hand, and between *noncovalent* and *covalent interactions* (or bonds) on the other. Conflating these two sets of terms in chemistry is comparable to conflating *protons* and *neutrons* in particle physics and first (words –> sentences) and second (letters –> words) articulations in linguistics (Culler 1991). The conformation of a molecule is a three-dimensional arrangement of atoms that can be altered without breaking or forming covalent bonds, while the configuration of a molecule is a three-dimensional arrangement of atoms in a molecule that cannot be changed unless at least one of the covalent bonds in the molecules is broken. Covalent bonds are strong taking 50–100 kcal/mol to break, since they are formed between two or more nuclei through sharing of one or more pairs of valence electrons (i.e., the electrons residing in the outermost electronic shell in an atom or a molecule). Noncovalent bonds are relatively weak taking only 1–3 kcal/mol to break, because they do not require sharing any electron pairs.

It is very common to hear experts in X-ray crystallography of biopolymers or in the field of signal transductions say that the "phosphorylation of group X in protein Y produced *conformation* changes." Such statements, strictly speaking, are incorrect (Ji 1997a). The correct expression entails replacing *conformation* with *configuration*. To understand why, it is necessary to know how these two terms are defined in physical organic chemistry (Fig. 3.5).

Notice that all that is needed to convert a trans-conformer to a cis-conformer is to rotate the carbon atoms around the carbon–carbon single bond relative to each other, and no covalent bond needs be broken or formed in the process. Configurational changes in contrast involve breaking or forming at least one covalent bond, and are usually slow activation energy barriers being in the order of several dozen Kcal/mole. Conformational changes are fast because they implicate the activation energy barriers in the range of thermal energies, that is, about 1–3 kcal/mol. The biological importance of distinguishing between *conformational* (also called noncovalent) structures and *configurational* (or covalent) structures rests on the following facts:

1. All protein–protein, protein–nucleic acid, and RNA–DNA interactions are completely determined by the three-dimensional shapes of proteins and nucleic acids.
2. Molecular shapes carry molecular information (e.g., the molecular shape of a transcription factor is recognized by and influences the structure and activity of a regulatory segment of DNA).
3. There are two kinds of molecular shapes, to be denoted as Type I and Type II:

   "Type I shapes" can be changed from one to another through conformational (i.e., noncovalent) changes only.

   "Type II shapes" can be changed from one to another through configuration (i.e., covalent) changes only.

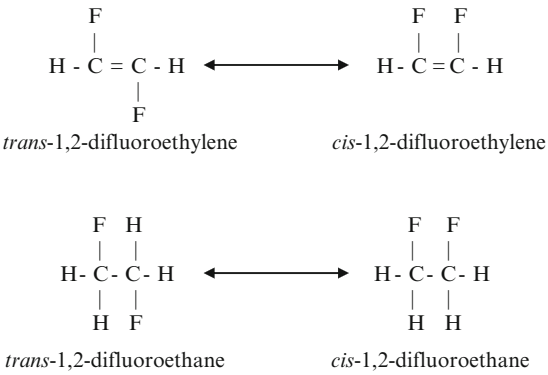


Fig. 3.5 Distinguishing between *configurations* and *conformations*. (*Upper*) A configuration refers to the arrangement of atoms in a molecule that cannot be changed without breaking or forming at least one covalent bond. One of the two C–C bonds must be broken and reformed to convert the trans-1,2-difluoreethylene to the cist isomer. (*Lower*) A conformation is the arrangement of atoms in a molecule that can be changed by bond rotations without breaking or forming any covalent bonds. No covalent bond needs to be broken to convert the trans-1,2-difuoroethane conformation to the cis conformer. *Conformers* are defined as the molecular structures that can be interconverted without breaking any covalent bonds

4. Type I shapes are sensitive to microenvironmental conditions (e.g., temperature, pH, ionic strength, electric field gradient, mechanical stress gradient, etc.), while Type II shapes are relatively insensitive to such factors.
5. It was postulated that Type I shapes are utilized to transmit information through space, while Type II shapes are used to transmit information through time (Ji 1988).

Therefore, it may be reasonable to conclude that one possible reason for there being two (and only two) kinds of molecular interactions and shape changes in molecular and cell biology is to mediate *information transfer* through *space* and *time* in living systems.

3.3 The Principle of Microscopic Reversibility

In formulating possible mechanisms for an enzyme-catalyzed reaction, it is important to obey two principles – the generalized Franck–Condon principle (GFCP) introduced in Sect. 2.2.3 and the principle of microscopic reversibility (PMR) described below. PMR is well known in the field of chemical kinetics (Gould 1959; Hine 1962; Laidler 1965) and statistical mechanics (Tolman 1979), and is succinctly stated by Hine (1962, pp. 69–70) in the form that is useful in enzymology:

> . . . the mechanism of reversible reaction is the same, in microscopic detail . . . for the reaction in one direction as in the other under a given set of conditions. . . . (3.9)

Gould (1959, p. 319) describes PMR in another way:

> ... if a given sequence of steps constitutes the favoured mechanism for the forward reaction, the reverse sequence of these steps constitutes the favoured mechanism for the reverse reaction. .... (3.10)

Enzymologists often write a generalized enzymic reaction thus:

$$S \underset{a}{+} E \leftrightarrow S \cdot E \underset{b}{\leftrightarrow} P \underset{c}{+} E \tag{3.11}$$

where E is the enzyme, S the substrate, and P the product. Clearly, Scheme 3.11 is not microscopically reversible, since the sequence of events followed in the direction from left to right is not the same as that from right to left. There is no P·E in the scheme. In order to modify Scheme 3.11, so as to make it microscopically reversible, it is necessary to use GFCP (Sect. 2.2.3) as shown in Scheme 3.12:

$$\underset{}{S} + \underset{a}{E} \leftrightarrow \underset{}{S} + \underset{b}{E*} \leftrightarrow \underset{e}{S \cdot E*} \leftrightarrow \underset{d}{[S \cdot E^{\ddagger} \Leftrightarrow P \cdot E^{\ddagger}]} \leftrightarrow \underset{e}{P \cdot E*} \leftrightarrow \underset{f}{P} + \underset{g}{E*} \leftrightarrow \underset{h}{P} + E \tag{3.12}$$

where the two superscripted Es represent the so-called Franck–Condon states, which are conformationally strained high-energy states that are in thermal equilibrium with their associated ground states (Reynolds and Lumry 1966). Of the two Franck–Condon states, E* is long-lived (with lifetimes thought to be much longer than ~10^{-12} s, the typical time required for electronic transitions) and $E^{\ddagger}$ is short-lived, lasting long enough for electronic transitions to take place as a part of a chemical reaction, that is, covalent rearrangements. Hence, we may refer to E* and $E^{\ddagger}$ as "stable" and "unstable" Franck–Condon states, the latter often symbolized by square brackets, [...] (Ji 1974a, 1979). Evidently, Scheme 3.12, which is a species of Eq. 2.26, is microscopically reversible, that is, the scheme is mechanistically *symmetric* with respect to the inversion around the symbol ⇔.

There are several unusual features about Scheme 3.12 that require special attention:

1. Enzymes are postulated to undergo thermal fluctuations between their ground state, E, and energized states, E* (called "stable Franck-Condon states") in the absence of its substrate.
2. The substrates bind only to the stable Franck–Condon states of enzymes, E*, and not to its ground state, E. This contrasts with the traditional induced-fit hypothesis of Koshland (1958). To highlight this difference, the Franck–Condon principle-based mechanism of ligand binding is referred to as the "pre-fit" hypothesis.
3. Enzyme-catalyzed chemical reactions can occur only at the unstable Franck–Condon state, denoted as $E^{\ddagger}$ and enclosed within the square brackets, [...].
4. The energy stored in E* at state *b* is thermally derived and hence cannot be utilized to do any work lest the Second Law of Thermodynamics is violated (see Sect. 2.1.4), but the energy stored in E* at state *c* is derived from the

free energy binding of S to E* and thus able to do work either internally (e.g., modulation of the rate of electronic transition) or externally on enzyme's environment as in myosin head exerting a force on the actin filament (see Sect. 11.4).

5. The transition from *a* to *c* (without being mediated by state *b*) is what is involved in the *Circe mechanism of enzymatic catalysis* as proposed by Jencks (1975). Since this mechanism is not based on the generalized Franck–Condon principle, the Circe effect mechanism may be viewed as theoretically incomplete.

In Sect. 11.3, PMR as stated in Statements 3.9 and 3.10 and GFCP will be applied to elucidate the molecular mechanisms underlying the action of cholesterol oxidase based on the single-molecule fluorescence measurements made in (Lu et al. 1998).

Chapter 4
Biology

4.1 The Simpson Thesis

As already alluded to in *Preface*, the American paleontologist Gaylord Simpson (1964) made a statement to the effect that

> Physicists study the principles that apply to all phenomena; biologists study phenomena to which all principles apply. (4.1)

In view of its potential importance in differentiating *physics* and *biology*, we may refer to Statement 4.1 as the "Simpson conjecture," the "Simpson thesis, or the "Simpson doctrine." Consistent with this thesis, the general theory of the living cell presented in this book embodies a large number of concepts, laws, and principles drawn from many disciplines, including physics, chemistry, biology, engineering, mathematics, computer science, linguistics, and philosophy (Ji 1997a). It would not be surprising if it turns out that modeling the cell and higher-order bionetworks would entail importing and utilizing all the major concepts, laws, and principles developed in the entire history of sciences. There are about 26 different principles, laws, and concepts that were incorporated into the Bhopalator model of the cell as of 1997 (Table 5 in Ji 1997a). Since then at least six more additional laws and concepts have been incorporated into the cell model as of January 2011. For the analogy between cell biology and general relativity theory, see Smith and Welch (1991), and for the analogy between special relativity and biology, see Table 2.5 in Sect. 2.3.1. For the roles of linguistic and semiotic principles in biology, see (Ji 1997a, 1999b, 2005a).

One of the most recent ideas to be added to the cell theory is that of "coincidence detector," namely, the idea that enzymes can be viewed as molecular devices which receive two inputs (Brownian motions and chemical substrates) within narrow time gaps (i.e., more or less simultaneously) leading to the production of ordered molecular motions, including catalysis and vectorial movements of ligands (see Sect. 7.2.2). The conformon model of enzymic catalysis proposed in 1974

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_4,

(Ji 1974a, b) already embodies these features of coincidence detectors which were recognized only recently. The concept of coincidence detectors are widely used to account for neuronal behaviors (Mikula and Niebur 2003).

4.2 Molecular Machines, Motors, and Rotors

The living cell can be viewed as space- and time-ordered systems (or networks) of *molecular machines* (Alberts 1998), proteins that can utilize the free energy of chemical reactions such as ATP hydrolysis to carry out goal-directed or teleonomic molecular motions (Ishii and Yanagida 2000). The molecular mechanisms responsible for such goal-directed molecular motions of biopolymers are postulated to be provided by *coformons*, conformational strains resident in sequence-specific sites within biopolymers that are generated from chemical reactions based on the generalized Franck–Condon principle (Sect. 8.2) (Green and Ji 1972a, b; Ji 1974a, 1979, 2000, 2004a).

Concept of molecular machines (McClare 1971; Ji 1991; Alberts 1998; Ishii and Yanagida 2000, 2007; Xie and Lu 1999; Xie 2001) is one of the most important contributions that biology has made to our understanding of how the living cell works. Like macroscopic machines, molecular machines must exert forces on their environment during their work cycle and this means that molecular machines must possess mechanical energies stored in them, since energy is required to generate forces. Such stored internal energies of molecular machines have been referred to as *conformons* (Green and Ji 1972a, b; Ji 1974a, b, 1991, 2000). Molecular machines that perform work on their environment without utilizing internally stored mechanical energy (e.g., conformons) violate the First and Second Laws of Thermodynamics (McClare 1971).

Most metabolic processes inside the cell are catalyzed by combinations of two or more proteins that form functional units through noncovalent interactions. Such protein complexes have been variously referred to as metabolons (Srere 1987), modules (Hartwell et al. 1999), hyperstructures (Norris et al. 1999, 2007a, b). The number of component proteins in complexes varies from 2 to over 50 (Aloy and Russell 2004). More recent examples of the protein complexes that involve more than 50 components include eukaryotic RNA polymerases, or *transcriptosomes* (Halle and Meisterernst 1996), *spliceosomes* (catalyzing the removal of introns from pre-mRNA), *molecular chaperones* (catalyzing protein folding), and *nuclear pore complexes* (Blobel 2007; Dellaire 2007; Dundr and Misteli 2001). These protein complexes are theoretically related to dissipative structures of Prigogine (1977, 1980) and SOWAWN machines discussed in Sect. 2.4.4. Therefore, it may be convenient to view them as members of the same class of molecular machines called “dissipatons” defined in Sect. 3.1.5.

4.3 What Is Information?

The concept of information is central not only to computer science (Wolfram 2002; Lloyd 2006), physics (Wheeler 1990), and biology (e.g., this chapter) but also to philosophy and theology (Davies and Gregersen 2010). Molecular machines require both *free energy* and *genetic information* to carry out goal-directed molecular work processes. The definition of free energy is given in Sect. 2.1.2. In this section, the term *information* is defined, primarily, within the context of molecular and cell biology. The dictionary definitions of *information* include the following (except the last two items, which are my additions):

1. Knowledge obtained from investigation, study, or instruction.
2. Intelligence, news, facts, data.
3. The attribute inherent in and communicated by one of two or more alternative sequences or arrangements of something (such as the nucleotides in DNA and RNA or binary digits in a computer program) that produce specific effect.
4. A quantitative measure of the uncertainty in the outcome of an experiment to be performed.
5. A formal accusation of a crime made by a prosecuting officer as distinguished from an indictment presented by a grand jury.
6. Anything or any process that is associated with a reduction in uncertainty about something.
7. Information is always associated with making a choice or a selection between at least two alternatives or possibilities.

It is generally accepted that there are three aspects to information (Volkenstein 2009, Chap. 7):

1. *Amount* (How much information can your USB store?)
2. *Meaning* (What is the meaning of this sequence of nucleotides? What does it code for?)
3. *Value* (What practical effects does this nucleotide sequence have on a cell?)

All of these aspects of information play important roles in biology, but only the quantitative aspect of information is emphasized by Shannon (1916–2001) (Shannon and Weaver 1949) who proposed that information carried by a message can be quantified by the probability of the message being selected from all possible messages as shown in Eq. 4.2:

$$H = -K \sum_{i=1}^{n} p_i \log_2 p_i \tag{4.2}$$

where H is the Shannon entropy (also called the information-theoretic entropy or *intropy*) of a message source, n is the total number of messages, and p_i is the probability of the ith message being selected for transmission to the receiver.

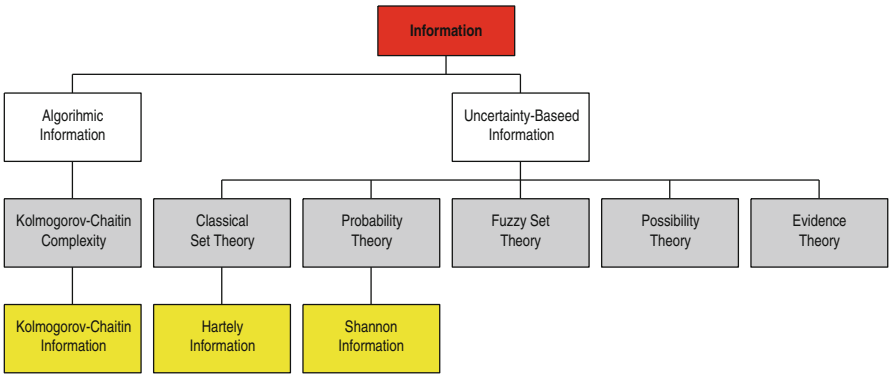


Fig. 4.1 A classification of information based on the quantitative aspect of information (Klir 1993)

The meaning of H is that it reflects the average *uncertainty* of a message being selected from the message source for transmission to the user. When the probabilities of the individual messages being selected are all equal, H assumes the maximum value given by Eq. 4.3, which is identical to the Hartley information (see Fig. 4.1):

$$H = \log_2 n \tag{4.3}$$

According to Klir (1993), there are two types of information – the *uncertainty-based* information and the *algorithmic* information (see Fig. 4.1). The amount of the uncertainty-based information, I_X, carried by a messenger, X, can be calculated using Eq. 4.3 leading to the following formula:

$$I_X = H_{before} - H_{after} = \log_2 n - \log_2 n' = \log_2 n/n' bits \tag{4.4}$$

where H_{before} and H_{after} are the Shannon entropies before and after the selection process, respectively, and n' is the number of messages selected out of the initial n. Evidently, I_X assumes a maximal numerical value when $n' = 1$ or $H_{after} = 0$. That is, when the selected message, X, reduces the uncertainty to zero.

It is possible to view Shannon entropy, H, as characterizing the property of the *sender* (i.e., the message source) while Shannon information, I, characterizes the amount of the information received by the *user* (Seife 2006). If there is no loss of information during the transmission through the communication channel, H and I would be quantitatively identical. On the other hand, if the channel is noisy so that some information is lost during its passage through the channel, I would be less than H. Also, according to Eq. 4.4, information, I_X, and Shannon entropy of the message source, H_{before}, become numerically identical under the condition where H_{afer} is zero (i.e., under the condition where the number of the message selected is 1). It is for this reason that the term "information" and "Shannon entropy" are almost

always used interchangeably or synonymously in the information theory literature, leading to the following general statement:

> Shannon entropy of a message source and the information content of a message selected from it is numerically identical if and only if the channel is noiseless and the number of messages selected is 1. (4.5)

Statement 4.5 may be referred to as the "non-identity of information and Shannon entropy (NISE) thesis." There are two types of information – *algorithmic* and *uncertainty-based* (Fig. 4.1). Algorithmic (also called descriptive) information is measured by the shortest possible program in some language (e.g., the binary digital language using 0′s and 1′s) that is needed to describe the object in the sense that it can be computed. Thus, algorithmic information is *intrinsic* to the object carrying the information. It is quantitated by the number of bits necessary to characterize the message. Uncertainty-based information is *extrinsic* to the object carrying information, since extrinsic information belongs to the property of the set to which the message belongs rather than to the message itself. Uncertainty-based (or uncertainty-reducing) information is measured by the amount of the uncertainty reduced by the reception of a message (see Eq. 4.4).

When the probability of occurrence is equal for all of the messages in a message source, we are dealing with the *Hartley information* (see Eq. 4.3), while, when the probabilities of occurrences are uneven (i.e., p_i's in Eq. 4.2 are not the same), we are dealing with the *Shannon information*. Consider an object or a message consisting of a string of ten deoxyribonucleotides:

$$\mathbf{TGCTTAGCCT} \tag{4.6}$$

which can be represented as a string of 0′s and 1′s as

$$11\ 01\ 10\ 11\ 11\ 00\ 01\ 10\ 10\ 11 \tag{4.7}$$

by adopting the following code (or convention),

$$\begin{aligned} \mathbf{A} &= 00 \\ \mathbf{C} &= 10 \\ \mathbf{G} &= 01 \\ \mathbf{T} &= 11. \end{aligned} \tag{4.8}$$

Thus, the algorithmic (also called Kolmogorov–Chaitin) information content of the ten-nucleotide message in String 4.6 is 20 bits, since the shortest program that can characterize the message contains 20 binary digits (as evident in Expression 4.7).

The Hartley information content of the same 10-nucleotide message can be calculated if we knew the "cardinality" (i.e., the size) of the set out of which the message was selected. The cardinality of the set involved is $6^{10} = 6.0466 \times 10^7$,

if we assume that each of the 10 positions in the 10-nucleotide message can be occupied by any one of the six nucleotides, A, C, G, T, A′ and T′, where A′ and T′ are covalently modified nucleotides. Hence the Hartley information content of the message would be $\log_2 (6^{10}) = 10 \log_2 6 = 10 \times 2.6 = 26$ bits. That is, if the above decanucleotide (deca = 10) is chosen out of all possible decanucleotides formed from the six elements, A, C, G, T, A′ and T′, then the amount of information that can be carried by the decanucleotide (or by any one of the rest of the set, including, say, TTTTTTTTTT or AAAAAAAAA) is 26 bits. Because Hartley information or Shannon information cannot distinguish between individual messages, they are unable to convey any meaning of a message.

Turvey and Kugler (1984) made the interesting suggestion that there are two kinds of information – (1) the orthodox information (also called the *indicational/injunctional information*), often associated with symbol strings, that *indicates* and *instructs* (e.g., stop signs, genes), and (2) the "Gibsonian" information (also called the *specificational information*), not expressible in terms of symbol strings that provides *specifications* (e.g., visual information from surrounds guiding a driver to stop at a desired location at a desired time). "Information" is akin to "compounds" in chemistry. Although all compounds are made out of one or more of the slightly more than 100 elements in the periodic table, the kinds of compounds found on this planet alone is astronomically large (10^9 –10^{12} ?), and chemists have come up with rational methods for denoting and classifying them. It is clear that the number of the kinds of information that we can conceive of is probably similarly large. Just as there are many ways of classifying chemical compounds (e.g., natural vs. synthetic, organic vs. inorganic, acid vs. base, biological vs. abiological, stable vs. unstable, toxic vs. nontoxic, monomers vs. polymers, volatile vs. nonvolatile, and solid vs. liquid vs. gas), there should be many ways of classifying information. The ones suggested in Fig. 4.1 and by Turvey and Kugler (1984) may represent just the tip of the iceberg of information.

The information concept plays a fundamental role in biology akin to the role of energy in physics and chemistry. The pivotal role of information in biology is illustrated by the following list of information-related expressions widely used in biology:

1. Genetic information.
2. The *sequence information* of proteins, RNA, and DNA
3. Functional versus structural information of biopolymers.
4. The *control information* carried by transcription factors.
5. The *regulatory information* encoded in the promoter regions of DNA.
6. DNA carries genetic information.
7. Hormones carry regulatory information.
8. Protein shapes carry the *information* specifying their target ligands or receptors.
9. Intracellular dissipative structures (or dissipatons) carry *genetic information* (called the Prigoginian form of *genetic information* [Ji 1988]).

10. Amino acid residues of protein domains carry *information* (Lockless and Ranganathan 1999; Süel et al. 2003; Socolich et al. 2005; Poole and Ranganathan 2006).

4.4 The Chemistry and Thermodynamics of Information

The concept of information in computer science is heavily influenced by the Shannon information theory (Shannon and Weaver 1949) and by symbol strings such as Expression 4.7. *Biological information*, however, may be too rich and deep to be adequately captured by the *quantitative theories of information* developed so far, including that of Shannon. The statement made by Prigogine (1991) two decades ago still holds:

> Traditional information theory was too vague, . . . , because it is not deeply enough rooted in physics and chemistry . . . (4.9)

The connection among (1) irreversible thermodynamics, (2) chemistry, and (3) information production was illustrated by Prigogine (1991) using a simple example. He considered a chemical system containing two monomers X and Y which can polymerize whenever the concentration of one of them exceeds some critical level. If the system is at equilibrium, the concentrations of these monomers would fluctuate randomly, obeying the Poisson law, leading to the production of a random or disordered polymer as shown in Reaction 4.10. However, when the system is under nonequilibrium conditions and exhibits irreversible dynamics with some regularity, the resulting polymer can encapsulate these regularities into nonrandom monomer sequences. One such sequence is shown in Reaction 4.11, which exhibits a long-range correlation among the trimeric units **XYX** whose correlation distance increases with time.

$$\text{Reversible Processes} \rightarrow \mathbf{XXYXYYYXYXYYXXXYXX} \tag{4.10}$$

$$\text{Irreversible Processes} \rightarrow \underline{\mathbf{XYX}}\underline{\mathbf{XYX}}\mathbf{YY}\underline{\mathbf{XYX}}\mathbf{YYY}\underline{\mathbf{XYX}} \tag{4.11}$$

Process 4.11 illustrate what Prigogine means when he states that:

> . . . chemistry plays a very specific role . . . it may "encapsulate" irreversible time into matter . . . In this way, irreversible processes may be made more permanent and transmitted over longer periods of time. This is of special importance for us, as we should be able to describe in these terms a world where the very existence of biological systems implies some recording of irreversible processes in matter . . . . . chemical molecules produced under non-equilibrium conditions keep some memory of the deviations from equilibrium which exists at the moment of their production. (4.12)

Process 4.11 together with Statement 4.12 may be viewed as defining a novel principle in nature which may be referred to as the *Principle of Encoding Time into Matter* or alternatively the *Principle of Encoding Dissipatons into Equilibrons*

(PEDE), since the left-hand sides of the arrows in Processes 4.10 and 4.11 can be identified as equilibrium structures (*equilibrons*) and dissipative structures (*dissipatons*), respectively (Sect. 3.1). The PEDE may be re-stated as follows:

> It is possible for some non-equilibrium chemical systems to encode *dissipatons* into *equilibrons*. (4.13)

Viewing species as dissipative structures (Brooks and Wiley 1986, p. 40) and genomes as equilibrium structures, Statement 4.13 can logically be interpreted as the *thermodynamic principle of biological evolution* (TPBE), i.e., the thermodynamic principle that *allows* the biological evolution (Chap. 14) to occur spontaneously on this planet, in analogy to the Second Law which is the thermodynamic principle that *disallows* the existence of the perpetual motion machines of the second kind (Atkins 2007).

Molecular biology is replete with examples of the processes that support the reverse of Statement 4.13, namely, the decoding of equilibrons (e.g., DNA sequences) into dynamic patterns of concentration changes of molecules, i.e., dissipatons (e.g., RNA trajectories in Fig. 12.2). This allows us to formulate another principle to be called the Principle of Decoding Equilibrons into Dissipatons (PDED):

> It is possible for some non-equilibrium chemical systems to decode *equilibrons* into *dissipatons*. (4.14)

Statements 4.13 and 4.14 can be combined into what may be termed the "Principle of Dissipaton-Equilibron Transduction (PDET)":

> It is possible for some non-equilibrium chemical systems to interconvert *equilibrons* and *dissipatons*. (4.15)

It seems logical to view Statement 4.15 as the *thermodynamic principle of organisms* (TPO), since organisms are the only nonequilibrium thermodynamic systems known that are equipped with mechanisms or molecular devices to carry out the interconversion between equilibrons and dissipatons.

Since organisms can both *develop* and *evolve*, it is possible to derive Statements 4.16 and 4.17 as the corollaries of Statement 4.15:

> Biological *evolution* results from non-equilibrium systems encoding dissipatons into equilibrons. (4.16)

> Biological *development* results from non-equilibrium systems decoding equilibrons into dissipatons. (4.17)

4.5 Synchronic Versus Diachronic Information

It is clear that the symbol string generated in Process 4.11 carries two kinds of information which may be referred to as *synchronic* and *diachronic information* in analogy to the *synchronic* and *diachronic* approaches in linguistics (Table 4.1) (Culler 1991). Synchronic information refers to the totality of the information that

Table 4.1 The definitions of synchronic and diachronic information

	Information	
	Synchronic	Diachronic
1. Refers to	Phenomena here and now	Phenomena long past
2. Meaning	Apparent in the structure of the message	Hidden behind the structure of the message
3. Laws obeyed	(a) Laws of physics and chemistry	(a) Laws of physics and chemistry
	(b) "Law of Requisite Information (LRI)"[a]	(b) "Law of Requisite Information (LRI)"[a]
	(c) "Synchronic laws"[b]	(c) "Diachronic laws"[c]
4. Philosophy	(a) Causality	(a) "Codality'[d]
	(b) Dyadic relation[e]	(b) Triadic relation[f]
	(c) Deterministic[g]	(c) Arbitrary[h]
	(d) Knowable[i]	(d) Unknowable[i]
	(e) Orthogonal to diachronic information[j]	(e) Orthogonal to synchronic information[j]
5. Alternative names	(a) Deterministic	(a) Nondeterministic
	(b) Ahistorical	(b) Historical
	(c) Physical	(c) Evolutionary
	(d) Law-governed	(d) Rule-governed
	(e) Objective	(e) Arbitrary

[a]In analogy to the Law of Requisite Variety (Sect. 5.3.2) (Heylighen and Joslyn 2001), which mandates that a certain minimum level of variety in the internal state of a machine is required for the machine to perform a complex task, so the proposed *Law of Requisite Information* states that no problem (machine) can be solved (output) without inputting the minimum amount of requisite information (input)

[b]The laws in physics and chemistry that have been recognized or abstracted from empirical observations here and now without having to rely on any historical studies. Most laws of physics and chemistry currently dominating natural sciences appear to be of this nature

[c]The regularities of nature that are revealed only when historical records are taken into account such as the evolutionarily conserved nucleotide sequences of genes belonging to different species

[d]"Codality" is a new word that I coined to indicate the "code-mediated" interactions such as the interactions between hormones and their target genes or between symbols and their meanings understood by human mind, in contrast to "causality" which is "cause-mediated" interactions including force- or energy-mediated interactions in physics. "Codality" is related to what Roederer (2003, 2004) refers to as "information-based interactions" while causality is related to his "force-driven interactions"

[e]The relation between *two* entities, e.g., the electron being attracted by the proton, and two cars colliding at an intersection, etc.

[f]The relation among three entities, e.g., a membrane receptor interacting with an ion channel mediated by a G-protein, and a Korean communicating with an Italian through a Korean-Italian interpreter

[g]For example, the physicochemical properties of protein domains are more or less completely *determined* by their amino acid sequences

[h]For example, the 3-dimensional structures of certain proteins are arbitrary from the point of view of physics and chemistry since they cannot be completely predicted solely based on the principles of physics and chemistry

[i]When we say that we know something, we usually mean that we can explain that something in terms of a set of principles, laws, and/or theories. When there are no such principles, laws, or theories that can be used to explain something, we say that something is *unknowable*. For example, the beginning (or the origin) of the Universe is *unknowable* from the point of view of the current laws of physics and chemistry because there is no guarantee that such laws were extant at $t = 0$

[j]The *orthogonality* means that synchronic information can vary independently of diachronic information and *vice versa*, just as the x-coordinate of a point on a 2-dimensional plane can vary independently of its y-coordinate, and *vice versa*

can be extracted from the symbol string *here* and *now* without having to know neither how it was generated in the past nor how it may be related to other symbol strings with similar functions. For example, the linear sequences of amino acid residues of proteins often carry sufficient "synchronic" information that allows proteins to spontaneously fold into the secondary structures such as α-helices and β-sheets, if not into their tertiary structures (see Sect. 11.1). In contrast, "diachronic" information refers to the information embodied in a symbol string that cannot be extracted or decoded from the structure of the string alone but must take into account its past history as left behind or recorded in the form of the correlations found among the symbol strings having similar or related functions. A good example of "diachronic information" is provided by the information buried in amino acid sequences of proteins belonging to a given family, e.g., the WW domain family studied by Ranganathan and his group (Lockless and Ranganathan 1999; Poole and Ranganathan 2006; Socolich et al. 2005; Süel et al. 2003). *Diachronic information* can be extracted if and only if multiple sequences of proteins belonging to a given family are compared and the frequencies of occurrences of their amino acid residues are measured at each position. The studies carried out on the WW domain family proteins by the Ranganathan group using the *statistical coupling analysis* (SCA) have revealed that only about 20% of the 36 amino acid residues constituting the WW domain proteins has coevolved, thus carrying evolutionary information (Lockless and Ranganathan 1999). Table 4.1 and its footnotes summarize the characteristics of *synchronic* and *diachronic* information in a self-explanatory manner, except for what is here referred to as the "Law of Requisite Information (LRI)," which can be stated as follows:

It is impossible to solve any problem without the requisite prior information. (4.18)

An example of the operation of LRI is provided by the well-known fact that an algebraic equation with *n* unknowns cannot be solved without knowing the numerical values of the (*n-1*) unknowns. For example, the intracellular concentration of an RNA molecule (z) is determined by the balance between two opposing rate processes – the transcription (x) and the transcript degradation rates (y) (Sect. 12.3):

$$z = x - y \tag{4.19}$$

However, many workers in the DNA microarray field erroneously assumed that x can be determined directly by measuring z alone (Sect. 12.6) (Ji et al. 2009a), which can be said to violate LRI: The information on z is not sufficient to solve Eq. 4.19 for x, because the information on y is also required.

Another example that illustrates the operation of LRI may be the cosmogenesis (Table 4.2). Just as the amino acid sequences of proteins analyzed above, the physical structure of the Universe that is observable by the astronomers of the twenty-first century may contain two kinds of information – (1) *synchronic information* that can be extracted from our own Universe here and now and (2) the *diachronic information* that is buried in (or hidden under) the structure of our observable Universe but not recognizable until and unless the structure of our Universe is compared with the

Table 4.2 The synchronic versus diachronic information in biology and physics

	Information	
	Synchronic	Diachronic
Biology	(a) Amino acid sequence of proteins	(a) Co-evolving subsets of amino acid residues of proteins
	(b) Enzymic catalysis	(b) Allosterism
	(c) *Causal* interactions between ligands and receptors	(c) *Encoded* interactions between primary and secondary messengers
Physics	(a) Traditional physics	(a) Quantum weirdness (e.g., nonlocality)
	(b) Hydrodynamics	(b) Cosmogenesis
	(c) Copenhagen interpretation	(c) Einstein-de Broglie-Bohm-Bell- (EDBB) interpretation[a]

[a]John S. Bell is included here because he mentioned the biological evolution as a metaphor for understanding the nonlocality in his lecture delivered at Rutgers several years before he passed away in 1990

possible structures of other Universes that might have been formed in parallel at $t = 0$ (Bacciagaluppi and Valentini 2009).

We can divide the history of the genesis of our Universe into two phases – (1) the initiation (singularity) phase at $t = 0$, also called the Big Bang, and (2) the post-Big Bang phase. The totality of the information carried by or encoded in the observable Universe of ours can be identified with the synchronic information. The information about those features of our Universe that correlate with similar features found in other possible Universes generated at $t = 0$ along with our Universe (but is too distant for our Universe to communicate with) can be defined as diachronic information. Since the interaction between our Universe and other possible Universes is not allowed by the laws of physics and chemistry operating in our current Universe, the diachronic aspect of our Universe transcends the laws of physics and chemistry, allowing for the possibility of nonlocality, e.g., (see Table 4.2).

It is clear that molecular biological phenomena carry both *synchronic* and *diachronic* informations as explained in Table 4.2. It may well be that quantum mechanical phenomena also carry *synchronic* and *diachronic* informations, but physicists might have been slower in recognizing this fact than biologists, possibly due to the paucity of clear experimental data indicating the effects of history. Table 4.2 summarizes some of the evidence supporting the roles of synchronic and diachronic informations in biology and physics.

If the content of Table 4.2 is right, it may be necessary to divide biology and physics into two branches – *synchronic* and *diachronic*, just as the linguistics is so divided (Culler 1991). One consequence of such a division in physics may be the reconciliation between Bohr's and Einstein's long-standing debate (Plotnitsky 2006; Murdoch 1987) about the completeness (or the lack thereof) of quantum mechanics thus:

> As Einstein claimed, quantum mechanics is incomplete because it does not address the diachronic aspect of the reality. As Bohr claimed, quantum mechanics is complete because it provides complete explanations for all synchronic phenomena in the Universe. (4.20)

4.6 The Quantum Information and Enzymic Catalysis

The term "bit" (from binary digit) is defined as the unit of "classical information" (*C-information*) which must be either 0 or 1. One bit of information allows a binary choice/decision to be made. The unit of *quantum information* (*Q-information*) is called "quibit" or "qbit" (from quantum binary digit). Unlike "bit", "qubit" can be 0, 1 or a superposition of both (i.e., both simultaneously). A qubit assumes the value of 0 or 1 only after being measured. In other words, a particle carrying Q-information can be in both 0 and 1states simultaneously and chooses to be in the 0 or the 1 state only when measured or observed.

An enzyme may be considered to carry both *C-information* and *Q-information* in the sense that the conformation of the enzyme can be either in the 0 (or substrate-bound) state, the 1 (or product-bound) state, or in the (0/1) state at the transition state, the state in which the active site conformation of the enzyme forces substrate S and product P to lose their identities and assume an intermediate configuration/conformation designated as (S⇔P). We may represent this idea diagrammatically as follows:

$$\begin{array}{ccccc} \mathrm{S}\cdot\mathrm{E}(0) & \leftrightarrow & [(\mathrm{S}\Leftrightarrow\mathrm{P})\cdot\mathrm{E}(0/1)]^{\ddagger} & \leftrightarrow & \mathrm{P}\cdot\mathrm{E}(1) \\ (\mathrm{C}\text{ - State}) & & (\mathrm{Q}\text{ - State}) & & (\mathrm{C}\text{ - State}) \end{array} \tag{4.21}$$

where S and P are the substrate and the product, (S⇔P) denotes the *metastable structure* or the *resonance hybrid,* intermediate between substrate and product, and E(0), E(0/1), and E(1) indicate the enzyme conformations that binds S, the transition intermediate, (S⇔P), and P, respectively, and the symbol $[\ldots]^{\ddagger}$ indicates the transition state conformation of the enzyme. In other words, the transition state of the enzyme-ligand complex can be treated as the superposition of the substrate-binding and the product-binding conformations, reminiscent of the ability of a quantum object (quon or wavicle) to be in two places at the same time, a phenomenon called the "nonlocality" in quantum physics (Herbert 1987). *The C- and Q-states indicate the conformational states of the enzyme where the classical (C) and quantum (Q) mechanical laws, respectively, are postulated to apply, thus providing a possible answer to the question raised by H. Frauenfelder in* (Abbott et al. 2009, p. 366) *about the relative importance of the classical and quantum mechanical laws in biology* (more on this point in Sect. 11.3.3).

If this description of enzyme catalysis is correct, we can view enzymes as carriers of quantum information or as quantum computers powered by the free energy of ligand-binding transformations. When a substrate binds to an enzyme or a hormone to a receptor, we can say that the substrate or the hormone has meaning for the enzyme and the receptor, since the latter recognizes the former. A messenger being recognized by (or meaningful to) its receptor is necessary but not sufficient to implement the information carried by the messenger. To effectuate (or implement, or reify) the information, it is necessary to transform the information into a form that can be recognized by the associated "effector" mechanisms so as to transform the

information into tangible effects. The information theory as applied to cell biology entails elucidating the molecular mechanisms of the following set of processes:

1. A hormone carries information to a cell.
2. The cell recognizes the hormone through its receptor.
3. The cell transduces the information carried by the messenger into a form that can be recognized by intracellular effector mechanisms.
4. The effector mechanism is activated to produce tangible consequences (e.g., expression of a set of genes) controlled by the information received.
5. All the enzymes inside a cell can be treated as "elementary quantum computers" (analogous to the silicon chips in man-made computers) whose interactions are organized in space and time, and the cell itself can be viewed as the *smallest autonomous quantum computer* powered by the free energy released from chemical reactions that store, transform, and utilize qubits to perform quantum computation.

4.7 The Information–Entropy Relations

Equation 4.4 is helpful in clarifying the theoretical relation between *information* and *entropy*, which has been the focus of debates in recent decades (Ji 2006d). On the basis of Eq. 4.4, it is possible to deduce the following conclusion:

Information and Shannon entropy are not identical. (4.22)

Statement 4.22 is consistent with Statement 4.5. I believe, in agreement with Wicken (1987), that Shannon entropy, H, given by Eq. 4.3 and thermodynamic entropy, S, given by Eq. 4.23 below, are not the same despite their similar mathematical formulas, only accidentally sharing the common name *entropy*:

$$S = k_B \log W \tag{4.23}$$

where k_B is the Boltzmann constant and W is the number of microstates (or molecular states) compatible with the observed macrostate of the thermodynamic system under consideration. The nonidentity between H and S expressed in Statement 4.22 can be transformed into Statement 4.24 without losing validity:

Information defined by Shannon and thermodynamic entropy are not quantitatively related. (4.24)

For convenience, we may refer to Statement 4.22 as the Principle of Non-identity of Information and Shannon Entropy (PNISE) and Statement 4.24 as the Principle of the Non-identity of Information and Thermodynamic Entropy (PNITE). Furthermore, since thermodynamic entropy, S, is a part of free energy (see Eq. 2.1), we can generalize Statement 4.24 by replacing "thermodynamic entropy" with "energy" to generate Statement 4.25:

Information and energy are not quantitatively related. (4.25)

An important corollary of Statement 4.25 is:

Information and energy cannot be interconverted. (4.26)

Statement 4.26 may be referred to as the *Principle of Information-Energy Independence* (PIEI), which is consistent with the *Principle of Information-Energy Complementarity* (PIEC) discussed in Sect. 2.3.2.

One of the most fundamental assumptions made in this book is that *information* (simply defined as the ability to select or to control, given free energy dissipation) and *energy* (the ability to do work, including selecting) are complementary aspects of a third entity called "gnergy" (Ji 1991) (see Sect. 2.3.2). The complementary relation between *information* and *energy* is a rather novel notion, and it is neither widely known nor widely accepted by contemporary scientists and thinkers. There are three schools of thoughts concerning the relation between *energy* and *information*:

1. *The monadic school*
   (a) Energy and information are identical. Brillouin's "Negentropy Principle of Information" (NPI) may represent the most widely discussed example of this school of thought (Brillouin 1953, 1956; Collier 1999; Leff and Rex 1962).
   (b) Energy is primary and information is derivable from it.
   (c) Information is primary and energy can be derived from it.
2. *The dyadic school*
   Energy and information are two separable and distinct primary entities on an equal footing. Two variations of this school may be recognized—
   (a) Energy and information are distinct and cannot be interconverted. Bohmian quantum mechanics (Bohm and Hiley 1993) and Laszlo's (2003) "connectivity hypothesis" may belong to this school.
   (b) Energy and information are distinct but can be interconverted (Bennett 1991; Layzer 1975), which would contradict Statement 4.26, the Principle of Information-Energy Independence.
3. *The triadic school*
   Energy and information are the two *complementary* aspects of a third entity. Spinoza's and Merleau-Ponty's ontologies seem to exemplify this school of thought. Spinoza (Scruton 1999; Curley 1994) referred to the third entity as S*ubstance* (also called *Nature* or *God*), while Merleau-Ponty referred to it as *Flesh* (Dillon 1997).

The *information-energy complementarity* thesis discussed in Sect. 2.3.2 belongs to the triadic school of thought and is supported by the following observations:

1. The units of energy (e.g., Kcal/mole) and information (e.g., bits) are different.
2. The energy of the Universe is constant (the First Law of Thermodynamics) but the information content of the Universe may not nor needs be constant, as illustrated by the extinction of innumerable biological species including *Dinosaurs*.

3. Energy is represented as a vector field while information is associated with the scalar field of the cosmic plenum according to Laszlo (2003).
4. In molecular machines in action, energy and information are indistinguishably intertwined into one entity called *conformons* (i.e., sequence-specific conformational strains of polymers) (Ji 1974a, b, 2000). Conformons can be viewed as specific instantiations (tokens) of *gnergy* (type) in the living cell. The conformon concept was supported by (1) the results of the statistical mechanical analysis of supercoiled DNA double helices in bacteria indicating that gene expression requires the storage of mechanical energies in sequence-specific sites within DNA duplexes (Benham 1996a, b; Benham and Bi 2004) (see Sect. 8.3) and (2) the simultaneous measurement of ATP hydrolysis and the single molecule movement of the myosin head along the actin filament indicates that chemical energy of ATP is temporarily stored as mechanical energy in the free myosin head (Ishijima et al. 1998) (see Sect. 11.4.1).

The confusion in the field of the information-entropy debate is so great that A. Ben-Naim (2008) recently went so far as to state that

> . . . thermodynamics and statistical mechanics will benefit from replacing the unfortunate, misleading and mysterious term 'entropy' with a more familiar, meaningful and appropriate term such as information, missing information or uncertainty. (4.27)

Although I sympathize with Ben-Naim's frustrations with the current state of affairs on the information-entropy debates that began with the seemingly haphazard suggestion by von Neumann to Shannon about naming the entity defined by Shannon's equation, Eq. 4.2, as "entropy" based on its mathematical similarity to Boltzmann's equation for entropy, Eq. 4.23, I disagree with Ben-Naim about replacing *entropy* with *information*. On the contrary, I can justify recommending two possibilities that are the opposites of what Ben-Naim recommends:

> To restrict the meaning of "entropy" to its thermodynamic one as originally intended by Clausius and Boltzmann and remove the term "entropy" from all discussions on information as defined by Shannon (4.28)

Alternatively,

> Two different kinds of entropies be recognized (in analogy to the existence of the many different kinds of energies) – i) the Boltzmann-Clausius entropy referring to the entropy of thermodynamics and ii) the Shannon entropy defined by Shannon's equation which is a more general kind of entropy that can include the Boltzmann entropy (just as free energy includes Gibbs free energy and Helmholtz free energy).

These recommendations are summarized in the second row of Table 4.3, which also includes the similarities and differences between entropy and information at many levels. The fact that two entirely opposite solutions, Ben-Naim's and mine, can be suggested for the problem of the information-entropy paradox may be of some significance in itself. According to the *philosophy of complementarism* (Pais 1991; Ji 1993, 1995), when two entirely opposite solutions can be suggested for a given problem, the most likely possibility is that the two suggested solutions constitute the *complementary aspects* of the true solution to the problem under

Table 4.3 A comparison between *entropy* and *information*

	Entropy (S)	Information (I)
1. Alternative names	Thermodynamic entropy Boltzmann entropy (Boltzmann–Clausius entropy)	Informational entropy ("intropy") Information-theoretic entropy Shannon entropy (H)
2. Recommended names	Entropy (S) Boltzmann–Clausius entropy (S)	Information (I) Shannon entropy (H)
3. Mathematics[a]	$S = k \ln W$ $(W \geq 1)$ where w = the number of the microscopic arrangements	$I = K \log P$ where K = negative number, and $P \leq 1$ is the probability associated with a message
4. Principles obeyed	Second law of thermodynamics	Fourth law of thermodynamics? (see Table 14.9 for a more detailed discussion)
	"The entropy of isolated systems increases with time."	"Not all irreversible processes produce information."
	"All irreversible processes produce entropy."	"Some irreversible processes can decrease information."
5. Temperature sensitivity	Yes[b]	Not always[c]
6. Cross-relation[d]	P in $S = k \ln P$ is a form of I[e]	S increase or S production is required for I transmission
7. Relation to energy	Direct (i.e., $dS = dQ/T$)	Indirect (i.e., $C = B \log_2 (1 + P/N)$[f])
8. Subsethood[g]	$S \leq I$	
9. Fields of study[h]	Thermodynamics	Informatics
10. Common principle[i]	The principle of information-energy complementarity (Sect. 2.3.2)	

[a]The term W cannot be less than 1 due to the constraint imposed by the Third Law of thermodynamics which states that the entropy content of perfect crystals is zero at the zero degree of the absolute temperature and hence S cannot be negative

[b]This statement is true because all material objects have positive heat capacities

[c]When one heats up a book such as the Bible, the *thermodynamic entropy* associated with molecular motions of the paper constituting the pages of the Bible will increase but the *informational entropy* associated with the arrangement of letters in the Bible will not be affected until the temperature increases high enough to burn the Bible. This is thought experiment may be conveniently referred to as *the Bible test*

[d]The relation between S and I

[e]The term P in the equation for S refers to the *statistical weights* P of all possible microstates and as such represents a form of *information* different from the *information* defined by Shannon as the logarithmic function of the *probabilities of event* P. Hence, we can recognize two kinds of *informations* – (1) the *logarithmic* or *indirect information* as defined by Shannon and (2) *nonlogarithmic* or *direct information* as perceived by the human brain directly. We may also refer to the former as the *second-order information* and the latter as the *first-order information*

[f]This is the channel capacity (denoted as C) equation of Shannon (Shannon and Weaver 1949), Eq. 4.29, which states that no information can be transmitted when no energy is dissipated (or no power P is expended, or no entropy is produced), i.e., when $P = 0$, $C = 0$. B is the bandwidth of the communication channel. Please note that P appearing in the channel capacity equation is not the same as the P appearing in the equation for Shannon entropy or Shannon information

(continued)

Table 4.3 (continued)

[g] The subsethood is defined here as follows. When (1) all the elements of set A are also the elements of set B but (2) not all the elements of B are the elements of A, set A is referred to as the subset of B which is denoted as A $<$ B. *In this sense, S is a subset of I,* i.e., $S < I$

[h] Thermodynamics is the study of the *energy and thermodynamic entropy changes* accompanying physicochemical processes of material systems, whereas informatics is the study of the *informational changes* accompanying both physicochemical processes and their consequents, namely, mental processes and their causations

[i] According to the Information-Energy Complementarity Principle (Sect. 2.3.2), *thermodynamics* and *informatics* are complementary disciplines both of which are essential for a complete understanding/description of nature, including the phenomenon of life

consideration. If this principle applies here, both Ben-Naim's and my suggestions to the solution of the entropy-information debates may be considered *complementary*, the former prescinding (Sect. 6.2.12) the informational aspect and the latter taking into account both the energy and entropy (i.e., free energy) aspects, in agreement with the *information-energy complementarity thesis* (see Row 10 in Table 4.3) (see Sect. 2.3.2).

4.8 The Minimum Energy Requirement for Information Transmission

In addition to Eq. 4.2 that defines what was later referred to as the Shannon entropy, H, Shannon derived another important equation, the *channel capacity equation*, Eq. 4.29:

$$C = W \log_2(1 + P/N) \text{ bits/s} \tag{4.29}$$

where C is the channel capacity or the capacity for a communication channel to transmit information in unit time, W is the bandwidth of the channel or the range of frequencies (also called the "degree of freedom") used in communication, P is the power or the rate of energy dissipation needed to transmit the signal, and N is the thermal noise of the channel.

According to Eq. 4.29, when no power is dissipated, i.e., when $P = 0$, the channel capacity C is zero, indicating that no information can be transmitted through the channel. Calculations show that the amount of energy needed to transmit the minimum amount of information, i.e., 1 bit, is 0.6 kcal/mol or 2.4 Joules/mol (Pierce 1980). Therefore, it is possible to formulate the following general statement which may be referred to as the *Principle of Minimum Energy Dissipation for Information Transmission* (PMEDIT):

It is impossible to transmit information without dissipating energy. (4.30)

4.9 Info-Statistical Mechanics and the Gnergy Space

Traditionally, the dynamics of any N-particle systems in statistical mechanics is completely described in terms of the 6-dimensional *phase space* consisting of the 3N positional coordinates and 3N momenta, where N is the number of particles in the system (Tolman 1979; Prigogine 1980). Unlike the particles dealt with in statistical mechanics which are featureless and shapeless, the particles of importance in biology have characteristic shapes and internal structures that determine their biological properties. In other words, the particles in physics are completely described in terms of energy and matter (in the phase space) but the description of the particles in living systems require not only the energy and matter of the particle but also the genetic information carried by the particle, consistent with the information-energy complementarity (or gnergy) postulate discussed in Sect. 2.3.2. Thus, it seems necessary to expand the dimensionality of the traditional phase space to accommodate the *information* dimension, which includes the three coordinates encoding the *amount* (in bits), *meaning* (e.g., recognizability), and *value* (e.g., practical effects) of information (see Sect. 4.3). Similar views have been expressed by Bellomo et al. (2007) and Mamontov et al. (2006). Thus the expanded "phase space" would comprise the 6N phase space of traditional statistical mechanics plus the 3N information space entailed by molecular biology. Therefore, the new space (to be called the "gnergy space") composed of these two subspaces would have 9N-dimension as indicated in Eq. 4.31. This equation also makes contact with the concepts of *synchronic* and *diachronic* informations discussed in Sect. 4.5: It is suggested that the traditional 6N-dimensional phase space deals with the *synchronic information* defined in Sect. 4.5 and thus can be alternatively referred to as the *Synchronic Space* while the 3N-dimensional information space is concerned with the consequences of history and evolution encoded in each particle and thus can be referred to as the *Diachronic Space*. The resulting space will be called the *gnergy space* (since it encodes not only *energy* but also *information*) and represented diagrammatically as shown in Fig. 4.2.

$$\underset{(Synchronic\ Space)}{\textbf{6N-D Phase Space}} + \underset{(Diachronic\ Space)}{\textbf{3N-D Information Space}} = \textbf{Gnergy Space} \tag{4.31}$$

Figure 4.2 depicts the independence of *genetic information* from *free energy,* which is equivalent to the assertion that that genetic information is not reducible to the laws of physics and chemistry (see **Exclusivity** in Sect. 2.3.1 and Statements 4.25 and 4.26). There are many other ways of expressing the same concept, just as there are many equivalent ways of stating the Second Law of Thermodynamics, including the following:

1. The genetic information versus free energy orthogonality
2. The independent variations of free energy and genetic information (Statements 4 25 and 4.26)
3. The genetic information versus free energy complementarity

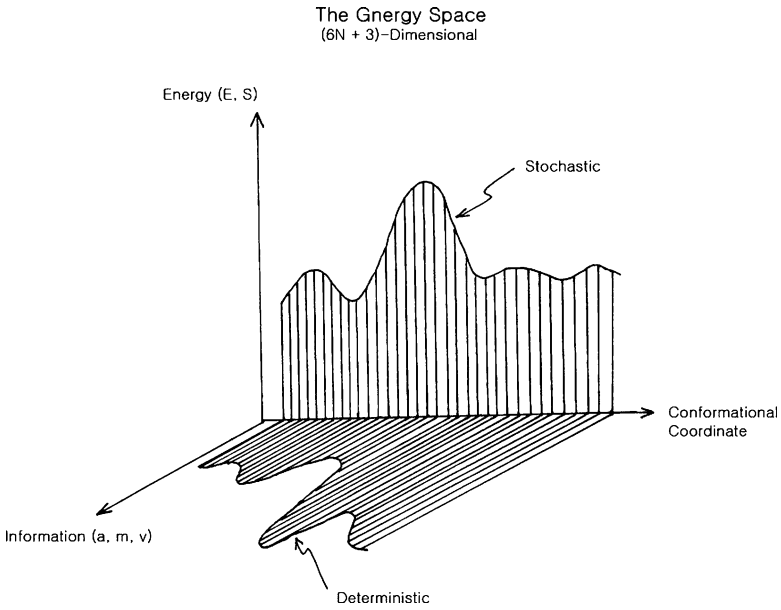


Fig. 4.2 *The gnergy space*. The gnergy space comprises two complementary subspaces – the 6N-dimensional phase space (or the *synchronic space*) and the 3N-dimensional information space (or the *diachronic space*). Energy here refers to free energy, which is a function of both *internal energy* E and system *entropy* S. Here, physical entropy S is presumed to be fundamentally different from Shannon's entropy, H, in agreement with Wicken (1987) but in contradiction to the information theory of Brillouin (1953, 1956) (see Table 4.3). For a review of this controversial field, see (Leff and Rex 1962) and (Ji 2006d). Information has three dimensions: a = amount, m = meaning, and v = value. Only the quantitative aspect of information, namely, a, is captured by Shannon entropy (see Sect. 4.3). The time evolution of an N-particle system traces out what may be referred to as a semi-stochastic trajectory in the gnergy space which projects a stochastic shadow onto the phase space and a deterministic shadow onto the information space. It should be noted that the trajectories shown above represent the averages of their corresponding ensembles of trajectories (Prigogine 1980). "Stochastic" processes are the apparently random processes that exhibit regularities although not predictable. Deterministic processes exhibit properties that are predictable

It is suggested here that, to study the dynamics of living systems such as genome-wide kinetics of mRNA levels measured with DNA microarrays (Watson and Akil 1999), treated as N-particle systems, it is necessary to employ the gnergy space. Since living systems trace out trajectories that are both *stochastic* and *deterministic* (see the legend to Fig. 4.2 for the definitions of "stochastic" and "deterministic"), the study of living processes in the gnergy space has been referred to as the *info-statistical mechanics* (Ji 2006a)

The orthogonality between *information* and *free energy* depicted in Fig. 4.2 may be described in yet another way, using the photosynthetic process as an example. Figure 4.3 shows the complex interactions among *light*, *chemical reactions*, *heat*, *evolution*, and *catalysis* in producing the phenomenon of life.

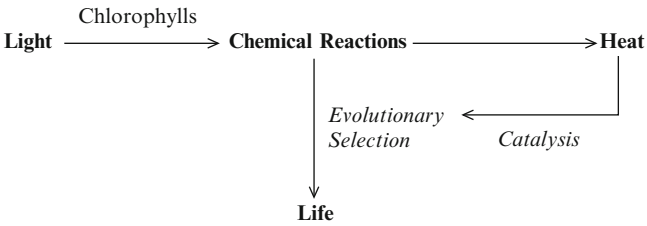


Fig. 4.3 A bionetwork representation of the interactions among *light, chemical reactions, heat, biological evolution*, and *catalysis*. Chemical reactions driven by *free energy* occur along the *horizontal arrows* (i.e., in the synchronic space) while the evolutionary selection process controlled by or producing *genetic information* occurs along the vertical arrow (i.e., in the diachronic space), which supports the notion that *free energy* and *genetic information* are orthogonal

All living processes ultimately depend on the absorption of light by chlorophyll molecules in the leaves of plants or in photosynthetic bacteria. The photons absorbed by chlorophylls activate and drive the endergonic (i.e., free energy requiring) chemical reactions leading to the synthesis of carbohydrates and oxygen, starting from carbon dioxide and water, as summarized in Reaction (4.32). In the process, most of the light energy is converted to thermal energy or heat (see the top horizontal arrows in Fig. 4.3). Living systems then utilize glucose and oxygen (or other electron acceptors such as sulfur) to synthesize ATP which provides most of the thermodynamic driving force for living processes.

$$nH_2O + nCO_2 \xrightarrow[Heat]{Light} C_nH_{2n}O_n + nO_2 \tag{4.32}$$

The evolution of life and the attendant genesis of biological information depended on a set of chemical reactions that has been selected (through the action of enzyme-mediated catalysis) out of all possible reactions allowed for by the laws of physics and chemistry under prevailing environmental conditions, through the process of natural selection, which is represented by the vertical arrow in Fig. 4.3. Let us recall that any selection process implicates information (either as used or as produced). One important point to notice in Fig. 4.3 is the postulate that natural selection (generating genetic information) favors those systems that can utilize *even* the waste product of chemical reactions, namely, *heat*, as indicated by the bent arrow labeled "Catalysis," without violating the Second Law (see Sect. 2.1.4.). As is well known, the Second Law prohibits using heat to do any useful work without temperature gradients. In (Ji 1974a), I proposed one possible molecular mechanism by which enzymes might be able to utilize thermal energy (i.e., heat) without violating the Second Law, and this mechanism was, in part, based on the generalized Franck–Condon principle imported from the chemical kinetics literature as pointed out in Sect. 2.2.3.

Because the physicochemical processes (or *energy processes*) occur along the *horizontal* direction (or in the synchronic space) and the biological evolution

Table 4.4 A comparison between the postulated "info-statistical mechanics" of life and the traditional statistical mechanics of abiotic physicochemical processes

	Heat	Life
1. Parent science	Thermodynamics	Molecular and cell biology
2. Microscopic theory	Statistical mechanics	Info-statistical mechanics
3. Landmark event	1877	1953
	Boltzmann's equation[a] $S = k_B \ln Q$	Watson and Crick's DNA; genetic code conformons as packets of genetic information and mechanical energy
4. Field named	1884 (W. Gibbs, Yale University)	2006 (The 96th statistical mechanics conference, Rutgers University) (Ji 2006a)
5. Key concepts	Energy and entropy (synchronic information)	Energy, entropy and information (synchronic and diachronic informations)
6. Laws	First and second laws of thermodynamics	Fourth law of thermodynamics (?) (see Fig. 2.2 and Table 14.9)
7. Theoretical tools	6N-dimensional *phase space*	9N-dimensional *gnergy space* (Fig. 4.2)

[a]S = thermodynamic entropy; k_B = the Boltzmann constant; Q = the number of microstates of a thermodynamic system underlying the observed microstates of the system

(i.e., *information processings*) occurs along the *vertical* direction (or in the diachronic space), Fig. 4.3 well illustrates the notion of the "genetic information - free energy orthogonality," or the "information-energy complementarity" (Ji 1991). In other words, Fig. 4.3 depicts the paradox between physics/chemistry (in the synchronic space) and biology (diachronic space): They are *orthogonal*, or mutually exclusive, in the sense of the Bohr's complementarity (see Sect. 2.3).

Biology is more complex than physics and chemistry, primarily because it implicates components that are the products (e.g., enzymes) of *biological evolution* and hence encodes the history (or memory) of the interactions between biological systems and their environment. These elusive environmental influences derived from the past can only be described in the language of the *information theory* that accommodates at least three degrees of freedom – *amount, meaning*, and *value* of information as indicated in Sect. 4.3. Thus, the theory of life, taking these mutually exclusive components into account, may be referred to as "info-statistical mechanics," or "informed statistical mechanics"' (Ji 2006a). The "info-" component is associated with the vertical arrow and the "statistical mechanics" component with the horizontal arrows in Fig. 4.3. "Info-statistical mechanics" is compared with *traditional statistical mechanics* in Table 4.4. Info-statistical mechanics discussed here may share a common ground with "info-dynamics" discussed by Weber and Depew (Salthe 1996).

Just as statistical mechanics is the *microscopic theory* of thermodynamics, so *info-statistical mechanics* may be viewed as a microscopic *theory* of molecular and

cell biology (see the first two rows). And yet, the traditional molecular and cell biology, although often couched in the concepts of information does not, in the real sense of the word, involve any information theory at all (as attested by the fact that no major biochemistry or molecular biology textbooks currently in print, to the best of my knowledge, define what *information* is!). Thus traditional molecular cell biology can be regarded mostly as an applied field of chemistry and physics (i.e., a synchronic science, the science dealing with *synchronic information*; see Sect. 4.5), devoid of any truly *information-theoretical* contents (i.e., diachronic science, the science dealing with *diachronic information*). Linguists distinguish between *synchronic* (i.e., ahistorical) and *diachronic* (i.e., historical) studies of language (Culler 1991). Similarly it may be assumed that traditional molecular biology can be viewed as the synchronic study of life on the molecular level (which is indistinguishable from physics and chemistry) and info-statistical mechanics as both synchronic and diachronic studies of life. One of the landmark developments in statistical mechanics is the mathematical derivation by Boltzmann of the formula for entropy. The comparable event in info-statistical mechanics may be suggested to be the discovery of the double helical structure of DNA in 1953, that is here postulated to be the carriers of *molecular information* and *mechanical energy*, namely, conformons (Benham 1996a, b, Benham and Bi 2004; Ji 1985a, b, 2000) (see Chap. 8).

4.10 The Free Energy–Information Orthogonality as the "Bohr–Delbrück Paradox"

Bohr's "Light and Life" lecture in 1933 influenced Max Delbrück (1906–1981) to switch his field from physics to biology (McKaughan 2005). By applying the reductionist, physicochemical approaches to biology as far as possible (in which effort, he was so successful as to win a Nobel Prize in Physiology or Medicine in 1969), Delbrück hoped to uncover a biological situation where the reductionist approach would lead to a paradox akin to the wave-particle paradox in quantum physics. To the best of my knowledge, Delbrück was unable to discover any new paradox or any complementarity in molecular biology beyond the mechanism-function complementarity that Bohr already discussed in 1933. We may refer to the kind of paradox that Bohr predicted and Delbrück looked for in molecular biology as the *Bohr–Delbrück paradox*.

It asserted here that the information-energy complementarity discussed in Sect. 2.3.2 and Figs. 4.2 and 4.3 qualifies to be a Bohr–Delbrück paradox. The information-energy complementarity (or paradox) can be graphically represented as in Fig. 4.2. This figure embodies a paradox from the point of view of physics, because, in physics, the concept of energy (including entropy as a part of free energy) rules supreme (i.e., is both necessary and sufficient to explain all

phenomena studied in physics), and all else are secondary to it (or derivable from it). But the information-energy complementarity postulate states that information is different from energy, cannot be derived from energy, and plays a role in biology that is as fundamental as energy, ultimately because what drives living processes is not free energy nor information alone but a third entity called gnergy, of which information (gn-) and energy (−ergy) are the complementary aspects (Ji 1991).

4.11 What Is Gnergy?

The concept of gnergy may be related to the concept of the *substance* discussed by Socrates, Aristotle, and Spinoza. According to the theory of hylomorphism (from Greek roots "hylo-" meaning "wood, matter," and "–morph-" meaning "form") which originated with Socrates, substance is composed of matter and form or form inheres in matter. Aristotle believed that matter and form are real and exist in substance. This view is known as Aristotelian realism. Hylomorphism may be diagrammatically represented as shown in Fig. 4.4, where the triangle symbolizes the inseparability of substance, matter, and form, and the H in the center of the triangle symbolizes the philosophical perspective of hylomorphism.

The concept of gnergy as the complementary union of information and energy (see Sect. 2.3.2) can be conveniently depicted using the same triangular scheme as shown in Fig. 4.4. One feature added to Fig. 4.5 is the designation of two levels of philosophy – *ontology*, the study of being or what is, and *epistemology*, the study of how we know about the being. Gnergy transcends the level of energy and information since gnergy is what is or exists (i.e., ontic or ontological) regardless of whether we, *Homo sapiens* are here to observe it or not, while energy and information are about how we, Homo sapiens, know what is (i.e., epistemic or epistemological).

As can be seen, the nodes of Figs. 4.4 and 4.5 are very similar (i.e., Substance ~ Genergy, Matter ~ Energy, and Form ~ Information), and the two triangle can be made identical (or symmetric) by equating *hylomorphism* with *complementarism*. If this analysis is right, we may regard hylomorphism of Greek philosophers as the

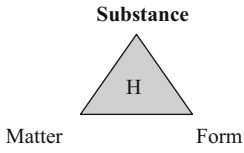


Fig. 4.4 A diagrammatic representation of the philosophy of hylomorphism (H) of Socrates and Aristotle

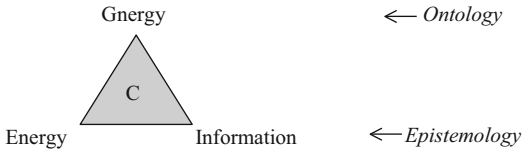


Fig. 4.5 A diagrammatic representation of the concept of gnergy in the context of the philosophy of complementarism (C) (Ji 1993, 1995)

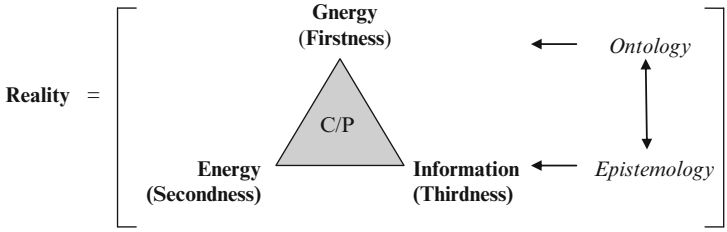


Fig. 4.6 The *Triadic Theory of Reality* (TTR). A diagrammatic representation of the relations among *reality, ontology, epistemology, energy/matter, information, and substance,* based on the Bohr's principle of complementarity (C) and Peircean metaphysics (P) (Firstness = Substance; Energy/Matter = Secondness; Information = Thirdness). The right-hand portion of the figure symbolizes the *transcendental relation* (symbolized by the *double-headed vertical arrow*) between ontology and epistemology

forerunner of complementarism of Bohr (Pais 1991) and his followers (Ji 1993, 1995). Biology played an important role in both theorizings, and the difference between *hylomorphsism* and *complementarism* may be traced to the difference between the biology of the ancient Greece and that of the twentieth and twenty-first centuries.

It can be readily recognized that Fig. 4.5 contains two kinds of complementarities:

1. The "horizontal" (H) complementarity between *energy/matter* and *information*
2. The "vertical" (V) complementarity between *ontology* and *epistemology*

This would be natural if the principle of complementarity is universal, as Bohr seemed to have believed when he inscribed on his coat of arms the following dictum (Pais 1991):

Contraries are complementary. (4.33)

Figure 4.5 contains two pairs of contraries – the energy ~ information pair, and the ontology ~ epistemology pair, and, if Bohr is right, it may be anticipated that, associated with these two pairs, there should be two kinds of complementarities – H and V, as indicated above. Thus, it may be permitted to name these complementarities as follows:

1. Horizontal (H) complementarity = *Energy-information complementarity*, and
2. Vertical (V) complementarity = *Ontic-epistemic complementarity*.

If this analysis is right, *reality* may be associated with the complementary union of two kinds of complementarities, H and V, reminiscent of recursivity in computer science (see Sect. 5.2.4). In other words, the principle of complementarity may be both *universal* and *recursive,* satisfying the principle of closure (see Sect. 6.3.2), and underlies the ultimate reality. These ideas are organized into a coherent system of thoughts utilizing the geometry of a triangle inspired by the metaphysics of C. S. Peirce (see Sect. 6.2) as depicted in Fig. 4.6. For the sake of convenience, we may refer to the complex system of ideas depicted in Fig. 4.6 as the *triadic theory of reality* (TTR).

4.12 Two Categories of Information in Quantum Mechanics

The First Postulate of Quantum Mechanics (QM) (Morrison 1990) states that:

> Every physically-realizable state of a system is described in quantum mechanics by a single state function Ψ that contains all accessible physical information about the system in that state. (4.34)

The First Postulate of QM may be viewed as the definition of the "information" concept as used in physics. It is clear that there are *two categories of information* in quantum mechanics, symbolized by Ψ and Ψ^2, the former given by Statement 4.34 and the latter related to measurement or observation (Herbert 1987; Morrison 1990). The relation between these two categories of physical information may be diagrammatically represented as:

$$\underset{(1)}{\Psi} \xrightarrow[(2)]{\text{Measurements}} \underset{(3)}{\Psi^2} \tag{4.35}$$

Applying Peircean triadic metaphysics (Sect. 6.2), it appears reasonable to suggest that Ψ belongs to or is associated with Firstness (1); Measurement with Secondness (2); and Ψ^2 is by default left to pair with Thirdness (3), which category including theories, knowledge, and representations. Thus Eq. 4.35 can be graphically represented as shown in Fig. 4.7.

The contents of Eq. 4.35 and Fig. 4.7 agree well with the results obtained through somewhat different routes as described in the next section.

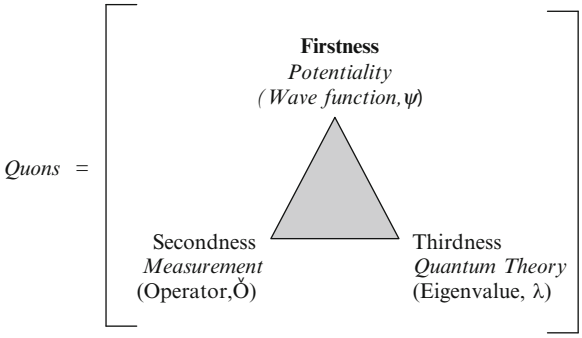


Fig. 4.7 **A** semiotics-based metaphysics of quantum theory. *Quons* are material entities exhibiting quantum properties such as wave-particle duality, nonlocality, and entanglement (Herbert 1987) (Reproduced from Fig. 1 of the NECSI [New England Complex Systems Institute, Boston] post entitled "quantum mechanics and semiotics" dated August 11, 2005 [see Appendix K]. *An exact copy of this figure appears in an article by Prashant Singh published in arXiv:physics/0605099v2 [physics.gen-ph] entitled "Quantum Semiotics: A Sign Language for Quantum Mechanics", submitted on May 12, 2006 and last revised on January 11, 2007, without referring to the original publication reproduced in Appendix XI*)

4.13 Information-Energy Complementarity as the Principle of Organization

For the purpose of discussing living processes, it appears sufficient to define "organization" as the nonrandom arrangement of material objects in space and time. I have long felt that both *energy* and *information* are required for any organization, from the Belousov–Zhabotinsky reaction–diffusion system (Sect. 3.1.1) to the living cell (Fig. 2.11) and higher structures. This vague feeling may now be given a more concrete expression by asserting that "organization" is the *complementary union* of *information* and *energy* or that *information* and *energy* are the complementary aspects of organization (Fig. 4.8). In other words, the *information-energy complementarity* may well turn out to be the elusive physical principle underlying all organizations not only in living systems but also nonliving systems including the Universe Itself (see Table 4.5 and Fig. 15.12). *Organization* in living systems require intrasystem and intersystem communications, and communications require transferring information in space (through waves) and time (through particles) obeying a set of rules embodied in a language, thus implicating both language and the wave-particle duality or complementarity (Table 4.5). Since no information can be transferred without utilizing energy, according to Shannon's channel capacity equation (see Sect. 4.8), communication necessarily implicate the

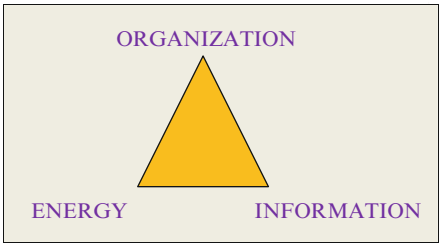


Fig. 4.8 Information and energy as the complementary aspects of organization. Since gnergy is the complementary union of information and energy, organization and gnergy may be viewed as synonymous

Table 4.5 The information/energy complementarity as the ultimate principle of organization

Energy	Information	Organization
Mattergy (matter–energy) ($E = mc^2$; matter as a highly condensed form of energy)	"Liformation" (life-information; life as a highly condensed form of information) (Table 2.5)	Self-organization (Sect. 3.1)
Force	Structure	Control, regulation
Space	Language	Law of requisite variety
Time	Communication, purpose	Curvature of spacetime

The principle of complementarity (wave/particle & information/energy complementarities)

information/energy complementarity. I assume that any organization has a purpose or equivalently that systems of material components organize themselves (i.e., self-organize) to accomplish a purpose or a goal, the final cause of Aristotle.

4.14 The Quantization as a Prelude to Organization

Quantization (or discretization) may be essential for any organization, since organization entails selection and selection in turn requires the existence of discrete entities to choose from. In Sects. 11.3.3 and 12.12, experimental evidence is presented that indicates that biological processes such as single-molecule enzymic activities (Lu et al. 1998; Ji 2008b), whole-cell RNA metabolism (Ji and So 2009d), and protein folding (Ji 2012) are quantized because they all obey mathematical equations similar in form to the blackbody radiation equation (see Table 4.6) that was discovered by M. Planck in physics in 1900 which led to the emergence of *quantum mechanics* two and a half decades later (Herbert 1987; Kragh 2000; Nave 2009).

To make the blackbody radiation data fit a mathematical equation, Planck had to assume that the product of energy and time called "action" is quantized in the unit later called the Planck constant, h, which has the numerical value of 6.625×10^{-27} erg · s. This quantity seems too small to have any measurable effects on biological processes which occur in the background of thermal fluctuations involving energies in the order of kT, where k is the Boltzmann constant, 1.381×10^{-16} erg/degree and T is the absolute temperature. The numerical value of kT is 4.127×10^{-14} ergs at room temperature, $T = 298°K$, which is 13 orders of 10 greater than h. Thus, it appears reasonable to assume that biological processes are quantized in the unit of k rather than in the unit of h as in physics, which leads me to suggest that

The Boltzmann constant k is to biology what the Planck constant h is to physics. (4.36)

Thus, by combining the evidence for the quantization of biological processes provided by Table 4.6 and Statement 4.36, it appears logical to conclude that

Biological processes at the molecular and cellular levels are quantized in the unit of the Boltzmann constant k. (4.37)

Statement 4.37 may be referred to as the "Boltzmann Quantization of Biological Processes" (BQBP). If Statement 4.37 turns out to be true, we will have two types of quantizations in nature – (1) the *Planck quantization* in the unit of h and (2) the *Boltzmann quantization* in the unit of k. These two types of quantizations are compared in Table 4.7, the fifth row of which suggests the *final cause* of the two types of quantizations, and the last row suggests that the Planck quantization is to Boltzmann quantization what atoms are to quantum dots (more on this in Sect. 4.15).

The relation between the *Planck quantization* and the *Boltzmann quantization* postulated in Row 5 may be summarized as in Statement 4.38 and schematically represented in Fig. 4.9:

Quantization precedes organization. (4.38)

Table 4.6 Blackbody radiation law-like equation (BRE) is obeyed by (1) blackbody radiation, (2) single-molecule enzymic activity of cholesterol oxidase, (3) whole-cell RNA metabolism in budding yeast, and (4) protein stability data (see Sects. 11.3.3 and 12.12 for more details)

	$y = a(Ax + B)^{-5}/(e^{b/(Ax + B)} - 1)$						
Process	a	b	A	B	a/b	y	x
1. Blackbody radiation	5×10^{-15}	4.8×10^{-13}	1	0	1.04×10^{-2}	Spectral intensity	Wavelength
2. Single-molecule enzymic catalysis	3.5×10^{5}	2.0×10^{2}	1	0	1.75×10^{3}	Frequency of occurrences	Waiting time[a]
3. Distances between RNA pairs in the concentration space; catalysis by *enzyme complexes*[b]	8.8×10^{8}	50	2.23	3.21	1.7×10^{7}	Frequency of occurrences	Phenotypic similarity classes[c]
4. Protein stability/ unfolding	1.8×10^{10}	300	14	18	6.0×10^{7}	Frequency of the occurrence of ΔG	Δ G, i.e., the Gibbs free energy of the native conformation of a protein

[a]The time an enzyme waits until it begins its next cycle of catalysis. The longer the waiting time, the slower the catalytic rate constant. See Rows 6 and 7 in Table 1.9

[b]The parameter a in BRE may reflect the number of enzymes forming an *enzyme complex*. If this conjecture is right, transcriptosomes and degradosomes together may contain over 10^2 individual enzymes, just as a quantum dot contains 10^2–10^3 individual atoms (see Table 4.7)

[c]The classes (or bins) of the quantitative measure of the similarity between two RNA trajectories

Table 4.7 Two types of quantizations in nature

	Planck quantization	Boltzmann quantization
1. Symbol of quantum	h	k
2. Unit of quantization	erg · s	erg/degree
3. Numerical value	6.625×10^{-27}	1.381×10^{-16}
4. Name of quantum (dimensions)	action (energy × time)	entropy (energy/temperature)
5. Final cause for (or is prelude to)	Physical organization	Biological organization
6. Analogy	Atoms	Quantum dots (?)

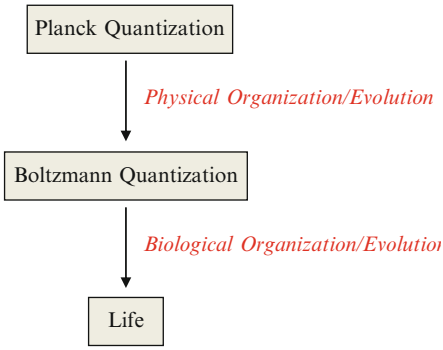


Fig. 4.9 A schematic representation of the "quantization before organization" postulate

Statement 4.38 may be referred to as the "Quantization before organization (QBO) hypothesis" (Fig. 4.9).

Two recent developments may support the QBO hypothesis:

1. Gilson and McPherson (2011) demonstrate that Boltzmann's constant k ($= 1.3805 \times 10^{-16}$ erg K^{-1}) is quantized in terms of cosmological scale quantities according to the formula $k = N_B k_q$ where $N_B = 10^{13}$, thus indicating that the concept of quantization first introduced by Plank in 1900 need not be confined to the microscopic scale characterized by the Planck constant, h ($= 6.6252 \times 10^{-7}$ ergs).
2. When 10^2–10^3 atoms form a nanoparticle (nano $= 10^{-9}$ m), they can exhibit electronic properties that are intermediate between those of individual atoms (typically 10^{-10} m in diameter) and those of bulk semiconductors (http://en.wikipeia.org/wiki/Quantum dot). Such nanoparticles are called "quantum dots" because they possess new quantum mechanical properties that are determined by the shape and the size of the particle as a whole. For example, as the size of the quantum dot increases, the frequencies of light emitted after excitation of the dot decreases leading to a shift of color from blue to red. This indicates that the electronic energy levels of the quantum dot are quantized in a new way reflecting the shape and size of the quantum dot unlike the quantization of individual atoms whose energy levels are largely determined by the internal structure of atoms. For this reason, quantum dots are also called "artificial atoms."

4.15 Simple Enzymes Are to Enzyme Complexes What Atoms Are to Quantum Dots

The quantization of energy levels is not only observed in atoms but also in *quatum dots*, *single-molecule enzymes* (Ji 2008b) and *enzyme complexes* (Ji and So 2009d), promoting me to suggest that *enzymes* and *enzyme complexes* are biological quantum dots (or bio-quantum dots more briefly). This conjecture is elaborated in Table 4.8. What connects the quantum dot and enzymes (e.g., cholesterol oxidase) on the one hand and the quantum dot and enzyme complexes (e.g., transcriptosomes, degradosomes) on the other is the *quantization of energy levels* beyond the energy levels within atoms that results from the *quantum confinement effect* (http://www.answers.com/topic/potential-well) (see Row 6 in Table 4.8). The quantum confinement effect is observed when the diameter of the particle involved is of the same magnitude as the wavelength of electron's quantum mechanical wave function, ψ (Cahay 2001). When materials are this small (see Row 3 in Table 4.8), the energy levels become quantized and separated by the so-called *bandgap*, i.e., the separation in energy levels between the *valence* and *conduction bands* in semiconductors. The bandgap is given by

$$\Delta E = \hbar^2/\mathrm{ma}^2 \tag{4.39}$$

where $\hbar$ is the Planck constant divided by 2π, m is the mass of the electron (or any quon) and a is the width of the potential well confining the electron/quon movement. Since the light emitted from quantum dot is determined by bandgap, which is in turn inversely proportional to the width of the potential well, a, Eq. 4.39 predicts that the color of a quantum dot (i.e., fluorescence) should shift from red to blue as the size of the dot decreases. Thus, the experimental observation of the size-dependent mission wavelengths of quantum dots (see the first figure in http://en.wikipedia.org/wiki/Quantum_dot) confirms the validity of the principle of quantum confinement (Row 6 in Table 4.8). The emergent properties of the "bio-quantum dots" are suggested to be the conformation-dependent catalytic rate constants (see Row 7) that will be discussed in Sects. 11.3.3 and 12.12. Potentially significant differences between "physical" quantum dots and "bio-quantum dots" is the static boundaries of the former and deformable and dynamic boundaries of the latter (see Row 4, Table 4.8). Consequently, the relation between the size of the physical quantum dots and their emission wavelengths is fixed and constant while the relation between the conformational states of "bio-quantum dots" and their catalytic properties is predicted to be variable and dynamic. This latter prediction is supported by the so-called "dynamic disorder" or "dynamic heterogeneity" of enzymes predicted in (Zwanzig 1990) and experimentally observed by (Lu et al. 1998) (see Sect. 12.12).

One of the major difficulties that prevent biologists to make rapid advances in their research is the occurrence of multiplicity of names, nomenclatures, and terms referring to common entities. For example, molecular biologists rarely distinguish

Table 4.8 A hypothesis: *Enzymes* and *enzyme complexes* as "bio-quantum dots"

		"Bio-quantum dots"	
	Quantum dots	Enzymes	Enzyme complexes
1. Components	Atoms	Molecules (e.g., amino acids)	Enzymes, RNA, DNA
2. Number of components	10^2–10^3	~500 (e.g., cholesterol oxidase)	10–10^2 (?)
3. Size of the system (diameter in nm)	5–10 (Jin et al. 2010)	~4	3×10^2–10^3 (e.g., transcriptosomes; Gall et al. 1999)
4. Boundary	Static	Dynamic	Dynamic
5. Quantization of energy levels unique to	Quantum dots	Enzymes (e.g., cholesterol oxidase)	Enzyme complex (e.g., transcriptosome)
6. Physical principle	Quantum confinement[a]	Quantum confinement[a]	Quantum confinement[a]
7. Emergent properties	Size-dependent electronic properties	Conformation-dependent rate constants (Sect. 11.3.3)	Conformation-dependent rate constants (Sect. 12.12)
8. Alternative names	Artificial atoms	"Simple molecular machines"[b]	"Complex molecular machines"[b]
		Molecular machines (McClare 1971; Ji 1974a, b; Alberts 1998)	"Supermolecular machines," Metabolons (Srere 1987), Hyperstructures (Norris et al. 2007a, b), Modules (Hartwell et al. 1999), and SOWAWN machines (Ji 2006b; Sect. 2.4)

[a]See Eq. 4.39 and attendant explanations
[b]Single quotation marks indicate a term introduced in this table for the first time

between "enzymes" and "enzyme complexes," referring to both as "molecular machines." But, if Table 4.8 is right, *enzymes are to enzyme complexes what atoms are to quantum dots* (see the second and fourth columns). Therefore, *biologists not distinguishing between enzymes and enzyme complexes may be akin to physicists not differentiating between atoms and quantum dots*. For this reason, I suggest in Row 8 in Table 4.8 that enzymes be referred to as "molecular machines" (or "simple molecular machines," or "s-mm") and enzyme complexes as "supermolecular machines" (or "complex molecular machines," or "c-mm"). One of the benefits we can derive from Table 4.8 (assuming that the table is right) is the clarification of the relation between previously unrelated concepts and terms such as "metabolons," "hyperstructures," "modules," and 'SOWAWN machines," which are now all viewed as different labels for *enzyme complexes* (see the fourth column in Table 4.8).

4.16 "It From Bit" and the Triadic Theory of Reality

The following excerpt from "Geon, Black Holes & Quantum Foam: A Life inPhysics" by Wheeler (1998) explains what is meant by his often-quoted phrase "It from Bit" (Wheeler 1990):

> . . . one enormous difference separates the computer and the universe–chance. In principle, the output of a computer is precisely determined by the input . . .. Chance plays no role.
>
> In the universe, by contrast, chance plays a dominant role. The laws of physics tell us only what may happen. Actual measurement tells us what is happening (or what did happen). Despite this difference, it is not unreasonable to imagine that information sits at the core of physics, just as it sits at the core of a computer.
>
> Trying to wrap my brain around this idea of information theory as the basis of existence, I came up with the phrase "it from bit." The universe and all that it contains ("it") may arise from the myriad yes-no choices of measurement (the "bits"). Niels Bohr wrestled for most of his life with the question of how acts of measurement (or "registration") may affect reality. It is registration – whether by a person or a device or a piece of mica (anything that can preserve a record) – that changes potentiality into actuality. I build only a little on the structure of Bohr's thinking when I suggest that we may never understand this strange thing, the quantum, until we understand how information may underlie reality. Information may not be just what we learn about the world. It may be what makes the world.

The last sentence reminded us of the Peircean metaphysics (described in Sect. 6.2) of Firstness (e.g., quality, feeling, and potentiality), Secondness (e.g., facts, actuality), and Thirdness (e.g., reason, knowledge, representation) (Peirce 1903), motivating me to suggest another triadic representation of reality as shown in Fig. 4.10:

The three aspects of reality appearing in Wheeler's dictum are shown in Fig. 4.11 as capitalized words and the texts related to them are identified as follows:

1. IS = "Information. . .may be what makes the world. . . "
2. MEASURED = ". . .the myriad yes-no choices of measurement. . ."
3. KNOWN = ". . .we understand how information may underlie reality. Information may not be just what we learn about the world . . ."

In Fig. 4.11, the content of Fig. 4.10 is re-displayed using the format of the triadic theory of reality (TTR) shown in Fig. 4.6. The similarity between Wheeler's

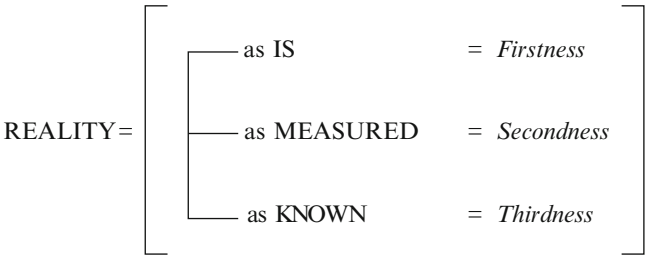


Fig. 4.10 An analysis of Wheeler's dictum "It from bit" based on the Peircean metaphysics

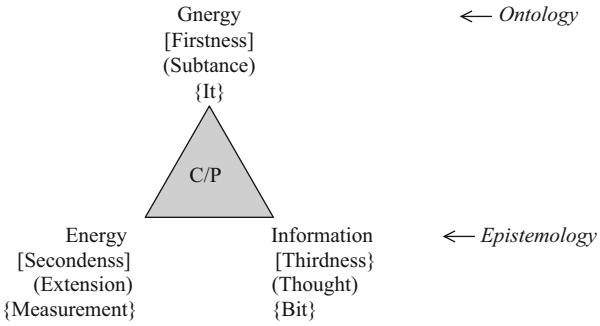


Fig. 4.11 A diagrammatic representation of complementarism (and the Spinozan metaphysics in parenthesis). Also displayed are Wheeler's "it" and "bit." The philosophical perspectives underlying this figure are complementarism (C) (described in Sect. 2.3.4) and Peircean metaphysics (P) (described in Sect. 6.2)

metaphysics (marked by {...}) and Peirce's metaphysics (marked by [...]) is striking in Fig. 4.11, leading to the following identifications of the nodes, which is consistent with Fig. 4.10:

If the speculation expressed in Fig. 4.10 is valid that there are three fundamental aspects to reality, then there must also be three categories of information to represent them, namely, the *information* about the REALITY AS IS, the *information* about the REALITY AS MEASURED or REGISTERED, and the *information* about the REALITY AS KNOWN to the community of *Homo sapiens* throughout the human history, which may be denoted as the *Firstness information, the Secondness information,* and the *Thirdness information*. If we denote these different types of informations as "1-I," "2-I," and "3-I," respectively, we can write information, I, as a combination of three components:

$$\mathrm{I} = (1-\mathrm{I})^{\wedge}(2-\mathrm{I})^{\wedge}(3-\mathrm{I}) \tag{4.40}$$

where the symbol ^ indicates a complementary relation. Equation 4.40 may be referred to as the "triadic theory of information" (TTI), which in turn may be regarded as the *information-theoretic version* of the triadic theory of reality (TTR) described in Fig. 4.6.

We can apply the complementarian logic (see Sect. 2.3.3) to Wheeler's "it from bit," leading to the following possible identities:

$$\begin{aligned} &1.\ \mathrm{A} = \text{Measurement} \\ &2.\ \mathrm{B} = \text{Bit, and} \\ &3.\ \mathrm{C} = \text{It.} \end{aligned} \tag{4.41}$$

If this set of identities is valid, it may be concluded that "it" cannot derive from "bit," because *it* transcends *bit* according to the Transcendentality criterion of the complementarian logic described in Sect. 2.3. To be consistent with the complementarian logic as applied to Identities 4.41, Wheeler's original dictum may need to be rephrased into one of the following expressions, which are admittedly not as poetic, but perhaps closer to truth, than Wheeler's original phrase:

$$''\text{It from Bit.}'' \Rightarrow ''\text{It as Gnergy.}'' \tag{4.42}$$

$$''\text{It is Gnergy.}'' \tag{4.43}$$

$$''\text{From It to Bit and Erg.}'' \tag{4.44}$$

$$''\text{Bit and Erg from It.}'' \tag{4.45}$$

where *erg* is the unit of (or represents) energy just as *bit* is the unit of (or represents) information.

Chapter 5
Engineering

5.1 Microelectronics

5.1.1 Enzymes as "Soft-State" Nanotransistors

Molecular and cell biologists may benefit conceptually from a generalized notion of *the transistor*, an abbreviated combination of "transconductance" and "resistance," that includes *any physical device that can activate a physicochemical process when energized.* Given such a generalization, we can readily recognize two distinct classes of transistors – (1) *artificial* transistors made out of *solid-state materials* and (2) *natural* transistors, that is, enzymes, made out of *deformable* (or *soft*) *heteropolymers* of amino acids, namely, proteins and polypeptides.

Solid-state transistors conduct electricity when energized by applied voltage, while *soft-state transistors* enable or cause chemical reactions to occur when energized by substrate binding (Ji 2006e; Jencks 1975). Just as transistors are the basic building blocks of the digital computer, so enzymes are the basic building blocks of the living cell, the smallest molecular computer in Nature (Ji 1999a). This provides a theoretical framework for comparing the properties of and the physical principles underlying solid-state transistors and enzymes (see Table 5.1). A similar table was discussed in NECSI Discussion Forum (Ji 2006e).

The content of Table 5.1 is mostly self-explanatory, but the following items deserve special attention:

1. *Process*. The process enabled by a solid-state transistor when energized is the flow of electrons through it. In contrast, the process enabled by an enzyme when energized is the flow of electrons from one atomic grouping to another within a given molecule (most often a substrate) or from one molecule to another (Row 1).
2. *Size*. The linear dimension of the cell is at least 10^3 times smaller than that of the digital computer, and this is reflected in the physical dimension of enzymes relative to that of typical transistors (see Row 2).

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_5,

Table 5.1 Enzymes as self-organizing soft-state nanotransistors. Important items are highlighted

	Solid-state transistor (artificial transistor)	Soft-state transistor (natural transistor)
1. Process	Conducts electricity when energized	Catalyzes chemical reactions when energized by substrate binding
2. **Size**	*Microns (10^{-6} m)*	*Nanometers (10^{-9} m)*
3. **Mechanical property**	*Rigid (thermally immobile)*	*Deformable/soft (thermally fluctuating)*
4. Field of study	Solid-state physics	"Soft-state physics," i.e., enzymology
5. **Mechanism of energization**	*Current or voltage applied to gate*	*Substrate-binding-induced activation* of conformational substates of Frauenfelder et al. (2001)
6. Terminals	Input (source, emitter)	Reactants
	Trigger (gate, base)	Enzyme
	Output (drain, collector)	Products
7. Electron flow	10^5 electrons per switching event (mega-electron transistor)	One electron per switching event (single-electron transistor)
8. **Component connection**	*Static and artificially organized (covalent bonds, 50–100 kcal/mol)*	*Dynamic and self-organizing (Sect. 3.1) (noncovalent bonds, 1–5 kcal/mol)*
9. **Mobile objects**	*Electrons*	*Molecules*
	Holes	*Ions*
	Phonons	*Conformons (Chap. 8)*
10. Number of units in a logical gate	~20	1 ~ 50
11. Number of units in a processor	$\sim 10^{11}$	$\sim 10^9$
12. **Behavior**	*Deterministic (binary, crisp logic)*	*Nondeterministic (multivalued, fuzzy logic)*

3. *Deformability*. Traditional transistors are rigid and large enough to resist the randomizing effects of thermal motions of the structural components of a transistor. Enzymes are flexible (i.e., soft) and small enough to undergo thermal fluctuations or Brownian motions that are essential for their functions (Ji 1974a, 1991) (Row 3). This is why enzymes can be viewed as "soft-state transistors," the study of which may be referred to as "soft-state physics" (e.g., enzymology) in contrast to solid-state physics. Examples of soft-state physics include the study of protein folding, single-molecule enzymology (Xie and Lu (1999); 2001), the informatics of biopolymers, and artificial polymers with mechanically activatable chemical moieties (Lenhardt et al. 2010).
4. *Self-organizing circuits*. Solid-state transistors are fabricated by humans, while soft-state transistors have resulted from spontaneous chemical reaction-diffusion processes or *self-organizing processes* (Prigogine 1977, 1980) selected by biological evolution. The principle of self-organization is rooted in (1) the dissipation of free energy and (2) the principle of structural complementarity as exemplified by the Watson-Crick base pairing and the enzyme-substrate complex

formation and applies not only to the interactions among the components of a soft-state transistor (Row 8) but also to the interactions among a set of soft-state transistors needed to construct logical gates and processors (Rows 10 and 11). In both intra- and inter-transistor interactions, solid-state transistors utilize strong, *covalent bonds* (50 ~ 100 kcal/mol), whereas soft-state transistors depend mainly on weak, *noncovalent bonds* (1–5 kcal/mol) (Row 8).

These weak interactions, coupled with the principle of structural complementarity, appear to be necessary and sufficient for the production, operation, and destruction (after their task is completed) of self-organizing biological circuits of soft-state transistors which then can be identified with hyperstructures and SOWAWN machines (Sect. 2.4) or bio-quantum dots (see Table 4.7).

5. *Logic*. The behavior of solid-state transistors are deterministic, obeying the Aristotelian or binary logic of the excluded middle. The behavior of a soft-state transistor, however, is nondeterministic and fuzzy (Sect. 4.6) (Ji 2004a) because of its structural deformability and thermal fluctuations, giving rise to not one but a range of rate constants per enzyme distributed nonrandomly (see the histogram of waiting times in Fig. 11.24) (Lu et al. 1998) (Row 12).

5.2 Computer Science

5.2.1 The Principle of Computational Equivalence and a New Kind of Science (NKS)

This principle proposed by Dr. Stephen Wolfram in 2002 states that all rule-governed processes, whether natural or artificial, can be viewed as *computations*. According to Wolfram (2002), it is possible to model any complex structure or phenomena in nature using simple computer programs (or algorithms) based on cellular automata that can be applied n times repeatedly (or recursively), where n ranges from 10^3 to 10^6. In other words, underlying all complex phenomena (including living processes), there may exist surprisingly simple sets of rules, the repetitive application of which inevitably leads to the complex phenomena or structures found in living systems. The following set of quotations from his book, *A New Kind of Science* (Wolfram 2002), illustrate his ideas:

> Three centuries ago science was transformed by the dramatic new idea that rules based on mathematical equations could be used to describe the natural world. My purpose in this book is to initiate another such transformation, and to introduce a new kind of science that is based on the much more general types of rules that can be embodied in simple computer programs. . . . If theoretical science is to be possible at all, then at some level the systems it studies must follow definite rules. Yet in the past throughout the exact science it has usually been assumed that these rules must be ones based on traditional mathematics. But the crucial realization that led me to develop the new kind of science in this book is that there is in fact no reason to think that systems like those we see in nature should follow only such traditional mathematical rules [p. 1]. (5.1)

When mathematics was introduced into science it provided for the first time an abstract framework in which scientific conclusions could be drawn without direct reference to physical reality. Yet, despite all its development over the past few thousand years, mathematics itself has continued to concentrate only on rather specific types of abstract systems – most often ones somehow derived from arithmetic or geometry. But the new kind of science that I describe in this book introduces what are in a sense much more general abstract systems, based on rules of essentially any type whatsoever.

One might have thought that such systems would be too diverse for meaningful general statements to be made about them. But the crucial idea that has allowed me to build a unified framework for the new kind of science that I describe in this book is that just as the rules for any system can be viewed as corresponding to a program, so also its behavior can be viewed as corresponding to a computation.

Traditional intuition might suggest that to do more sophisticated computations would always require more sophisticated underlying rules. But what launched the whole computer revolution is the remarkable fact that universal systems with fixed underlying rules can be built that can in effect perform any possible computation. . ..

But on the basis of many discoveries I have been led to a still more sweeping conclusion, summarized in what I call the Principle of Computational Equivalence (PCE): that whenever one sees behavior that is not obviously simple – in essentially any system – it can be thought of as corresponding to a computation of equivalent sophistication . . . it immediately gives a fundamental explanation for why simple programs can show behavior that seems to us complex. For like other processes our own processes of perception and analysis can be thought of as computation. But though we might have imagined that such computations would always be vastly more sophisticated than those performed by simple programs, the Principle of Computational Equivalence implies that they are not. And it is this equivalence between us as observers and the systems that we observe that makes the behavior of such system seem to us complex [pp. 4–6]. (5.2)

The key unifying idea that has allowed me to formulate the Principle of Computational Equivalence is a simple but immensely powerful one: that all processes, whether they are produced by human effort or occur spontaneously in nature, can be viewed as computations. . . . it is possible to think of any process that follows definite rules as being a computation – regardless of the kinds of elements it involves. . ..

So in particular this implies that it should be possible to think of processes in nature as computations. And indeed in the end the only unfamiliar aspect of this is that the rules such processes follow are defined not by some computer program that we as humans construct but rather by the basic laws of nature.

But whatever the details of the rules involved the crucial point is that it is possible to view every process that occurs in nature or elsewhere as a computation. And it is this remarkable uniformity that makes it possible to formulate a principle as broad and powerful as the Principle of Computational Equivalence. . .. For what the principle does is to assert that when viewed in computational terms there is a fundamental equivalence between many different kinds of processes. . .. [pp. 715–716]. (5.3)

[This statement is almost identical to the idea of universal computation advocated by S. Lloyd (2006).]

The traditional mathematical approach to science has historically had its great success in physics – and by now it has become almost universally assumed that any serious physical theory must be based on mathematical equations. Yet with this approach there are still many common physical phenomena about which physics has had remarkably little to say. But with the approach of thinking in terms of simple programs that I develop in this book it finally seems possible to make some dramatic progress. And indeed in the course of the book we will see that some extremely simple programs seem able to capture the essential

> mechanisms for a great many physical phenomena that have previously seemed completely mysterious [p.8]. (5.4)

> . . . traditional mathematical models have never seemed to come even close to capturing the kind of complexity we see in biology. But the discoveries in this book show that simple programs can produce a high level of complexity. And in fact it turns out that such programs can reproduce many features of biological systems – and seem to capture some of the essential mechanisms through which genetic programs manage to generate the actual biological forms we see. [p. 9]. (5.5)

> Over and over again we will see the same kind of thing: that even though the underlying rules for a system are simple, and even though the system is started from simple initial conditions, the behavior that the system shows can nevertheless be highly complex. And I will argue that it is this basic phenomenon that is ultimately responsible for most of the complexity that we see in nature. [p. 28]. (5.6)

> . . . intuitions from traditional science and mathematics have always tended to suggest that unless one adds all sorts of complications, most systems will never be able to exhibit any very relevant behavior. But the results so far in this book have shown that such intuition is far from correct, and that in reality even systems with extremely simple rules can give rise to behaviors of great complexity. [p. 110]. (5.7)

It may be asserted here that Statements (5.6) and (5.7) apply to biology. If so, these statements would represent the most important contributions that Wolfram has made to biology. Based on his numerous computer experiments, often involving millions of iterations of a set of simple rules applied to simple initial conditions, Wolfram concluded that complex structures can arise from simple programs. For example, he was able to simulate complex structures and processes such as the shapes of shells (Fig. 5.1) and trees and turbulence, using simple rules governing the behavior of cellular automata, from which he inferred that all complex structures and phenomena in nature can originate from recursive operations of sets of simple rules. The similarity between the computer-generated shell shapes and the real ones shown in Fig. 5.1 is striking and seems to provide credibility to Wolfram's assertions, i.e., Statements (5.1)–(5.7).

Although I do agree with Wolfram that his NKS does have the ability to represent or simulate certain complex phenomena in nature that could not even be approached using traditional mathematical tools, I suggest that both the traditional mathematics and NKS may still be subject to the constraints of the *cookie-cutter paradigm* described in Sect. 2.3.9. That is, no matter which model one adopts, either traditional mathematical or NKS, models always cut out only those aspects of reality that fit the model (i.e., the cookie cutter) and leave behind "holes" and the rest of in the dough that are beyond the capability of the models employed. We may depict this idea as shown in Fig. 5.2.

5.2.2 *Complexity, Emergence, and Information*

Ricard (2006) defines a complex system as a composite system whose properties or degrees of freedom cannot be predicted from those of its components. In other

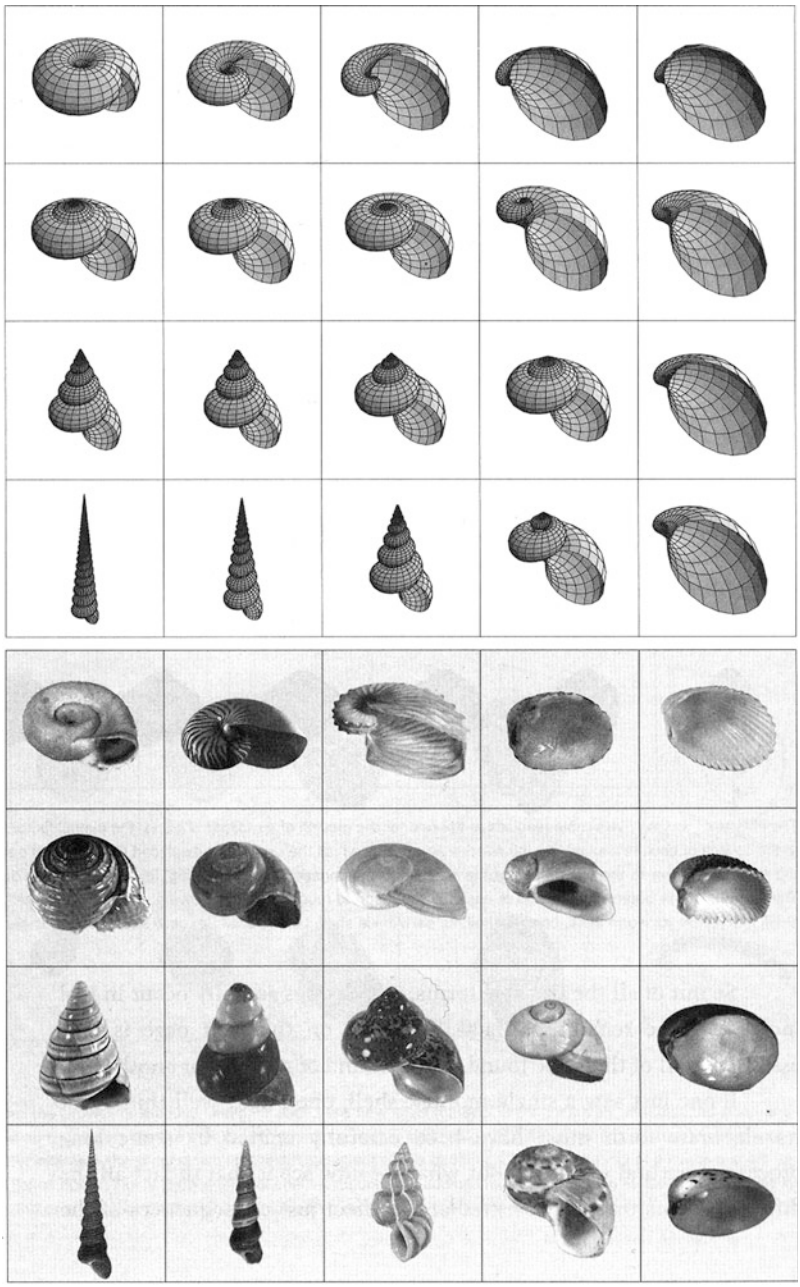


Fig. 5.1 Shell shapes generated by the simple cellular automaton models (see the *top four rows*) and found in nature (see *bottom four rows*). Two parameters are systematically changed: (**a**) the overall factor by which the size increases in the course of each revolution and (**b**) the relative amount by which the opening is displaced downward at each revolution (Reproduced from Wolfram 2002, p. 416. With permission)

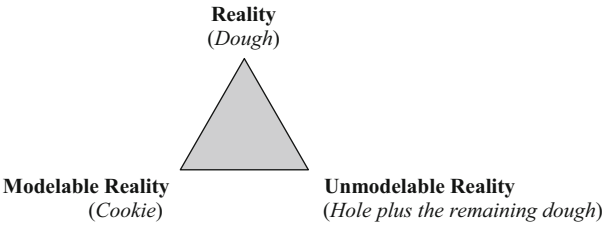


Fig. 5.2 Reality as the complementary union of the *modelable* and *unmodelable*

words, a complex system, according to Ricard, is a system that has "more potential wealth, or more degrees of freedom" than its component sub-systems or displays "properties that are emergent relative to those of the component sub-systems." He represents his idea formally as follows:

$$H(X, Y) > H(X) + H(Y) \tag{5.8}$$

where H(X,Y) is a mathematical function that describes the properties of a system XY made up of two sub-systems X and Y, and H(X) and H(Y) are the mathematical functions that describe the properties of X and Y, respectively. In short, the system XY is complex because its properties cannot be explained in terms of the sum of the properties of X and Y.

Since the concept of emergence is intrinsic to any complex system, according to Ricard, it would follow that the mechanisms of emergence would be synonymous with the mechanisms of complexification. So, Inequality 5.8 can be re-expressed using the concept of mechanisms:

$$X + Y \xrightarrow{\text{Mechanism}} XY \tag{5.9}$$

Thus, Process 5.9 can be viewed either as the mechanism of emergence or that of complexification.

One major difference between Inequality 5.8 and Process 5.9 may be that the former emphasizes the phenomenological and information-theoretic aspects, while the latter brings out the mechanisms and kinetic/dynamic aspects of the process of emergence and complexification that entails dissipation of free energy.

The terms, *complexity, emergence,* and *information*, frequently occur together in many contemporary discourses in natural, computer, and social sciences, but the relation among them appears not to have been clearly defined as yet, to the best of my knowledge. To rigorously define the relation among these terms, it may be helpful to utilize a table organized according to the triadic metaphysics of Firstness, Secondness, and Thirdness of C. S. Peirce (see Sect. 6.2) as shown in Table 5.2. The table is constructed on the basis of the assumption that *complexity* can be identified with Firstness, *emergence* with Secondness, and *information* with Thirdness.

Table 5.2 A Peircean triadic relation among complexity, emergence, and information suggested based on Peircean metaphysics. According to Peirce, all phenomena (or appearances) have three inseparably fused aspects termed Firstness (e.g., feeling, potentiality), Secondness (e.g., actuality, interactions), and Thirdness (e.g., relation, representation). The symbol "1" stands for the identity relation

	Firstness (Complexity)	Secondness (Emergence)	Thirdness (Information)
Complexity	1	Evolution	Subjective information (formal information, temperature-independent)
Emergence	Evolution	1	Objective information (physical information, temperature-dependent)
Information	Subjective information	Objective information	1

Table 5.2 is a 3 × 3 matrix which is symmetric with respect to the diagonal because the relation between any two elements of the table is commutative (e.g., the relation between complexity and information is the same as the relation between information and complexity). This leaves only three cells or relations in the interior of the table (out of the total of 3 × 3 = 9) left to be defined:

1. *Evolution* = It is the relation between *complexity* and *emergence*. Evolution refers to the *mechanism* by which certain properties of material entities are manifested both synchronically and diachronically (Sect. 4.5), which are novel relative to the properties of the interacting entities. In this view, what emerges may be thought to be not complexity but rather novelty, since complexity as the Firstness of Peirce is *intrinsic to reality itself*.
2. *Subjective information* = The information that depends on the workings of the human mind. For example, UV photons cannot carry any information to the human eye but can do so to the UV-sensing eyes of certain nonhuman brains. The historical information contained in the Bible is understood only by humans but not by nonhuman species and is furthermore temperature-independent. That is, raising the temperature of the Bible from room temperature by, say, 30°C would not change the biblical information content whereas the entropy content of the book will increase (see the "Bible test" described in Footnote c in Table 4.3).
3. *Objective information* = The information that exists independently of the human mind. Examples include the information encoded in the universal constants such as the speed of light and the electronic charge, the information encoded in the microstates of matter which is temperature-dependent to varying degrees.

One of the reasons for the difficulty in defining the three terms appearing on the margins of Table 5.2 may be traced to the fact that one of these terms, "information," occurs both on the *margins* and the *interior* of the table. What makes the situation even more difficult is the appearance of the two different kinds of information in the interior of the table – *Objective* and *Subjective* information. Thus, there are three different kinds of informations appearing in Table 5.2, reminiscent of the numerous

kinds of energies in physics – thermal, kinetic, potential, chemical, mechanical, nuclear, Gibbs free energy, and Helmholtz free energy, etc. Little confusion arises in distinguishing different kinds of energies in physics because of the availability of the principles of classical mechanics, quantum mechanics, statistical mechanics, and thermodynamics. To be able to differentiate among different kinds of information in biology, computer science, and philosophy on the one hand and between informations and energies on the other, it may be essential to utilize not only the laws and principles of physics and chemistry but also those of *semiotics*, the study of signs as developed by Peirce (1903) more than a century ago (see Sect. 6.2).

5.2.3 *Two Kinds of Complexities in Nature: Passive and Active*

We can recognize two kinds of "complexities" in nature – *active* and *passive*, in analogy to *active* and *passive* transport. For example, snowflakes (Fig. 5.3) exhibit *passive* complexity or complexification, while living cells (see the book cover) exhibit *active* complexity in addition to passive complexity. Unlike passive complexity, active complexity is exhibited by living systems utilizing free energy, and organisms with such a capability is thought to be more likely to survive *complex* environment than those with passive complexity only. According to the Law of Requisite Variety (LRV) (Sect. 5.3.2), no simple machines can perform complex tasks. Applying LRV to cells, it can be inferred that

No simple cells can survive complex environment. (5.10)

If this conjecture is true, it is not only to the advantage of cells (both as individuals and as a lineage) but also essential for their survival to complexify (i.e., increase the complexity of) their internal states.

One strategy cells appear to be using to complexify their internal states is to vary the amino acid sequences of a given enzyme or of the subunits of an enzyme complex such as ATP synthase and electron transfer complexes, each containing a dozen or more subunits. This strategy of increasing the complexity of sequences may be forced upon cells because they cannot increase, beyond some threshold imposed by their physical dimensions, the variety of the spatial configurations of the components within their small volumes. In other words, it is impossible to pack in more than, say 10^9, enzyme particles into the volume of the yeast cell, about 10^{15} m^3, but the yeast cells can increase the variety of their internal states by increasing the variety of the amino acid sequences of their enzymes and enzyme complexes almost without limit, as a simple combinatorial calculus would show. For example, there would be at least $2^{100} = 10^{33}$ different kinds of 100-amino acid-residue polypeptides if each position can be occupied by one of at least two different amino acid residues. This line of thought led me to infer that there may be a new principle operating in living systems, here referred to as the "Maximum

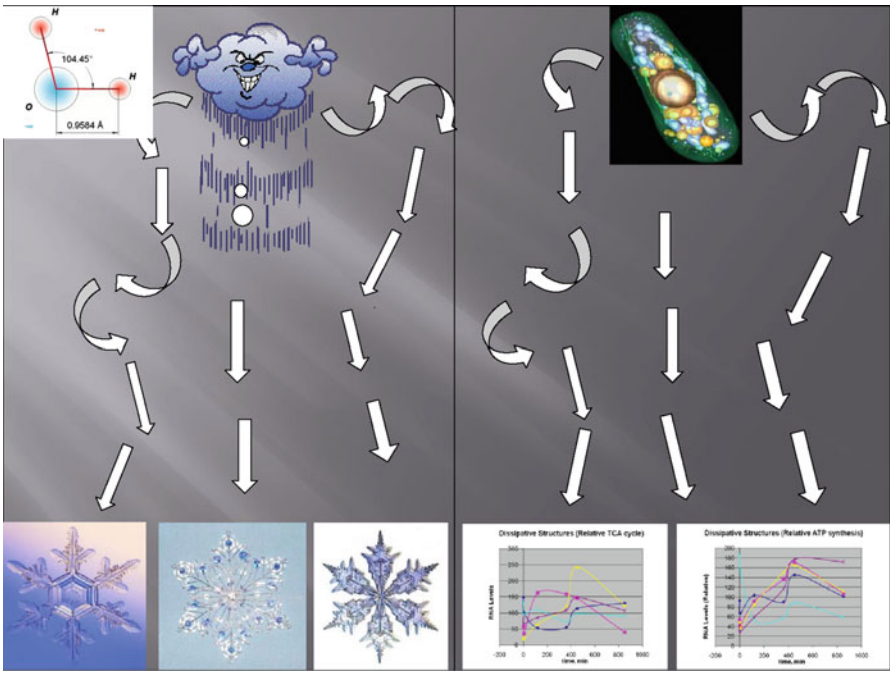


Fig. 5.3 Just as the shape of snowflakes reflect their trajectories through the atmosphere, so the different RNA trajectories measured from yeast cells are postulated to reflect the different microenvironmental conditions (see Fig. 12.28) under which RNA molecules are synthesized in the nucleus and degraded in the cytosol. Snowflakes are *equilibrium structures* or *equilibrons* whose sixfold symmetry are determined by the geometry of the water molecule, while RNA trajectories are *dissipative structures* or *dissipatons* (Sect. 3.1) whose shapes reflect the fact that cells are themselves *dissipative structures* maintaining their dynamic internal structures (including RNA trajectories) by continuously dissipating free energy. For the experimental details concerning the measurement of the RNA trajectories shown above, see Sect. 12.2 (Figure 5.3 was drawn by one of my undergraduate students, Ronak Shah, in April, 2009)

Variation Principle (MVP)" or the "Maximum Complexity Principle (MCP)," which states that:

> The variety of the internal states of living systems increases with evolutionary time. (5.11)

or

> The complexity of the internal states of living systems increase with evolutionary time. (5.12)

Statement (5.12) resembles that of the Second Law ("The entropy of an isolated system increases with time."), which may lead conflating MVP with the Second Law unless care is taken. MVP cannot be derived from the Second Law, because MVP embodies the evolutionary trajectories (or contingencies) of living systems (i.e., slowly changing environmental variations encountered by rapidly changing

short-lived organisms during evolution) just as the shapes of snowflakes (see Fig. 5.3) cannot be derived or predicted from the Second Law because these embody the trajectories (or a series of boundary conditions of Polanyi 1968) traversed by incipient snowflakes through the atmosphere, the information about which being lost to the past, except whatever is recorded in snowflakes.

Although all snowflakes exhibit a sixfold symmetry due to the unique structure of the water molecule (see the lower panels in Fig. 5.3), no two snowflakes look alike, and this phenomenon has now been well understood as the result of experimental works on artificial snowflakes produced in laboratories (see Sect. 15.1) (Libbrecht 2008): No two snowflakes look alike because no two snowflakes traverse the same trajectories from the atmosphere to the ground as they evolve from the incipient clusters of a few water molecules formed high up in the atmosphere to the final macroscopic snowflakes seen on the ground (see the left-hand panel in Fig. 5.3). Similarly, no two RNA trajectories measured from the yeast cell undergoing the glucose-galactose shift look exactly alike (see the bottom of the right-hand panel in Fig. 5.3), most likely because (1) no two RNA polymerases inside the nucleus and (2) no two RNA molecules in the cytosol experience identical microenvironments (see the RNA localizations in Drosophila embryios, Fig. 15.3). Consequently, no two RNA molecules are associated with identical rates of production (through transcription) and degradation (catalyzed by RNases or ribonucleases). In analogy to the sixfold symmetry exhibited by all snowflakes reflecting the geometry of the water molecule, all RNA trajectories share a common feature of being above the zero concentration levels reflecting the fact that the yeast cell is a dissipative structure, continuously dissipating free energy to maintain its dynamic internal structures, including RNA trajectories. Most of the discussions on complexity in the past several decades in the field of computer science and physics concern "passive complexity," which was taken over by biologists *apparently* without realizing that living systems may exhibit a totally new kind of complexity here dubbed "active complexity." The time- and space-dependent heterogeneous distributions of RNA molecules observed in developing *Drosophila* embryo (Fig. 15.1) provide a prototypical example of "active complexity," since depriving energy supply to the embryo would certainly abolish most of the heterogeneous RNA distributions.

5.2.4 *The Principle of Recursivity*

A "recursive definition," also called "inductive definition," defines something partly in terms of itself, that is, *recursively*. A clear example of this is the definition of the Fibonacci sequence:

$$\mathrm{F(n)} = \mathrm{F(n-1)} + \mathrm{F(n-2)} = 1, 1, 2, 3, 5, , \quad \text{.....} \quad (5.13)$$

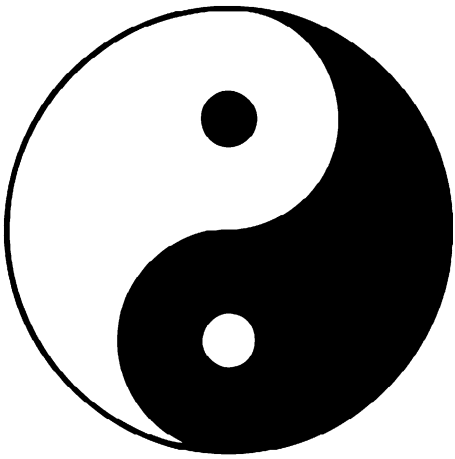


Fig. 5.4 The Yin-Yang symbol visualizing the concept of *embeddedness* (i.e., the *black dot* in the *white background*, and the *white dot* in the *black background*) and the *intertwining* (between the *white* and *black tear-drop* shapes) http://commons.wikimedia.org/wiki/File:Yin_yang.svg

where n is a natural number greater than or equal to 2. As can be seen, Eq. 5.13 defines the (n + 1)th Fibonacci number in terms of two previous Fibonacci numbers. A linguistic example of recursivity is provided by the acronym GNU whose definition implicates itself: "GNU is not Unix." A biological example of *recursivity* may be suggested to be the self-relication of the DNA double helix, since it implicates replicating the DNA double helix using the original DNA as the template: Self-replication of the DNA double helix is *self-referential*, or *recursive*. The growth of an organism from a fertilized egg cell can be viewed as recursive process in the sense that the fertilized egg serves as a template to form its daughter cell, the daughter cell in turn serving as the template for the production of the next generation cell, etc. The cell division is recursive or results from a series of recursive actions. On the basis of these analyses, it may be concluded that life itself is recursive.

Many physical, chemical, biological, engineering, and logical principles are mutually *inclusive* and *intertwined* in the sense that it is impossible to separate them completely. This principle is represented in the familiar Yin-Yang symbol of the Taoist philosophy (Fig. 5.4): The dot of the Yin (dark) is embedded in the sea of the Yang (light) and the dot of the Yang is embedded in the sea of the Yin. The embeddedness of the Yin in Yang (and vice versa) is reminiscent of the embeddedness of a sentence within a sentence in human language or the embeddedness of an algorithm within an algorithm in computer programming, both of which exemplify the *recursivity* (or the recursion and self-similarity) widely discussed in computer science (Hofstadter 1980).

The complementarity principle of Bohr seems to embody the principle of recursivity as the following argument shows. As is well known, Bohr in 1947 inscribed on his coat of arms the following motto:

Contraria sunt complementa. or (5.14)

Contraries are complementary. (5.15)

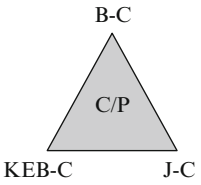


Fig. 5.5 A diagrammatic representation of the complementarity of complementarities, or the "recursive complementarity"

It is interesting to note that Statement 5.15 can be interpreted as either of the following two contrary statements, P and not-P:

All contraries are complementary. (5.16)

Not all contraries are complementary. (5.17)

Statement 5.17 is synonymous with 5.18:

Only some contraries are complementary. (5.18)

Statement 5.16 reflects the views of Kelso and EngstrØm (2006) and Barab (2010) who list over 100 so-called complementary pairs in their books. I favor Statements (5.17) and (5.18) based on the complementarian logic discussed in Sect. 2.3.3.

Since 5.16 and 5.17 are contraries, they must be COMPLEMENTARY to each other according to 5.15. That is, defining the relation between 5.16 and 5.17 as being complementary entails using Statement 5.15. This, I suggest, is an example of "recursive definition," similar to the definition of the Fibonacci sequence 5.13. To rationalize this conclusion, it appears necessary to recognize the three definitions of complementarities as shown below (where B, KE, and J stand for Bohr, Kelso and Engstrom, and Ji, respectively):

B-Complementarity (B-C) = Contraries are complementary. (5.19)

KEB-Complementarity (KEB-C) = All contraries are complementary. (5.20)

J-Complementarity (J-C) = Not all contraries are complementary. (5.21)

Since, depending on whether or not the complementarian logic is employed, the B-complementarity can give rise to either the KEB-or the J-complementarity, respectively, it appears logical to conclude that the KEB- and J-complementarities are themselves the complementary aspects of the B-complementarity. This idea can be represented diagrammatically as shown in Fig. 5.5.

After formulating the idea of the "recursivity of complementarity," I was curious to find out if anyone else had a similar idea. When I googled the quoted phrase, I was surprised to find that Sawada and Caley (1993) published a paper entitled "Complementarity: A Recursive Revision Appropriate to Human Science." This paper may be viewed as an indirect support for the conclusion depicted in Fig. 5.5. However, upon further scrutiny, there is an important difference between the perspective of Sawada and Caley (1993) and mine: Sawada and Caley believe that, in order to introduce the idea of recursivity to complementarity, Bohr's original complementarity must be revised (by taking the observer into account explicitly). In contrast, my view is that Bohr's original complementarity is

intrinsically recursive, due to its ability to generate two contrary statements, P and not-P, that is, Statements 5.16 and 5.17.

Finally, it should be pointed out that, if not all contraries are complementary (as I originally thought in contrast to the views of Kelso and EngstrØm (2006) and Barab (2010)), there must be at least one other relation operating between contraries. In fact, there may be at least three noncomplementary relations operating between contraries:

1. SUPPLEMENTARITY = C is the sum of A and B (e.g., energy and matter).
2. DUALITY = A and B are separate entities on an equal footing (e.g., Descartes' *res cogitans* and *res extensa*).
3. SYNONYMY = A and B are the same entity with two different labels or names (e.g., Substance and God in Spinoza's philosophy; the Tao and the Supreme Ultimate in Lao-Tzu's philosophy).

5.2.5 *Fuzzy Logic*

There are two kinds of logic – *classical* (also called Aristotelian, binary, or Boolean) *logic* where the truth value of a statement can only be either *crisp* yes (1) or no (0), and *multivalued logic* where the degree of truthfulness of a statement can be *vague or fuzzy* and assume three or more values (e.g., 0, 0.5, and 1). Fuzzy logic is a form of multivalued logic based on fuzzy set theory and deals with approximate and imprecise reasoning. In fuzzy set theory, the set membership values (i.e., the degree to which an object belongs to a given set) can range between 0 and 1 unlike in crisp set where the membership value is either 0 or 1. In fuzzy logic, the truth value of a statement can range continuously between 0 and 1. The concept of fuzziness in human reasoning can be traced back to Buddha, Lao-tze, Peirce, Russell, Lukasiewicz, Black, Wilkinson (1963), and others (Kosko 1993; McNeill and Freiberger 1993), but it was Lotfi Zadeh who axiomatized fuzzy logic in the mid-1960s (Zadeh 1965, 1995, 1996a).

Variables in mathematics usually take numerical values, but, in fuzzy logic, the non-numeric *linguistic variables* are often used to express rules and facts (Zadeh 1996b). Linguistic variables such as age (or temperature) can have a value such as young (warm) or old (cold). A typical example of how a linguistic variable is used in fuzzy logic is diagrammatically illustrated in Fig. 5.6.

5.2.6 *Fuzzy Logic and Bohr's Complementarity*

In Sect. 5.2.4, it was shown that the principle of Bohr's complementarity embodies the principle of recursivity as well, which may be seen as an example of the *intertwining among principles* as symbolized by the dark and white objects in the Yin-Yang diagram (Fig. 5.4). Bohr's complementarity exhibits fuzziness.

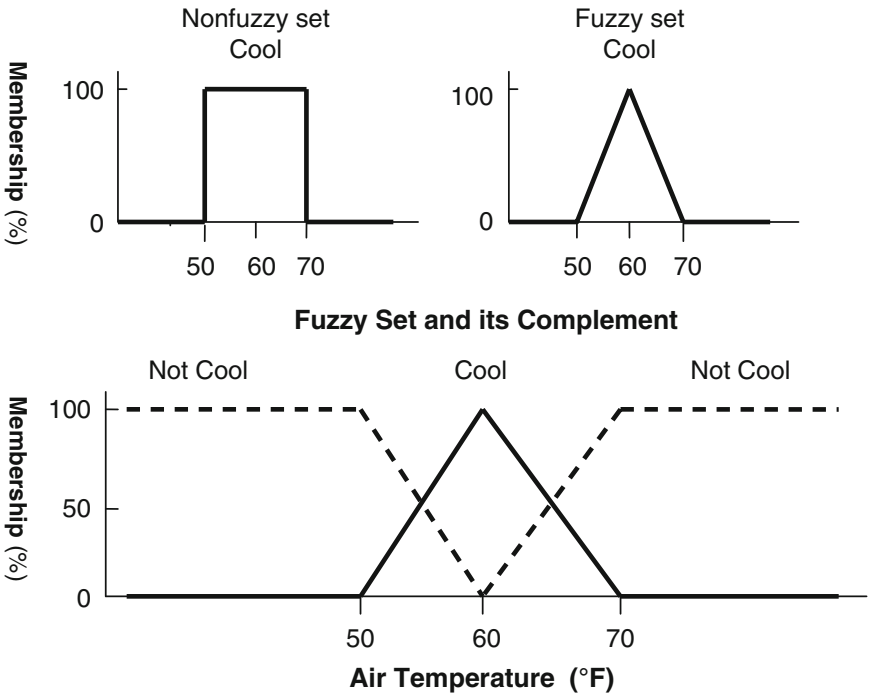


Fig. 5.6 Diagrammatic representations of *binary logic* and *fuzzy logic*. In standard logic, objects belong to a set completely (100%) or not at all (0 %) (see *top left*). In fuzzy logic, objects belong to a fuzzy set only to some degree (*top right*) and to the complement of the set to some other extent (*bottom*), the sum of the partial memberships always summing up to unity. For example, the air temperature of 50°F is 0% cool and 100% not cool; 55°F is 50% cool and 50% not cool; 60°F is 100% cool and 0% not cool; 65°F is 50% cool and 50% not cool; and 70°F is 0% cool and 100% not cool

According to fuzzy/vague/multivalence theorists, including Peirce, Russell, Black, Lukasiewicz, Zadeh, and Kosko (1993), words are fuzzy sets. The word "young" is an example of the fuzzy set. I am neither "young" (0) or old (1) but both young (to a degree of say 0.2) and old (to a degree of say 0.8). In other words I am both "young" and "not-young" (i.e., old) at the same time to certain degrees. Similarly, it can be suggested that the word "complementary" or "complementarity" is also a fuzzy set, since what is complementary to some scholars may not be complementary to others. For example, Kelso and EngstrØm list hundreds of complementary pairs in their book, *The Complementary Nature* (2006). Although their complementary pairs do satisfy Bohr's definition of complementarity, Statement (5.16), they certainly do not satisfy the definition of complementarity given in Sect. 2.3.3, which is based on three criteria of the complementarian logic:

1. *Exclusivity* (A and B are mutually exclusive)
2. *Essentiality* (A and B are both essential to account for C)
3. *Transcendentality* (C transcends the level where A and B have meanings)

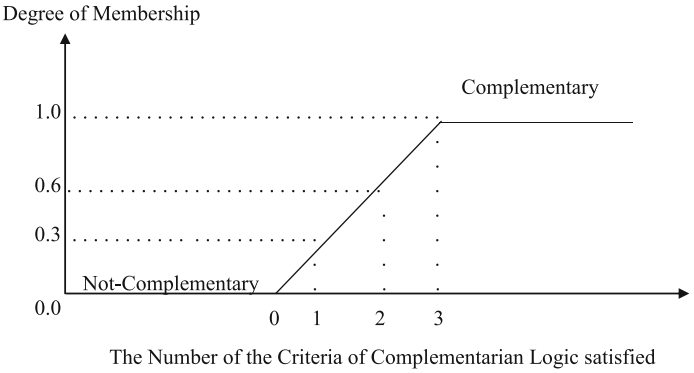


Fig. 5.7 The concept of complementarity as a fuzzy set

Table 5.3 Some examples of the complementary pairs of Kelso and EngstrØm whose degree of complementarity has been calculated on the basis of the three criteria of the complementarian logic discussed in Sect. 2.3.3 (These calculations are somewhat subjective)

Complementary pairs of Kelso and EngstrØm	Criteria of the complementarian logic			Degree of complementarity
	Exclusivity	Essentiality	Transcendentality	
Wave ~ particle	+	+	+	1.0
Information ~ energy	+	+	+	1.0
Energy ~ matter	−	+	−	0.3
Energy ~ time	+	+	−	0.6
Space ~ time	+	+	+	1.0
Mind ~ body	+	+	+	1.0
Object ~ subject	+	+	+	1.0
Abrupt ~ gradual	−	+	−	0.3
Even ~ odd	−	+	−	0.3
Perception ~ action	−	+	−	0.3
Vitalism ~ mechanism	+	−	+	0.6

Thus, some of the complementary pairs of Kelso and EngstrØm satisfy only one and some two of the above three criteria, and only a small number of them satisfy all of the three criteria. We may designate these complementary pairs as the 0-, 0.3-, 0.6-, and 1.0- complementary pairs, respectively, the fractions indicating the degree of membership to the complementary set (see the dotted lines in Fig. 5.7) calculated as the ratio of the number of the criteria satisfied over the total number of the criteria. Some examples of complementary pairs having different degrees of complementarities are listed in Table 5.3.

5.2.7 The Knowledge Uncertainty Principle (KUP)

The first line of the Taoist text, The Lao-Tze, states that

The Tao, once expressed, is no longer the permanent Tao. (5.22)

Table 5.4 The question and answer (QA) matrix. 1 = Yes; 0 = No

Answers	Binary questions				
	1	2	3	...	N
1	0	1	1	...	0
2	0	0	1	...	1
3	1	0	0	...	0
.	.	.	.	.	.
.	.	.	.	.	.
.	.	.	.	.	.
2^N	0.	0	0	...	1

which in Chinese can be written with just six characters that read in Korean thus:

Doh Gah Doh, Bee Sahng Doh.

We may refer to Statement 5.22 as the "Principle of Ineffability," probably one of the most important principles of the Taoist philosophy.

The purpose of this section is to formulate an "algebraic geometric" version of the Principle of Ineffability, which will be referred to as the "Knowledge Uncertainty Principle (KUP)" in analogy to the Heisenberg Uncertainty Principle (HUP) in quantum mechanics. For the purpose of the present discussion, I will differentiate "knowledge" from "information" as follows: *Knowledge* refers to actuality and *information* to potentiality, just as physicists differentiate between the probability wave function Ψ symbolizing "possible information" and its square Ψ^2 referring to measured information or probability (Herbert 1987; Morrison 1990). It may well turn out that KUP subsumes HUP as suggested by Kosko (1993). The KUP is based on the following considerations:

1. All human knowledge (including scientific knowledge) can be represented as sets of answers to N binary questions (i.e., questions with *yes* or *no* answers only), where N is the number of questions that defines the universe of discourse or the system plus its environment under observation/measurement. This resonates with Wheeler's "It from bit" thesis (1990) that *information* is as fundamental to physics as it is for computer science and that humans participate in producing all scientific information by acquiring the *apparatus-elicited answers* to yes-or-no questions as in *the game of 20 questions* (Sect. 4.15). Recently Frieden (2004) has claimed that all major scientific laws can be derived from maximizing the Fisher information of experimental data.
2. As shown in Table 5.4, each answer in (1) can be represented as a string of N 0's and 1's, for example (0, 1, 1, . . ., 0) for Answer #1, and (1, 0, 0, . . ., 0) for Answer #3, etc.
3. There will be a total of 2^N *N-bit strings* as the possible answers to a set of N questions (see the last row in Table 5.4).
4. The *N-bit strings* in Table 5.4 can be represented geometrically as the vertices of an N-dimensional hypercube (Kosko 1993, p. 30). An N-dimensional hypercube is a generalization of an ordinary cube which can be viewed as a

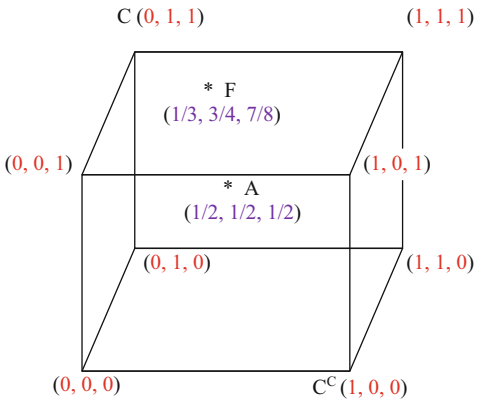


Fig. 5.8 A three-dimensional hypercube. One of the eight vertices is arbitrarily located at the origin (0, 0, 0) of the (x, y, i) coordinate system. Point A denotes the center of the hypercube. The closest vertex to point F is C(0, 1, 1), whose complement is vertex C^C(1, 0, 0)

three-dimensional hypercube (see Fig. 5.8). A square (e.g., one of the six aspects of a cube) can be treated as a two-dimensional hypercube. To generate a cube from a square, it is necessary only to move a square in a new direction (i.e., along the z-axis) perpendicular to the preexisting axes, the x- and y-axes in the case of a square. This operation can be repeated to generate an N-dimensional hypercube from an (N − 1)-dimensional one, where N can be any arbitrarily large number.

5. According to the principle of excluded middle, also called *the Aristotelian logic* or *crisp logic* (McNeill and Freiberger 1993; Kosko 1993), an answer is either true (1) or false (0), and no answer can have any truth values intermediate between 0 and 1. That is, no "crisp" answer can reside in the interior or on the edges of the hypercube, only on the vertices.
6. In contrast, the theory of fuzzy sets or the fuzzy logic (Zadeh 1965, 1995, 1996a, b; Kosko 1993) allows the truth value of an answer to be any positive number between 0 and 1, inclusive. For example, an answer with a truth value (i.e., the degree of membership to a set of true answers) of 3/4 is more true (1) than false (0); an answer with a truth value of 1/2 is both true and not-true at the same time, etc. The unit of fractional truth values is referred to as "fits" or "fuzzy units" (Kosko 1993).
7. Based on (5) and (6), we can conclude that "crisp" answers (expressed in bits) reside at the vertices or nodes of an N-dimensional hypercube, while fuzzy or vague answers (expressed in fits) reside in the interior or on the edges of the N-dimensional hypercube. For example, a fuzzy answer with a truth value of (1/2, 1/2, 1/2) will be found at the center of the cube (see point A in Fig. 5.8), whereas a fuzzy answer with truth value of (1/3, 3/4, 7/8) will be located at point F in Fig. 5.8.
8. It is postulated here that when the human mind is challenged with a set of N questions, it generates a fuzzy answer (say, F in Fig. 5.8) *unconsciously* (guided by intuition and previous experience), but, in order to communicate (or articulate) it to others, the human mind *consciously* search for the *nearest vertex*, say (0, 1, 1) in Fig. 5.8. Thus, *articulated* or *represented* crisp answers can be

assigned degrees of *truthfulness* or *certainty* measured as a ratio of two numbers, that is, D_1/D_2, where D_1 is the distance between the fuzzy answer (located at coordinate F) in the N-dimensional hypercube and its nearest vertex located at C and D_2 is the distance between F and the vertex, C^C, that is irreconcilably opposite to C. (C^C is called the *complement* of C.) The bit values of crisp C^C are obtained by subtracting the corresponding bit values of C from 1. For example, the complement of C(1, 0, 1) is C^C (1-1, 1-0, 1-1), or C^C (0, 1, 0). The distance, D_{AB}, between the two points, A ($a_1, a_2, a_3, \ldots, a_k$) and B ($b_1, b_2, b_3, \ldots, b_k$), can be calculated using the Pythagorean theorem:

$$D_{AB} = \left[(a_1 - b_1)^2 + (a_2 - b_2)^2 + (a_3 - b_3)^2 + ..., + (a_k - b_k)^2\right]^{1/2} \quad (5.23)$$

Applying Eq. 5.23 to points C and F, and C^C and F in Fig. 5.8, the ratio of D_1 over D_2 can be calculated, which Kosko referred to as *fuzzy entropy* (Kosko 1993, pp. 126–135), one of many fuzzy entropies defined in the literature. For convenience, we will refer this ratio as the *Kosko entropy*, denoted by S_K, in recognition of Kosko's contribution to the science of fuzzy logic. S_K now joins the list of other well-known *entropies* in physics and mathematics – the Clausius (which may be denoted as S_C), Boltzmann (as S_B), Shannon (as S_S), Tsalis entropies (as S_T), etc. The Kosko entropy of a fuzzy answer is then given by:

$$S_K = D_{CF}/D_{FC}{}^c \quad (5.24)$$

where D_{CF} is the distance between crisp point C and fuzzy point F and $D_{FC}{}^c$ is the distance between crisp point C^C and fuzzy point F. Formally, Eq. 5.24 constrains the numerical values of S_K to the range between 0 and 1:

$$1 \geq S_K \geq 0 \quad (5.25)$$

However, both the Principle of Ineffability, Statement 5.22, and the Einstein's Uncertainty Thesis, Statement 5.38 (see below), strongly indicate that S_K cannot be equal to 1 or to 0, leading to Inequality 2.26:

$$1 > S_K > 0 \quad (5.26)$$

According to Inequality 5.26, the maximum value of S_K is less than 1 and its minimum value is greater than 0. If we designate the minimum uncertainty that no human knowledge can avoid with *u* (from uncertainty) in analogy to the Planck constant *h* below which no *action* (i.e., the energy integrated over time) can exist, Inequality 5.26 can be rewritten as:

$$1 > S_K \geq u \quad (5.27)$$

where u is a positive number whose numerical values probably depend on the measurement system involved.

9. The Kosko entropy of fuzzy answer F in Eq. 5.28 is given by:

$$\begin{aligned} S_K(F) &= \left[(0-1/3)^2+(1-3/4)^2+(1-7/8)^2\right]^{1/2} / \left[(1-1/3)^2+(0-3/4)^2 \right. \\ &\qquad \left. +(0-7/8)^2\right]^{1/2} \\ &= \left[(2/3)^2+(1/4)^2+(1/8)^2\right]^{1/2} / \left[(2/3)^2+(-3/4)^2+(-7/8)^2\right]^{1/2} \\ &= [4/9+1/16+1/64]^{1/2} / [4/9+9/16+49/64]^{1/2} \\ &= [0.4444+0.0625+0.016] / [0.4444+0.5625+0.7656] \\ &= 0.5229/1.7725 \\ &= 0.2950 \end{aligned} \tag{5.28}$$

10. As evident in (8) and (9), it is possible to calculate the numerical value of the *Kosko entropy* of any fuzzy answer F, $S_K(F)$. But what is the meaning of $S_K(F)$? It is here suggested that the Kosko entropy, S_K, of fuzzy answer F is a *quantitative measure of the uncertainty* that F is C (or C is F, for that matter). By multiplying $S_K(F)$ with 100, we can express this uncertainty in the unit of %:

$$S_K(F) \times 100 = \text{ The percent uncertainty that F is C (or C is F)} \tag{5.29}$$

Applying Eq. 5.29 to the result in Eq. 5.28, we can conclude that

It is 29.5% certain that fuzzy answer located at (1/3, 3/4, 7/8) is equivalent to (and hence can be represented by) the crisp answer located at (0, 1, 1). (5.30)

If we assume that

All crisp answers are approximations of their closest fuzzy answers (5.31)

we can reexpress Statement 5.30 as follows:

The uncertainty of crisp answer C (0,1,1) is (100 - 29.5) = 70.5 %. (5.32)

11. Statements 5.31 and 5.32 would gain a strong support if we can associate the interior of the N-dimensional hypercube defined in Table 5.4 with *reality* or the source of the apparatus-elicited answers of Wheeler (1990) and its vertices with possible, theoretical, or represented answers. The apparatus-elicited answers may have two aspects – the "registered" aspect when artificial apparatuses are employed and "experienced" aspect when living systems are involved as measuring agents. Frieden (2004) associates the former with *Fisher information* (I) and the latter with what he refers to as "bound information" (J), that is, the algorithmic information needed to characterize the "source effects" that underlie registered data or crisp answers. In the case of Frieden (2004), it seems clear that the registered answers (carrying Fisher information, I) belong to the vertices of the N-dimensional hypercube and the "experienced" answers or

"bound information," J, belong to the interior of the N-dimensional hypercube. If these identifications are correct, the following generalizations would follow:

All crisp answers are uncertain. (5.33)

All crisp answers have non-zero Kosko entropies. (5.34)

No crisp answers can be complete. (5.35)

Reality cannot be completely represented. (5.36)

The ultimate reality is ineffable. (5.37)

12. Einstein stated (cited, e.g., in Kosko 1993, p. 29) that

As far as the laws of mathematics refer to reality, they are not certain; and as far as they are certain, they do not refer to reality. (5.38)

Since Statement 5.38 is very often cited by physicists and seems to embody truth, it deserves to be given a name. I here take the liberty of referring to Statement 5.38 as the *Einstein's Uncertainty Thesis* (EUT).

EUT can be accommodated by the Knowledge Uncertainty Principle (KUP) as expressed in Statements 5.33–5.38, if *we identify the volume or the interior of the N-dimensional hypercube with "reality"* as already alluded to in (11) *and its surface (*i.e.*, some of its vertices) as the "laws of mathematics"*. Again, we may locate crisp articulations of all sorts (including mathematical laws and logical deductions) on the vertices of the N-dimensional hypercube and the "ineffable reality" in the interior or on the edges of the hypercube. If this interpretation is correct, at least for some universes of discourse, we may have here a possible *algebraic-geometric (or geometro-algebraic) rationale* for referring to the *N-dimensional hypercube* defined in Table 5.4 as the "reality hypercube (RH)" or as "a N-dimensional geometric representation of reality," and Inequality 5.27 and Statement 5.38 as the keystones of a new theory that may be called the "Algebraic Geometric Theory of Reality (AGTR)." It is hoped that RH and AGTR will find useful applications in all fields of inquiries where uncertainties play an important role, including not only physics (see (13) below) but also biology, cognitive neuroscience, risk assessment, pharmacology and medicine (see Chap. 20), epistemology, and philosophy, by providing an objective and visual theoretical framework for reasoning.

13. The wave-particle duality of light (see Sect. 2.3.1) served as a model of the complementarity pair in the construction of the philosophy of complementarity by N. Bohr in the mid-1920s (Plotnitsky 2006; Bacciagaluppi and Valenti 2009), although it was later replaced with the more general "kinematics-dynamics complementarity pair" (Murdoch 1987). Assuming that the wave-particle duality of light embodies an uncertainty principle (in addition to a complementarity principle to a certain degree), it will be analyzed based on the KUP, Eq. 5.29. The analysis involves the following steps:

    1. *Classical concepts*: The concepts of *waves* and *particles* have been well established in human language, having developed over thousands of years as a means to facilitate communication among humans about physical processes.

Table 5.5 The QA matrix for the wave-particle duality of light. N = the number of questions

Possible answers (N^2)	Binary questions (N = 2)	
	1	2
[1]	0	0
[2]	0	1
[3]	1	0
[4]	1	1

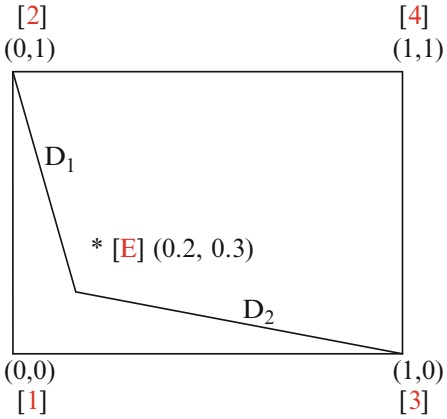


Fig. 5.9 The *N*-dimensional hypercube (where $N = 2$) representation of the QA matrix concerning the wave-particle duality of light

2. *Observations*: Light has been found to exhibit the dual properties of both waves and particles, depending on the measuring apparatus employed, which cannot be readily combined into one picture.
3. *Binary questions*: The paradoxical observation in (2) can be summarized in the form of two binary questions.

   Is light wave ? Yes = 1, No = 0
   Is light a particle? Yes = 1, No = 0

4. *The QA matrix*: The binary questions (Qs) have a finite number of possible answers (As) suggested by existing knowledge which can be represented as a QA matrix defined in (**2**) (Table 5.5).
5. *N-Dimensional hypercube*: The QA matrix can be transformed into an N-dimensional hypercube (Fig. 5.9), where N is the number of the binary questions related to the wave-particle duality of light. That is, the QA matrix and its associated N-dimensional hypercube are *isomorphic* in the sense that they obey the same set of common logical principles, including the principle of fuzzy logic (Kosko 1993).
6. *Apparatus-elicited answers (AEAs)*: To choose among the theoretically possible answers, experiments are designed and carried out to register AEAs, that is, the answers provided by nature (including the observer which, with Bohr, is thought to comprise a part of the experimental

arrangement and the registering device). Three AEAs are indicated in Fig. 5.9, two of which are well established and the third is hypothetical:

Photoelectric experiment = [2]
Two-slit experiment = [3]
A novel experiment = [E] (0.2, 0.3).

7. Kosko entropy, S_K: The Kosko entropy, defined in (**8**) above, of the fuzzy answer [E] can be calculated from the coordinates given in the two-dimensional hypercube, Fig. 5.9:

$$\begin{aligned} S_K(E) &= D_1/D_2 \\ &= \left\{(0-0.2)^2+(1-0.3)^2\right\}^{1/2} / \left\{(1-0.2)^2+(00.3)^2\right\}^{1/2} \\ &= \left\{4\times10^{-2}+49\times10^{-2}\right\}^{1/2} / \left\{64\times10^{-2}+9\times10^{-2}\right\}^{1/2} \\ &= (0.53^{1/2})/(0.73^{1/2}) \\ &= 0.726^{1/2} = 0.852 \end{aligned} \tag{5.39}$$

8. *Uncertainties of crisp (or nonfuzzy) statements*: Applying Eq. 5.29 to crisp answers [2] and [3], the associated uncertainties, defined in (**10**), can be calculated as:

$$S_K([2]) \times 100 = 0.85 \times 100 = 85\% \tag{5.40}$$

$$S_K([3]) \times 100 = (1-0.85) \times 100 = 15\% \tag{5.41}$$

Equations 5.40 and 5.41 indicate that crisp answers [2] and [3] are 85% and 15% uncertain, respectively, relative to the apparatus-elicited answer [E].

Applying Eq. 5.29 to the Airy experiment (AE) (Herbert 1987, pp. 62–63), two calculations are possible:

The Airy pattern is an experimental evidence that light is both waves and particles, that is, crisp answer [4] (1, 1), supporting the de Broglie equation, $\lambda = h/p$:

$$S_K([4]) = 0 \tag{5.42}$$

$$\text{Uncertainty } ([4]) = 0\% \tag{5.43}$$

The Airy pattern demonstrates that light is particles when observed over a short time period and waves when observed over a long period of time:

$$\begin{aligned} S_K(AE) &= 1, \text{ since } D_1 = D_2, \text{ and Uncertainty } = S_K(AE) \times 100 \\ &= 1 \times 100 = 100\% \end{aligned} \tag{5.44}$$

Equation 5.44 indicates that the Airy experimental result is 100% uncertain as to whether light is wave or a particle. In other words, the crisp answers [2], [3], and [4] are all 100% uncertain with respect to the question whether they are true relative to the Airy experimental data.

14. In Sect. 2.3.4, the logical relation between the HUP and Bohr's Complementarity Principle (BCP) was substantially clarified based on a geometric argument which may be viewed as a species of the so-called *table method* (Ji 1991, pp. 8–13). The result is that

The HUP presupposes Bohr's complementarity principle (BCP) and BCP can give rise to uncertainty principles including HUP. (5.45)

Statement 5.45 may be referred to as the *non-identity of the uncertainty and complementarity principles* (NUCP).

5.2.8 The Universal Uncertainty Principle

Although the quantitative form of the uncertainty principle was discovered by Heisenberg in physics in 1926 (Lindley 2008), the essential notion behind the uncertainty principle appears to be more general. Theoretical support for such a possibility can be found in the so-called "spectral area code" (Herbert 1987, pp. 87–89),

$$\Delta W \times \Delta M > 1 \tag{5.46}$$

where ΔW and ΔM are the spectral widths (or bandwidths) of conjugate waves W and M, respectively. A spectral width is defined as the number of waveforms into which a wave can be decomposed. The size of a bandwidth is inversely related to the closeness with which a wave resembles its component waveforms. Inequality 5.46 is called the "spectral area code," since the product of two numbers (i.e., bandwidths ΔM and ΔW) can be viewed as an area (*vis-à-vis* lines or volumes). When wave X is analyzed with the W prism (or software), a particular bandwidth ΔW of the output W waveforms is obtained, which is an inverse measure of how closely the input wave X resembles the members of the W waveform family. Similarly, when X is analyzed with the M prism, another bandwidth ΔM is obtained, which is an inverse measure of how closely the input wave X resembles the members of the M waveform family. Since W and M are mutual conjugates (i.e., polar opposites), it is impossible for wave X to resemble W and M both. Hence, there exists some restriction on how small these two spectral widths can get for the same input wave. Such a restriction is given by Eq. 5.46.

To relate the *spectral area* code to the Universal Uncertainty Principle, it is necessary to make two additional assumptions: (1) All human knowledge can be quantitatively expressed in terms of waves (each wave having three characteristic parameters, amplitude, frequency, and phase) and (2) The *Fourier theorem* and its

generalization known as the *synthesizer theorem* (Herbert 1987, pp. 82–84) can be used to decompose any wave, either physical or nonphysical, into a sum of finite set of component waveforms. The difference between the "physical wave" such as water waves and "nonphysical wave" such as quantum wave is this: The square of the amplitude of a *physical wave* is proportional to energy, whereas the square of the amplitude of *nonphysical wave* is proportional to the *probability* of the occurrence of some event.

Herbert (1987, pp. 87–89) provides an example of the spectral area code in action, namely, the complementary abilities of analog and digital synthesis techniques. An analog synthesizer can construct a sound wave X out of a range of sine waves with different frequencies k. Each wave X, depending on its shape, requires a certain spectral width Δk of sine waveforms for its analog synthesis. The sine wave's conjugate waveform is the impulse wave, which is the basis of digital music synthesis. A digital synthesizer forms a wave X out of a range of impulse waves with different values of position x. Each wave requires a certain spectral width Δx of impulse waves for its digital synthesis. According to the spectral area code, Eq. 5.46, the product of the spectral bandwidth of sine waves ant that of impulse waves must satisfy the *spectral area code*, leading to:

$$\Delta k \times \Delta x > 1 \tag{5.47}$$

Short musical sounds (such as from a triangle or a woodblock) have a narrow impulse spectrum. According to Inequality 5.47, to analog-synthesize such crisp sounds (i.e., with small Δx) requires a large range of sine waves (i.e., with large Δk). To synthesize an infinitely short sound, that is, the impulse wave itself, requires all possible since waveforms. In contrast, musical sounds that are nearly pure tones such as from a flute, an organ, or a tuning fork have a narrow sine spectrum. To digitally synthesize such pure tones, the spectral area code requires a large range of impulse waves. The spectral area code informs us that *analog* and *digital* music synthesizers are *complementary*: One is good for synthesizing long waveshapes, the other for short ones. Analogously, it may be stated that the *photoelectric effect devices* and *optical interference devices* are complementary to each other: One is good for measuring the particle nature of light, the other is good for measuring the wave nature of light. Thus, it may be concluded that the complementarity principle of Bohr is a natural consequence of the *spectral area code*, Inequality 5.46.

These considerations based on the *synthesizer theorem* and the *spectral area code* provide theoretical support for the notion that there are at least three kinds of uncertainty principles in nature – (1) the *Heisenberg Uncertainty Principle* in *physics* (see Inequalities 2.38 and 2.39), (2) the *Cellular Uncertainty Principle* in *cell biology* formulated in the late 1990s based on the molecular model of the cell known as the Bhopalator (Ji 1985a, b, 1990, 1991, pp. 119–122) as explained in Fig. 5.10 below, and (3) the *Knowledge Uncertainty Principle* in *philosophy* (see Sect. 5.2.7). One question that naturally arises is "What, if any, is the connection among these three uncertainty principles?" Is the HUP perhaps ultimately

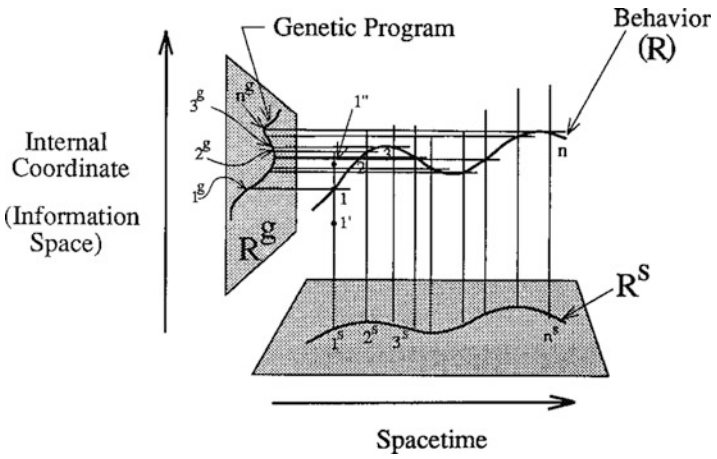


Fig. 5.10 The cellular uncertainty principle derived from living processes represented in the five-dimensional space, four dimensions of spacetime and one additional dimension for biological information (Reproduced from Ji 1991, p. 121)

responsible for the other two uncertainty principles? I do not think so. Rather I think it is more likely that these three uncertainty principles are *mutually exclusive* and constitute special cases of a more general principle, here termed the *Universal Uncertainty Principle* that operates in the Universe, leading to the following assertion:

> There exists a principle in this universe that manifests itself as the Heisenberg Uncertainty Principle, the Cellular Uncertainty Principle, or the Knowledge Uncertainty Principle, depending on whether the system under consideration is the *quantum object*, *the living cell*, or *the human brain*. (5.48)

Statement (5.48) will be referred to as the *Postulate of the Universal Uncertainty Principle* (PUUP). As already alluded to above, the ultimate basis for the validity of PUUP may be found in the *synthesizer theorem* and the *spectral area code* (Herbert 1987).

One utility of PUUP may be its ability to protect philosophers, literary critics, anthropologists, journalists, artists, and others from being criticized for invoking *Heisenberg's Uncertainty Principle* to describe "uncertain" situations/scenarios encountered in their own fields of specializations. For example, Lindley (2008), in his otherwise insightful and informative book on the history of the uncertainty principle in physics, chastised one editorialist who invoked the Heisenberg Uncertainty Principle by claiming that "the more precisely the media measures individual events in a war, the more blurry the warfare appears to the observer." Had the editorialist under attack invoked the PUUP instead of Heisenberg's uncertainty principle, he would have avoided Lindley's criticism on a sound logical basis.

The Cellular Uncertainty Principle (CUP) mentioned above is derived as follows (Ji 1991, pp. 118–122). It is assumed that the complete characterization of life

entails specifying the behavior of the smallest unit of life, the cell. The cell behavior is depicted as a curvy line denoted as **R** (from "river," the symbol of life) in Fig. 5.10. The genetic program responsible for the cell behavior is indicated as the projection $\mathbf{R}^{\mathbf{g}}$ of **R** onto the internal coordinate (or genetic information) space (see the vertical plane on the left in Fig. 5.10). The projection of **R** onto the spacetime plane produces its spacetime trajectory denoted as $\mathbf{R}^{\mathbf{s}}$.

The trajectory **R** is postulated to be composed of N sub-trajectories called "streams," where N is the number of biopolymers inside the cell. Each stream represents the behavior of one biopolymer inside the cell. The uncertainty about the behavior about the cell cannot be less than the uncertainty about the behavior of one of the N biopolymers. The uncertainty about the behavior of a biopolymer inside the cell can be estimated as follows:

1. There is a finite amount of uncertainty that is associated with the determination of the Gibbs free energy change underlying a given intracellular process catalyzed by a biopolymer. This uncertainty is designated as ΔG. Since driving any net biological process necessitates dissipating Gibbs free energy at least as large as thermal energies, kT, it would follow that the smallest uncertainty about the measurement of the Gibbs free energy change attending a biopolymer-catalyzed process inside the cell can be estimated to be

$$\Delta G \geq \text{kT} \quad \text{kcal/mol} \tag{5.49}$$

2. Due to ΔG, the cross section of the behavior trajectory **R** of the biopolymer possesses a finite size. This leads to an uncertainty about the internal coordinate (i.e., the genetic information) of the biopolymer, since there are at least two internal coordinates that can be accommodated within the cross section of **R** (see 1, 1', and 1" and their projections, not shown, onto the information space). Therefore, the uncertainty concerning the genetic information associated with the biopolymer behavior is at least one bit:

$$\Delta I \geq 1 \quad \text{bit} \tag{5.50}$$

3. Inequalities 5.49 and 5.50 can be combined by multiplication to obtain what was referred to as *the Cellular Uncertainty Principle* in (Ji 1991, pp. 119–122):

$$(\Delta G)(\Delta I) \geq \text{kT} \quad \text{bit kcal/mol} \tag{5.51}$$

The three uncertainty principles discussed above are given in the first rows of Tables 5.6, 5.7, and 5.8, the first two of which are the modified forms of Tables 2.9 and 2.10 in Sect. 2.3. The two forms of the HUP are reproduced in the first row of Table 5.6, that is, Inequalities 2.38 and 2.39. These inequalities are displayed in the table as the *horizontal* and *vertical* margins, respectively. As pointed out in Sect. 2.3.5, the *uncertainty relations are located on the margins of the table and the complementary relations such as the kinematics-dynamics duality are located in the diagonal boxes (or the interior) of the table*, suggesting that the uncertainty

Table 5.6 The relation between the *uncertainty principles* and *complementary relations* in physics, all thought to result from the numerical values of the critical parameters, h and c

Physics $\Delta q \cdot \Delta p \geq h/2\pi$ . . . . . (2.38) $\Delta t \cdot \Delta E \geq h/2\pi$ . . . . . (2.39)		
h, c	Position (q)	Momentum (p)
Time (t)	1. Wave 2. Spacetime 3. Kinematics 4. Globality 5. Continuity 6. Group (or superposition)	
Energy (E)		1. Particle 2. Momenergy 3. Dynamics 4. Locality 5. Discontinuity 6. Individuality

Table 5.7 The postulated relation between the *cellular uncertainty principle* and the *liformation-mattergy complementarity* in biology

Biology $\Delta G \cdot \Delta I \geq kT$ . . . . . (5.51) $\Delta L \cdot \Delta m \geq kT$ . . . . . (5.52)		
kT	Life (L)	Matter (m)
Information (I)	1. Wave 2. Kinematics 3. Liformation 4. Structure	
Energy (E)		1. Particle 2. Dynamics 3. Mattergy 4. Function

principles and the complementary principles belong to two different logical classes in agreement with Murdoch (1987, p. 67). Although the wave-particle duality is widely regarded as the empirical basis for Bohr's complementarity principle, this view is considered invalid since Bohr's complementarity principle has been found to be upheld in the so-called which-way experiments even when the HUP is not applicable (Englert et al. 1994). Therefore, the wave-particle duality must be viewed as valid only under some specified experimental situations such as the gamma-ray microscopic experiment (Murdoch 1987, p. 50) and not universally. Similarly, all of the *complementary pairs* listed in the diagonal boxes of Table 5.6 may hold true only under appropriate experimental or observational situations and not universally.

Table 5.8 The extension of the principles of uncertainty and complementarity from physics and biology to philosophy. M = mind, B = body, S = soul, and P = personality. The symbol u denotes the postulated minimum uncertainty below which no human knowledge can reach

Philosophy		
$\Delta M \cdot \Delta B \geq u$ . . . . . (5.53)		
$\Delta S \cdot \Delta P \geq u$ . . . . . (5.54)		
u	Soul (S)	Personality (P)
Mind (M)	1. Wave	
	2. Liformation	
	3. Fuzzy logic	
Body (B)		1. Particle
		2. Mattergy
		3. Crisp logic

If the Symmetry Principle of Biology and Physics (SPBP) described in Table 2.5 is valid, it may be predicted that the relation between the *uncertainty principle* and the *complementarity principle* as depicted in Table 5.6 may have a biological counterpart. One such possibility is shown in Table 5.7, which is almost identical with Table 2.7, except for the inclusion of the postulated uncertainty relations, Inequalities 5.51 and 5.52. In Inequality 5.51, which was derived on the basis of a geometric argument (Ji 1991, pp. 120–122), ΔG is the uncertainty about the measurement of the Gibbs free energy change accompanying an intracellular process at temperature T, ΔI is "the uncertainty about the biological significance of the cellular processes under study, for example, the uncertainty about the 'fitness' value of the cellular processes involved" (Ji 1991, p. 120), and k is the Boltzmann constant. It is assumed that the critical parameter in biology is the *thermal energy per degree of freedom*, that is, kT, which is thought to be analogous to h (see Statement (4.36)). Again, in analogy to the canonical conjugates in physics (i.e., the q–p and t–E pairs), it is assumed in Table 5.7 that the canonical conjugates in biology are information-life (I-L) and energy and matter (E–m) pairs. If this conjecture is valid, we can derive another uncertainty relation in biology, namely, $\Delta L \cdot \Delta m \geq kT$, where ΔL is the uncertainty about whether the object under investigation is alive or death, and Δm is the uncertainty about the material constitution or configuration of the living object under consideration.

Finally, if the complementarity principle revealed in *physics* and *biology* can be extended to philosophy as envisioned by Bohr (1934) and myself (Ji 1993, 1995, 2004b), it should be possible to construct a table similar to Tables 5.6 and 5.7 that applies to philosophy. One possibility is shown in Table 5.8. Just as the extension of the uncertainty and complementarity principles from physics to biology entailed recognizing a new complementary pair (i.e., *liformation* vs *mattergy* in Table 5.7), so it is postulated here that there exists a novel kind of complementarity observable at the philosophical level, and that complementary pair is here suggested to be the *crisp* versus *fuzzy logics* (see the diagonal boxes in Table 5.8).

Associated with the crisp versus fuzzy logics *complementarity* are suggested to be *two uncertainty relations,* Inequalities 5.53 and (5.54), where ΔM is the

uncertainty associated with defining the mind, ΔB is the uncertainty associated with defining the body, ΔS is the uncertainty about what constitutes soul, ΔP is the uncertainty about what determines one's personality, and u expressed in fits, the fuzzy units (Kosko 1993), is thought to be the minimum amount of uncertainty that necessarily accompanies all human knowledge and communication. "Knowledge" is here defined simply as the ability to answer questions, and the amount of the knowledge a person possess can be measured by the number of questions that can be answered by a person possessing the knowledge. Inequality (5.53) may be interpreted as stating that the more precisely one determines what mind is in nonmaterial terms, the less precisely can one define the role of the body in the phenomenon of mind. Similarly, the more precisely one determines what the body is from the biochemical and physiological perspectives, the less precisely can one determine what mind is from the psychological perspective. This complementarity-based view of mind appears to be consistent with the hologram-based theory of mind proposed by Pribram (2010). Inequality (5.54) may be interpreted to mean that the more precisely one determines what soul is, the less precisely can one determine what personality is. The more precisely one can determine what personality is, the less precisely can one determine what soul is. This conjecture was motivated by the statement made by a Japanese theologian in Tokyo in the mid-1990s to the effect that "it is relatively easy to know whether a human being has a personality but it is very difficult to know whether he or she has a soul."

The three kinds of the uncertainty principles described in Tables 5.6, 5.7, and 5.8 are recapitulated in Table 5.9, along with their associated complementarity principles.

Several features emerge from Table 5.9:

1. Although the first mathematical expression of the uncertainty principle was discovered in physics by Heisenberg in 1926 (Lindley 2008), the qualitative concept of uncertainty in human knowledge is much older, going back to Lao-tse, for example (see Statement 5.22). The mathematical expressions for the uncertainty principle applicable to cell biology and psychology/philosophy are formulated for the first time in this book (see the first and second rows in Table 5.9).
2. The intense discussions on Heisenberg's uncertainty principle in physics and philosophy of science during the past seven decades (Murdoch 1987; Plotnitsky 2006; Lindley 2008) have created the impression that there exists only one overarching principle of uncertainty, namely, that of Heisenberg. But Table 5.9 suggests that there exists a multiplicity of uncertainty principles, each reflecting specific mechanisms of interactions among the components of the system under consideration, from the atom to the cell to the human brain. Just as the complementarity principle advocated by Bohr on the basis of quantum mechanical findings was postulated to have counterparts in fields other than physics (Bohr 1933, 1958; Pais 1991; Ji 1991, 1993, 1995; Kelso and EngstrØm 2006; Barab 2010), so it appears that the uncertainty principle first recognized in quantum mechanics has counterparts in fields other than physics.

Table 5.9 The uncertainty principles in physics, biology, and philosophy

	Uncertainty principle		
	Heisenberg	Cellular	Knowledge
1. System (volume, m^3)	Atom (10^{-30})	Cell (10^{-15})	Brain (1)
2. Uncertainty inequality (minimum Uncertainty)	$\Delta q \cdot \Delta p \geq h/2\pi$ $\Delta t \cdot \Delta E \geq h/2\pi$ ($\sim 10^{-27}$ erg s)	$\Delta G \cdot \Delta I \geq \gamma$[a] ($\sim 10^{-14}$ erg)	$\Delta X \cdot \Delta Y \geq u$[b] ($\sim 10^{-2}$)
3. Complementary pairs	Wave versus particle	Linformation versus mattergy	Fuzzy versus crisp (*Kosko* 1993)
	Kinematics versus dynamics	Diachronicity versus synchronicity[c]	Continuity versus discontinuity
	Measuring instruments A versus B	Structure versus process	Local versus global
			Classical versus nonclassical epistemology (*Plotnitsky* 2006)
4. Key principles	Principle of the quantum (or the quantization of action, i.e., energy × time)	Principle of self-organization	Principle of ineffability (Statement 5.22)
		Principle of the conformon (or the quantization of biological action) (*Ji* 2000)	Einstein's uncertainty thesis (Statement 5.38)
			Principle of minimum uncertainty: i.e., $u > 0$ (see inequality [5.27])
5. Quantum (alternative names)	Action = h (**quons**, **ergons**[d])	Life = γ (conformons, gnergons[e])	Knowledge = u[f] (gnons[g])
6. Concerned with (discrete units)	Energy (ergons)	Gnergy (gnergons)	Information (gnons)
7. Field of study	Physics	Biology	Philosophy/psychology

[a] The minimum size of the conformon postulated to be kT or 4.127×10^{-14} ergs (or 0.594 kcal/mol) (Ji 1991, p. 32)

[b] To maintain the symmetry of the table, it is postulated that there exist one or more uncertainty pairs denoted as X and Y such that increasing the precision of describing X is possible if and only if the precision of describing Y is reduced proportionately so that their product is always greater than some minimum uncertainty symbolized by u. One example of X and Y may be suggested to be *natural language* and *mathematics*. The minimum uncertainty of human knowledge, u, may be represented in terms of the Kosko entropy, S_K, that cannot be reduced to zero nor exceeds 1. The numerical value of *u* has been conjectured to be about 10^{-2}, which is about 12 orders of magnitude greater than *kT*, the minimum size of the cellular uncertainty, and about 25 orders of magnitude greater than *h*, the minimum size of quantum mechanical uncertainty

[c] Cells are evolving systems whose current properties and processes have been selected by evolution and hence cannot be completely understood without taking into account their past history as recorded in their structures, for example, DNA. In other words, cells can be described in two complementary ways – via the *diachronic* and the *synchronic* approaches (see Sect. 4.5)

[d] The energetic aspect of gnergy, the complementary union of information and energy (Sect. 2.3.2)

[e] The discrete unit of gnergy (Sect. 2.3.2)

[f] The symbol u refers to the *minimum uncertainty* in human knowledge which is equivalent to the *maximum human knowledge,* because it takes a maximum amount of information to minimize uncertainty

[g] The informational aspect of gnergy (Ji 1991, pp. 1, 152 and 160)

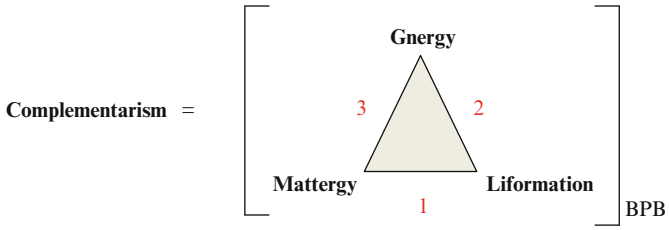


Fig. 5.11 A three-node network representation of *complementarism*

3. The uncertainty inequality differs from systems to systems as evident in the second row. The numerical value of the minimum uncertainty associated with a given system appears to increase approximately linearly with its material volume (compare the first two rows).
4. The complementarity pairs associated with their associated uncertainty inequalities also vary depending on systems (see the second and third rows).
5. The key principles underlying each uncertainty inequality and its associated complementarity pair depend on systems, the principle of self-organization for cells (discussed in Sect. 3.1) being a prime example (see the fourth row).
6. Just as the *action* is quantized in physics, so it is proposed here that *life* and *knowledge* are quantized in cell biology and psychology/philosophy (see the fifth row).
7. Somewhat simplifying, physics may be viewed as the study of *energy* (or ergons), cell biology as the study of *gnergy*, and philosophy/psychology as the study of *information* (or gnons) (see the sixth row).
8. One of the most significant conclusions suggested by Table 5.9 is that there is no overarching uncertainty principle nor is there an associated complementarity principle but these principles are all *system-dependent*, giving rise to a multiplicity of uncertainty principles and complementarity principles:

   Uncertainty principles and complementarity principles are system-dependent. (5.55)

   Statement (5.55) may be referred to as the System-Dependency of Uncertainty and Complementarity Principles (SDUCP).
9. Table 5.9 strongly indicates that the principles of uncertainty and complementarity are not confined to physics but are universal. Since complementarism (Sect. 2.3.4) is a philosophical framework based on the universality of complementarity and since the principle of complementarity is in turn thought to be related to that of uncertainty (see the second and third rows, Table 5.9), the question naturally arises as to how complementarism may be related not only to uncertainties but also to other cognate terms such as information (or *liformation* more generally, Sect. 2.3.1), energy (or *mattergy* more generally), and measurement (Plotnitsky 2006). One possible way to characterize the multifaceted relations among these terms is suggested in Fig. 5.11, utilizing the language of networks and the Peircean triadic template (see Fig. 4.6):

In Fig. 5.11, complementarism is suggested to be a network of three nodes – Gnergy, Mattergy, and Liformation – and three edges – Complementarity (1), Uncertainty (2), and Measurement (3). BPB stands for the Bernstein-Polanyi boundaries (explained in Sect. 3.1.5) that provides the context of discourses or specifies the system-dependency entailed by Statement (5.55). Just as "mattergy" embodies the intimate relation between *energy* and *matter* through Einstein's special relativity theory (Shadowitz 1968), so "liformation" embodies the inseparable relation postulated to exist between *life* and *information* in the gnergy theory of biology (Ji 1991, 2004b). Thus, as first suggested in (Ji 2004b), it may be concluded that:

> Just as matter is regarded as a highly condensed form of energy, so life can be viewed as a highly condensed form of information. (5.56)

Statement 5.56 may be referred to as the *information-life identity principle* (ILIP) just as $E = mc^2$ can be referred to as the *energy-matter identity principle* (EMIP).

5.3 Cybernetics

The term "cybernetics" comes from the Greek $\text{K}\upsilon\beta\varepsilon\rho\nu\acute{\eta}\tau\eta$ or kybernētēs, meaning "steersman," "governor," "pilot," or "rudder." Plato used the term to refer to government, but the term became widely used in modern times after Nobert Wiener published his book in 1948 entitled "Cybernetics, or control and communication in the animal and machine" (Wiener 1948). As the subtitle suggests, cybernetics is the science of control and *communication* in machines, both artificial and biological, that are endowed with the ability to achieve specific goals through feedback interactions. Both control and communication implicate information. Communication is concerned with encoding, transmitting, and decoding information, while control *utilizes* information. Hence, cybernetics can be considered to subsume information theory (see Sect. 4.3 for the concept of *information*).

5.3.1 Control Theory

Control theory is the science of controlling dynamical systems to achieve desired outcomes. It originated in engineering and mathematics but is now used in biology and social sciences. The concepts and principles developed in the control theory of artificial machines have been found useful in describing the behaviors of living systems and their components such as enzymes, metabolic pathways, and living cells themselves. Some of these concepts and terms are illustrated in Fig. 5.12. The desired output of a machine is referred to as *reference*. When one or more output variables of a machine must follow a certain reference, the *controller* of the machine manipulates the inputs to the system to obtain the desired output. A part of the output is directed to the *sensor* of the machine which feeds it back to the *controller* to adjust

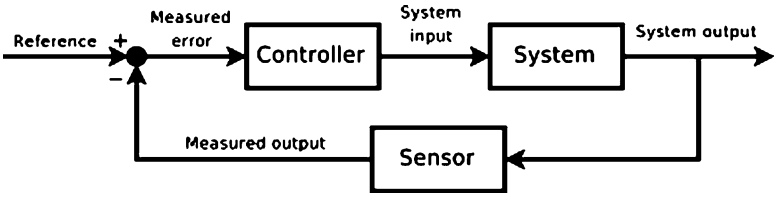


Fig. 5.12 A diagrammatic representation of a system with feedback control (Reproduced from http://en.wikipedia.org/wiki/File:Feedback_loop_with_descriptions.svg)

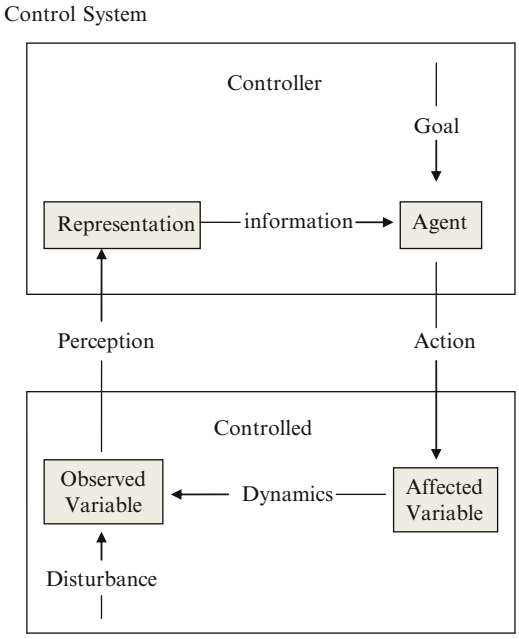


Fig. 5.13 The structure and function of a control system (Adapted from http://pespmc1.vub.ac.be/REQVAR.HTML)

the new input either negatively (leading to negative feedback) or positively (leading to *positive feedback*). In other words, feedback control is achieved when a portion of the output signal is operated on and fed back to the input in order to obtain a desired effect. A controller monitors its effect on the system and modifies its output accordingly. As an example, consider a thermostat. It has two inputs: the desired temperature or the reference and the current temperature (the latter is the feedback). The output of the thermostat changes in order to equalize the two inputs.

A more detailed diagram of the *control system* is given in Fig. 5.13. It consists of two subsystems – *the controller* or *controlling system* (denoted as C) and *the controlled* or *controlled system* (S). The interaction between C and S is asymmetric in that C has a complete control over S, to the extent of destroying the controlled.

Table 5.10 A comparison between thermodynamic and control systems

	Thermodynamic system (TS)	Control system (CS)
Scientific discipline	Thermodynamics	Cybernetics
Key characteristics[a]	(1) Energy, (2) Entropy, (3) T, (4) P, and (5) V	(1) Energy, (2) Entropy, (3) Controller, (4) Controlled, (5) Representation, (6) Agent, (7) Information, (8) Goal/Aim/ Teleonomy, (9) Action, (10) Perception, (11) Affected variable, (12) Observed variable, (13) Dynamics, and (14) Disturbances
Principles obeyed[b]	(1) First Law, and (2) Second Law	(1) First Law, (2) Second Law, (3) Principle of feedback control (Sect. 5.3.1), (4) Principle of the minimum energy requirement for information flow (Sect. 4.8), (5) Law of requisite variety (Sect. 5.3.2), and (6) Principle of Information and Energy Requirement for Organization (PIERO) (Sect. 3.1), which may be referred to as the *Law of Requisite Information* (LRI)
Relation[c]	TS > CS or TS < CS (depending on whether sets are defined extensionally or intensionally, respectively)	

[a] Some of the same concepts, factors and parameters essential for describing TS are also required to describe CS in addition to those unique to CS

[b] Thermodynamic laws are universal and hence obeyed by all material systems including CS. But there are the laws, rules or regularities found uniquely in control systems. These may be named as follows: (3) = the First Law of Cybernetics, (4) = the Second Law of Cybernetics, (5) = the Third Law of Cybernetics, and (6) = the Fourth Law of Cybernetics (see the second row and third column)

[c] All control systems are thermodynamic systems but not all thermodynamic systems are control systems

But S has only a small effect on C through the formation of perception. The controller consists of two components – *representation* of the controlled system and the *agent* responsible for the action of the controller. The relation between *representation* and *agent* is the *flow of information* which determines the actions of the agent. The controlled system can be described in terms of two variables – the *affected variable* that is altered by the action of the agent and the *observed variable* that is observed by the controller through perception. The observed variable also includes uncontrollable disturbances on the controlled system.

Just as *thermodynamics* is defined as the scientific study of the *thermodynamic system* (TS), *control theory* or *cybernetics* can be viewed as the scientific study of the *control system* (CS). In Table 5.10, TS and CS are compared in detail, treating them as sets of elements. The second and third rows of the table list two different classes of the elements of TS and CS. The second row lists system characteristics and the third row lists the laws and the principles being obeyed. Of the 5 elements of the TS set in the second row, only 2 are found in the CS set, while none of the 12 unique elements of the CS set is found in the TS set. All of the elements of TS in the third row are included as the elements of CS but none of the four unique elements of

CS are found in TS. Thus, at both these levels, more elements of TS are found to be the elements of CS than the other way around, which may be expressed as Inequality (5.57):

$$\text{TS} < \text{CS} \tag{5.57}$$

Inequality 5.57 may be interpreted as reflecting the relative complexities of TS and CS in the sense that

It takes a longer bit-string to describe a system viewed as a CS than as a TS. (5.58)

Based on the content of the third row of Table 5.10, it is clear that:

All control systems are thermodynamic systems; but not all thermodynamic systems are control systems. (5.59)

We may refer to Statement 5.59 as the "Principle of the Insufficiency of Thermodynamics for Controlled Processes" (PITCP). Statement 5.59 establishes that there are more thermodynamic systems than there are control systems or that CS is a subset of TS, leading to Inequality 5.60:

$$\text{TS} > \text{CS} \tag{5.60}$$

On the surface (i.e., on the syntactic or formal level), Inequalities 5.57 and 5.60 appear contradictory. However, on the semantic level, that is, if we take into account the different contexts under which the TS and CS sets are defined, no contradiction appears. There are two ways of defining a set – (1) *extensionally*, by listing sample members of a set, and (2) *intensionally*, by listing the characteristics of, or the rules obeyed by, the members of a set. It is here claimed that

If A is a subset of B, A is less complex than B extensionally and more complex than B intensionally. (5.61)

We may refer to Statement 5.61 as the "Complementarity of the Extensional and Intensional Definitions of a Set" (CEIDS), or, more briefly, the "Extension-Intension Complementarity" (EIC). Since the extensional definition of a set is akin to viewing a set *globally* and the intensional definition akin to viewing a set *locally*, EIC may be regarded as a species (or token) of what is often referred to as the "Forest-Tree Complementarity". Based on EIC, we can now account for the apparent contradiction between Inequalities 5.57 and 5.60 as a natural consequence of the complementarity between the extensional and intensional definitions of a set.

5.3.2 The Law of Requisite Variety

One of the most useful laws to be imported from engineering into biology is what is known in cybernetics as the Law of Requisite Variety (LRV). There are many ways

to state this law Heylighen and Joslyn (2001a, b) but the following definition adopted from Ashby (1964) is suitable for application to molecular and cell biology:

> When a machine (also called a system or a network) is influenced by its environment in a dominating manner (i.e., the environment can affect the machine but the machine cannot influence its environment to any significant degree), the only way for the machine to reduce the degree of the influence from its environment is to increase the variety of its internal states. (5.62)

The complexity of biological systems (or bionetworks), from enzymes to protein complexes to metabolic pathways and to genetic networks, is well known. One way to rationalize the complexity of bionetworks is to invoke the Law of Requisite Variety. We can express LRV quantitatively as shown in Eq. 5.63. If we designate the variety of the environment (e.g., the number of different environmental conditions or inputs to the system) as V_E and the variety of the internal states of the machine as V_M, then the variety of outputs of the machine, V_O, can be expressed as

$$V_O \geq V_E/V_M \tag{5.63}$$

One interpretation of Eq. 5.63 is that, as the environmental conditions become more and more complex (thus increasing V_E), the variety of the internal states of the machine, V_M, must increase proportionately to maintain the number of outputs, V_O, constant (i.e., keep the system homeostatic). Another way to interpret this equation is that, in order for a bionetwork to maintain its functional homeostasis (e.g., to keep the numerical value of V_O constant) under increasingly complexifying environments (i.e., increasing V_E), the bionetwork must increase its variety or complexity, namely, V_M.

The term "variety" appearing in LRV can be expressed in terms of either (1) the number of distinct elements, or (2) the binary logarithm of that number. When variety is measured in the binary logarithmic form, its unit is the bit. Taking the binary logarithm to the base 2 of both sides of Inequality 5.63 leads to Inequalities 5.64 and 5.65:

$$\log V_O \geq \log (V_E/V_M) \text{ or} \tag{5.64}$$

$$\log V_O \geq \log V_E - \log V_M \tag{5.65}$$

which is identical with the equation for LRV used by F. Heylighen and C. Joslyn (2001), except that the buffering capacity of the machine, K, is assumed to be zero here, that is, the machine under consideration is assumed to respond to all and every environmental perturbations. Since $\log V_x$ is defined as Shannon entropy H_x (see Eqs. 4.2 and 4.3), Inequality 5.65 can be transformed into a more convenient form:

$$H_O \geq H_E - H_M \tag{5.66}$$

where H_O is the Shannon entropy of the machine outputs, H_E is the Shannon entropy of the environmental inputs, and H_M is the Shannon entropy of the state of the machine or its controller. Two cautionary remarks are in order concerning Inequality 5.66:

1. The symbols for Shannon entropy, H, should not be confused with the symbol for enthalpy, H, in thermodynamics, and
2. The same term "entropy" is represented by H in information theory and by S in thermodynamics. In other words, there are two kinds of entropies – the *information-theoretic entropy* (referred to by some as "intropy") and *thermodynamic entropy*. There are two schools of thought about the relation between intropy, H, and entropy, S (Sect. 4.7). One school led by Jaynes (1957a, b) maintains that H and S are in principle identical up to a constant factor, whereas the other schools represented by Wicken (1987), myself (Ji 2004c), and others assert that H and S are distinct and cannot be quantitatively related (see Sect. 4.7).

Just as the Second Law of thermodynamics can be stated in many equivalent ways, so LRV can be expressed in more than one ways, including the following:

Simple machines cannot perform complex tasks. (5.67)

To accomplish a complex tasks, it is necessary to employ complex machines. (5.68)

Nature does not employ complex machines to accomplish simple tasks. (5.69)

If the internal structure of a biological machine is found to be complex, it is very likely that the task performed by the machine is complex. (5.70)

Thus, LRV provides one way to explain the possible biological role of the complex biological structures such as signal transduction pathways, transcriptosomes, nuclear pore complexes, both of which can implicate 50 or more proteins (Halle and Meisterernst 1996; Dellaire 2007). For example, it is possible that nuclear pore complexes had to increase the variety of their internal states to maintain functional homeostasis (e.g., transport right RNA-protein complexes in and out of the nuclear compartment at right times and at right speeds) in response to increasingly complexifying environmental (e.g., cytoplasmic) inputs or perturbations. In other words, nuclear pore complexes (viewed as molecular computers or molecular texts) had to become complex in their internal structures so as to process (or carry out computations on) more and more complex input signals from their microenvironment in order to produce the desired outputs without fail.

5.3.3 *Principles of After-Demand Supply (ADS) and Before-Demand Supply (BDS)*

There are three distinct ways for a system to interact with its environment or three distinct types of supply and demand: (1) The system adjust its internal states in

Table 5.11 Three mechanisms of interactions between systems and their environment predicted by the generalized Franck–Condon principle (Sect. 2.2.3). R_S rate of change of the system, R_E rate of change of environment, *BDS* before-demand supply, *SDS* synchronous demand and supply, *ADS* after-demand supply

Rates	$R_S << R_E$	$R_S = R_E$	$R_S >> R_E$
Mechanisms	BDS	SDS	ADS
Examples	Enzymic catalysis	Predator–prey interactions	Biological evolution

response to environmental demand (in which case the environmental demand must precede the internal state changes), (2) the system adjust its internal states simultaneously with the environmental demand, and (3) the system can readjust its internal state in anticipation of environmental demand (in which case the internal state changes must precede the environmental demand). We may refer to these mechanisms as (1) the "after-demand supply" (ADS), (2) the "synchronous demand and supply" (SDS), and (3) the "before-demand supply" (BDS), respectively. There are two rate processes involved – the rate, R_S, of internal state changes, and the rate, $R_{E,}$ of the change in environmental demand. There are three possible scenarios regarding the relative magnitudes of these rates as shown in Table 5.11, which also includes the suggested mechanisms for each scenario.

An example of SDS would be the uncertainty associated with a lion catching a deer because their running speeds are comparable, that is, $R_S = R_E$: Sometimes the lion succeeds in catching a deer and other times the deer gets away safely. An example of BDS is provided by the phenomenon of conformational rearrangements of enzymes (S) before they bind their substrates (E) since $R_S << R_E$, in agreement with the generalized Franck–Condon principle and in contradiction to the induced fit model of enzymic catalysis (Koshland 1958) (Sect. 2.2.3). Finally, an example of ADS would be the biological evolution where the life cycle of organisms (S) are faster than the rate of change of their environment (E), that is, $R_S >> R_{E,}$ so that, in order for organisms to evolve, the changes in their environment must first take place before better fit organisms survive and less fit ones get removed in order for the group (or lineage or taxon) to change its genome. Again this is the prediction consistent with the generalized Franck–Condon principle (Sect. 2.2.3).

Chapter 6
Linguistics, Semiotics, and Philosophy

6.1 Linguistics

6.1.1 The Biology-Linguistics Connection

The idea that language may provide a useful metaphor or analogy for describing and understanding the complexity inherent in living systems was expressed by Pattee (1968), Marcus (1974), and others more than four decades ago. The biology-linguistics connection was significantly strengthened by the uncovering of the isomorphism between cell and human languages (to be discussed in Sect. 6.1.2) (Ji 1997a, b, 1999b, 2001, 2002a). Unlike the familiar biology-physics connection, which is characterized by *determinism*, the biology-linguistic connection may be said to be characterized by *quasi-determinism* (Ji et al. 2009b), which is akin to the rule-governed creativity (RGC) in linguistics (see Sect. 6.1.4). RGC refers to the fact that humans are endowed with the ability to generate an indefinitely large number of *meaningful* sentences from a finite number of words and grammatical rules. RGC is also related to another linguistic phenomenon known as the *arbitrariness of signs*, that is, the *arbitrariness* of the relation between signs and their objects resulting from the lack of any physical laws mandating it (Sect. 6.1.4) (Lyons 1992, 1993; Culler 1991).

An indirect evidence for the quasi-deterministic nature of biology surfaced during the DIMACS (Discrete Mathematics and Computer Science) Workshop *on Bimolecular Networks: Topological Properties and Evolution*, held at Rutgers on May 11–13, 2005. At this meeting, Alfonso Valencia from the National Center of Biotechnology in Spain gave a lecture entitled "Biodegradation network, and all what we need for its study." Based on his research experience in the field of the structure-function correlations in proteins, he came to the conclusion that protein folds and functions might not be predictable from amino acid sequence data. Valencia's pessimism seems to go against the prevailing presupposition of

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_6,

biophysicists working in the field of protein folding that 3-dimensional folds of proteins should be ultimately predictable based on their amino acid sequence information alone, the view being referred to as the *Anfinsen's dogma* (Newman and Bhat 2007) in analogy to the *Central Dogma* in molecular biology (see Sect. 11.1). Anfinsen's dogma is based on Anfinsen's discovery in 1954 of the spontaneous refolding of ribonuclease A after denaturation. He found that the enzyme refolded into its native conformation if the environmental conditions employed were carefully controlled, that is, if the denaturant urea was removed before 2-mercaptoethanol, but the enzyme did not refold correctly if the order of removing the denaturants were revered. As will be discussed in Sect. 11.1, Anfinsen's dogma may not be fully supported by more recent experimental findings.

Valencia's pessimistic conclusion regarding protein structure-function correlation reminded me of a similar situation that transpired between the sixteenth and the mid-nineteenth century in the field of the *theory of algebraic equations* (Aleksandrov et al. 1984, pp. 261–278, Vol. I). The following is a list of the key events in the development of the theory of algebraic equations:

1. Ferrari (1522–1565) solved the general fourth-degree (i.e., quartic) polynomial equation of the type, $x^4 + ax^3 + bx^2 + cx + d = 0$ in the radical form (i.e., including the square root of n, where n is a positive number).
2. In 1824, Abel (1802–1829) proved that the fifth-degree (i.e., quintic) polynomial equations could not be solved in the radical form.
3. In "Memoir on the conditions of solvability of equations in radicals" published in 1846, Galois (1811–1832) explained why the quintic or higher-order polynomial equations cannot be solved in radicals. In the process, Galois was led to formulate a new mathematical theory, that is, the *group theory,* which has since been found to apply to a wide range of mathematical problems, providing a universal organizing principle in modern mathematics.

It is interesting to note that it took three centuries for mathematicians to realize that, although the fourth- and lower-order polynomial equations could be successfully solved in radical forms, the fifth- and higher-order ones could not be so solved. The reason for this was found to be that the coefficients of the quintic and higher-order equations belonged to a different *field* than the field to which the quartic and lower-order equations belonged, the former field being insoluble and the latter solvable (thus constituting the so-called *Galois group*) (http://en.wikipedia.prg/wiki/Galois_theory). Similarly, based on the experimental and theoretical evidences that have accumulated during the latter decades of the twentieth century and the first one of the twenty-first, I came to the conclusion between 2005 and 2009 that, even though the 2-D structures (i.e., α-helices and β-sheets) of proteins can be largely determined based on amino acid sequences alone, the 3-D and higher-order structures of proteins might not be so determined because the 3-D and higher-order structures of proteins are functions not only of their amino acid sequences but also of the time- and space-dependent microenvironmental conditions inside the cell under which proteins fold. A similar idea was

proposed by Klonowski and Klonowska (1982). This idea may be alternatively expressed as follows:

> The 2-D structures of proteins are deterministic and predictable based on their amino acid sequences alone which are largely time-independent, but their 3-D structures are non-deterministic and unpredictable because i) proteins are sensitive to the space-and time-dependent microenvironmental conditions under which they fold, and ii) the information concerning their environment is largely lost to the past. (6.1)

For the convenience of discussion, we may refer to Statement 6.1 as the postulate of the *unpredictability of the 3-D protein folds* (U3PF), which is here suggested to be analogous to the *insolvability of the fifth-order polynomial equations* (I5PE) in mathematics. The main point of constructing Table 6.1 (see below) is to suggest that, just as the centuries-long attempt to solve the fifth-order polynomial equation (5PE) in mathematics had been instrumental in establishing the *group theory*, so the decades-long effort on the part of biologists and biophysicists to solve the 3-D protein folds (3PF) problem may lead to the development of a novel theory of life, the beginning of which is here suggested to be the *theory of gnergons* (Sects. 2.3.2 and 4.9). According to this theory, all self-organizing processes in living systems (including protein folding) are driven by gnergons, discrete units of gnergy defined as the complementary union of information (gn-) and energy (−ergy). We can express these ideas more simply in terms of the following two formal statements:

$$\text{I5PE} \dashrightarrow \text{Group Theory} \tag{6.2}$$

$$\textbf{U3PF} \Longrightarrow \textbf{GnergonTheory} \tag{6.3}$$

where the arrow "X - - - - > Y" reads "X leads to Y via crisp logic" and "==>" reads "X leads to Y via fuzzy logic". In other words, the *group theory* was arrived at based on *crisp logic*, whereas the *gnergon theory* may involve uncertainties and fuzzy logic (Sect. 5.2.5).

The concept of gnergons may provide a theoretical framework for *the principle of rule-governed creativity* (Sect. 6.1.4), the *rule-governedness* reflecting the *energy* principle and the *creativity* reflecting the *information* that encodes the consequences of the historical contingencies associated with biological evolution. Rule-governedness is predictable and deterministic while *creativity* is unpredictable and nondeterministic. Thus, it may be concluded that the principle of *rule-governed creativity* embodies the principle of the complementarity between *determinism* and *nondeterminism* on the one hand and the *predictability* and *unpredictability* (*or creativity*) on the other. Alternatively, we may refer to rule-governed creativity as "freedom within constraints."

The possible analogy between the field of algebraic equations in mathematics and that of protein folding in biology is summarized in Table 6.1.

One possible reason why the protein structures and functions cannot be predicted based on their amino acid sequence data alone may be because biological systems in general (of which proteins are parts) obey the principle of complementarity between

Table 6.1 The postulated analogy between the insolvability of the fifth-degree (or quintic) polynomial equations (I5PE) and the *unpredictability of the 3-D folds* (U3PF) of proteins based on their amino acid sequence data

		Theory of	
		Algebraic equations	Protein folding
Solved	What is	Fourth-degree and lower-order polynomial equations	2-D folds (i.e., α-helices, β-sheets)
	By whom	Ancient mathematicians	Computational biologists of the twentieth century
Insolvable	What is	Fifth-degree and higher-order polynomial equations	3-D and higher-order folds based on amino acid sequence information alone
	Proved by	N.H. Abel in 1824	Experimental and theoretical results accumulated by 2010
	Insolvability explained	By E. Galois in 1846	Probably because the 3-D protein folds are the function of (1) amino acid sequence and (2) the time- and space-dependent intracellular micro-environmental conditions under which proteins fold, and the information concerning (2) is largely lost to the past
New theory	Emerged	Group theory	*A New theory of Life* based on the principle of *physical determinism* and *historical contingencies*, here identified with the *Gnergon theory*. Gnergons are defined as the discrete units of gnergy, the complementary union of information (*gn-*) and energy *(−ergy*) that are postulated to underlie all self-organizing processes in the Universe including life (Sects. 2.3.2, 6.1.2, and 11.1) (Ji 1991, pp. 152–156)

Table 6.2 A postulated relative importance of *laws* and *rules* in physics, biology, and linguistics

	Physics (law-based)	Biology (law-rule complementarity-based)	Linguistics (rule-based)
Laws (governing *matter*/*energy*)	+ + + + +	+ + +	+
Rules (governing symbols or signs carrying *information*)	+	+ + +	+ + + + +

the *predictable* or *determinism* (the domain of physics) and *the unpredictable* or *creativity* (the domain of evolutionary biology and linguistics; or the domain of rule-governed creativity [Ji 1997a; Lyons 1992]). It seems likely that (1) *rules* wrought by evolution or social conventions and (2) the physical *laws* of nature play equally fundamental roles in biology in agreement with Pattee (2008) and Barbieri (2003). We may refer to this idea as the *complementarity between determinism and nondeterminism* (CDN). CDN so defined may be unique to biology as indicated by the third column in Table 6.2. CDN is related to the concept of *matter-symbol complementarity* that has been advanced by H. Pattee (1982, 2001, 2008; Umerez 2001) over the past three decades, according to which all living systems embody two complementary aspects – the physical law-governed *energetic*/*material* aspect and the evolutionary rule-governed *symbolic* aspect. This idea was renamed as the *von Neumann-Pattee principle of matter-sign complementarity* in Ji (1999b) to reflect not only the history of the development of this important concept starting with von Neumann but also its affinity to the more general notion of information/energy *complementarity* embodied in the new biology-based philosophical framework known as *complementarism* (see Sect. 2.3, and Ji 1995). The theory of organic codes proposed by Barbieri (2003) may be viewed as another species of the biological theories based on the matter-symbol complementarity and the complementarity between determinism (matter) and nondeterminism (symbol, or codes) (CDN). Furthermore, it is suggested in Sect. 6.1.3 that CDN is related to the *arbitrariness of signs*, one of the 13 design features of human language, that may have evolved to maximize the ability of messages to transmit information (Ji 1997a, pp. 36–37). *Nondeterminism*, *arbitrariness,* and *creativity* may all reflect different aspects of the same essential feature of the message source of a communication system, that is, the freedom for a sender to choose different messages, which maximizes when all messages have an equal probability for selection and hence which message happens to be chosen is *arbitrary* (Ji 1997a, pp. 36–37).

If the content of Table 6.2 is correct, biology may be described as neither *physics* nor *linguistics* but *a combination of both*. This same idea may be expressed as follows:

Biology is a complementary union of physics and linguistics. (6.4)

Physics and linguistics are the complementary aspects of biology. (6.5)

Biology has two complementary aspects – physics and linguistics. (6.6)

Physics is law-based, linguistics is rule-based, and biology is based on both physical laws and evolutionary rules. (6.7)

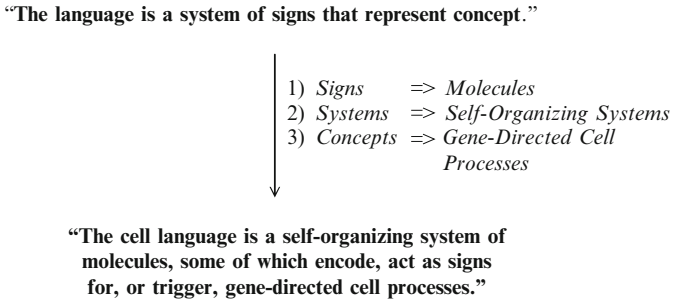


Fig. 6.1 The "formal" derivation of the definition of cell language from that of human language given by Saussure (Culler 1991; Ji 2002b)

To understand biology, it is necessary to understand both physics and linguistics. (6.8)

It is impossible to understand biology based on the laws of physics and chemistry alone. (6.9)

Since linguistics is an important branch of the more general theory of signs, namely, *semiotics*, it behooves us to inquire into the connection between biology and linguistics on the one hand (Sect. 6.1.2) and biology and semiotics on the other (see Sect. 6.2).

6.1.2 The Isomorphism Between Cell and Human Languages: The Cell Language Theory

Human language can be defined as a system of *signs* obeying a set of rules that enables humans to communicate with one another. In other words, human language is a necessary condition for human communication. Similarly, there must be a language unique to living cells in multicellular (Ji 1997a, b) as well as unicellular (Stock et al. 2000) organisms, since cells must communicate among themselves in order to survive by carrying out their specialized biological activities in a coordinated manner. Such a language was named "cell language" in Ji (1997a). Cell language was defined as "a self-organizing system of molecules, some of which encode, act as signs for, or trigger, gene-directed cell processes" (Ji 1997a). This definition of cell language was inspired by the definition of human language given by Saussure (Culler 1991): "The language is a system of signs that represent concept." The definition of cell language can be *formally* derived from that of human language given by Saussure by applying the following transformations: (1) replace "signs" with "molecules," (2) replace "systems" with "self-organizing systems;" and (3) replace "concepts" with "gene-directed cell processes" (see Fig. 6.1).

Human and cell languages obey a common set of *linguistic* (or more generally *semiotic*) principles (Sect. 6.2), including *double articulation, arbitrainess of signs*

(Sect. 6.1.4), *rule-governed creativity*, the *energy requirement* of information transduction, storage, and transmission (Sect. 4.8) (Ji 1997a, 2001). Both human and cell languages can be treated as 6-tuples, $\{L, W, S, G, P, M\}$, where L is the alphabet, W is the lexicon or the set of words, S is a set of sentences, G is a set of rules governing the formation of sentences from words (called the *first articulation*) and the formation of words from letters (the *second articulation*), P is a set of physical mechanisms necessary and sufficient to implement a language, and finally M is a set of objects or processes, both symbolic and material, referred to by words, sentences, and their higher-order structures (e.g., texts). In Table 6.3, cell and human languages are compared with respect to the components of the linguistic 6-tuple. Table 6.3 contains two important concepts, *conformons* and *IDSs*, which play fundamental roles in the *Bhopalator model* of the living cell (Ji 1985a, b, 1991, 2002b), the user of cell language, as discussed in Chaps. 8 and 9. It is convenient to refer to cell language as *cellese* and human language as *humanese* (Ji 1999b), and the science of *cell biology* may be viewed as the translation of *cellese* to *humanese*. To the best of my knowledge, the first concrete application of the cellese concept was made by Aykan (2007) in formulating his so-called message-adjusted network (MAN) model of the gastro-enteropancreatic endocrine system.

Just as human language can be viewed as a *linear* network of letters forming words (i.e., *second articulation*), words forming sentences (i.e., *first articulation*), and sentences forming texts (i.e., *third articulation* [Ji 2005a, pp. 17–18]), so bionetworks (e.g., individual proteins or their networks known as metabolic networks) can be viewed as *multidimensional* generalizations of linguistic networks, where, for example, amino acids can be compared to letters, proteins to words, complexes of proteins to sentences, and network of complexes as texts (see Rows 7, 8, and 9 in Table 6.3). In addition to these structural or morphological similarities, there is a set of conventional/evolutionary rules and physical principles that is common to both human and cell languages, including the following:

1. The principle of self-organization (PSO) (6.10)

The phenomenon of self-organization was first observed in physical (e.g., Bernard instability [Kondepudi and Prigogine 1998; Kondepudi 2008]) and chemical systems (e.g., Belousov–Zhabotinsky reaction) as discussed in Sect. 3.1. Since the cell is an example of self-organized systems, it would follow that one of its functions, namely, communication with its environment including other cells (and hence cell language itself), must be self-organizing. Self-organization on the cellular level entails generating molecular forces from exergonic chemical reactions occurring internally. Also, since human communication is built upon (or presupposes) cell communication, it too must be an example of self-organizing processes. Therefore, it can be concluded that both cell and human languages are rooted in (or ultimately driven by) self-organizing chemical reaction–diffusion systems.

2. The minimum energy requirement for information transmission (6.11)

Both human and cell languages can be viewed as means of transmitting information in space and/or time. All information transmission requires dissipating free energy as

Table 6.3 A *formal* comparison between human and cell languages (Ji 1997a, 1999b)

	Human language (*humanese*)	Cell language (*cellese*)
1. Alphabet (L)	Letters	4 Nucleotides (or 20 amino acids)
2. Lexicon (W)	Words	Genes (or polypeptides)
3. Sentences (S)	Strings of words	Sets of genes (or polypeptides) expressed (or synthesized) coordinately in space and time dictated by DNA folds[a] (cell states)
4. Grammar (G)	Rules of sentence formation	The *physical laws* and *biological rules* mapping DNA sequences to folding patterns of DNA (polypeptides) under biological conditions[b]
5. Phonetics (P)	Physiological structures and processes underlying phonation, audition, and interpretation, etc.	Concentration and mechanical waves responsible for information and energy transfer and transduction driven by *conformons*[c] and *intracellular dissipative structures* (IDSs)[d]
6. Semantics (M)	Meaning of words and sentences	*Codes* mapping molecular signs to gene-directed cell processes
7. First articulation	Formation of sentences from words	Organization of gene expression events in space and time through *non-covalent interactions*[e] between DNA and proteins (or Space- and time-dependent non-covalent interactions among proteins, DNA, and RNA molecules). Thus, macromolecular complexes can be viewed as molecular analogs of sentences
8. Second articulation	Formation of words from letters	Organization of nucleotides (or amino acids) into genes (or polypeptides) through covalent interactions[f]
9. Third articulation	Formation of texts from sentences	Organization of chemical concentration gradients in space and time called *dissipative structures* (Babloyantz 1986; Kondepudi and Prigogine 1998) or *dissipatons* (see Sect. 3.1.5) in order to "reason" and "compute"[g]

[a]Just as verbal sentences (as written) are strings of words arranged linearly in the Euclidean space, so the cell-linguistic (or molecular) sentences are visualized as series of gene expression events arranged in time leading to dissipative structures or dissipatons (Chap. 9)

[b]Of all the folds of DNA and polypeptides allowed for by the laws of physics and chemistry, only small subsets have been selected by evolution (thereby giving rise to *biological information*) to constitute the gernome of a cell

[c]Sequence-specific conformational strains that carry both free energy (to do work) and genetic information (to control work) (Ji 1974a, 2000) (Chap. 8). Conformons are thought to provide immediate driving force (or serve as the force generators) for all nonrandom molecular processes inside the cell. Experimental evidence for conformons is discussed in Sect. 8.3

(continued)

Table 6.3 (continued)

[d] Space- and time-specific intracellular gradients of ions, biochemicals, and mechanical stresses (e.g., of the cytoskeletal system) that serve as the immediate driving forces for all cell functions on the microscopic level (see Chap. 9)

[e] Also called "conformational" interactions which involve neither breaking nor forming covalent bonds and depend only on the rotation around, or bending of, covalent bonds. Non-covalent interactions implicate smaller energy changes (typically around 1–3 kcal/mol) than covalent interactions which entail energy changes in the range of 30–100 kcal/mol

[f] Molecular interactions that involve changes in covalent bonds, that is, changes in valence electronic configurations around nuclei of atoms within a molecule

[g] This row is added to the original table published in (Ji 1997a,b). The *third articulation* (Ji 2005a) is a generalization and an extension of *second articulation*. Intercellular communication through chemical concentration gradients is well established in microbiology in the phenomenon of *quorum sensing* (Sect. 15.7) (Waters et al. 2008; Stock et al. 2000), whereby bacteria express a set of genes only if there are enough of them around so that they can combine and coordinate their efforts to accomplish a common task which is beyond the capability of individual bacteria. This phenomenon can be viewed as a form of *reasoning* and *computing* on the molecular level and the cell therefore can be viewed as *the smallest computational unit* (Ji 1999a), which may be referred to as *the computon,* a new term used here for the first time

mandated by Shannon's channel capacity equation (see Sect. 4.8). For artificial communication systems, the requisite energy is provided *externally* (e.g., a power station); for natural communication systems such as cells, the needed energy is generated from chemical reactions occurring *internally* utilizing chemicals provided by their environment. This difference in the sources of energy may have profound role in determining the global differences between artificial and living systems (e.g., macro vs micro sizes of system components).

3. The complementarity between determinism and non-determinism (6.12)

The process of communication can be viewed as a complementary union of *determinism* and *nondeterminism*. The deterministic aspect of communication reflects both the energy requirement (e.g., PSO, MERIT) and the syntactic rules (e.g., grammar) inherent in the language employed in communication, and the nondeterministic aspect (e.g., the principle of the arbitrariness of signs [PAS], the principle of rule-governed creativity [RGC], both described in Sect. 6.1.4) reflects the freedom of choice available to the sender of a message. Shannon's formula, Eq. 4.2, coupled with the definition of information given in Eq. (4.4), clearly indicates that, when there is no choice (i.e., no uncertainty), there is no information (Pattee 2008, p. 119), since "no choice" means "no selection," which in turn signifies "no reduction" in uncertainty.

To summarize, cell and human languages are *symmetric* with respect to at least five principles. Thus, to borrow the idioms of the group theory in mathematics, it may be stated that cell and human languages are the members of a *symmetry group* that has five "symmetry operators," here identified with (1) PSO, (2) MERIT, (3) CDN, (4) PAS, and (5) RGC, and hence may be designated as SG(5), where S and G stand for symmetry and group, respectively, and the Arabic numeral indicates the number of the principles that remain unchanged (or invariant, or symmetric) when

Table 6.4 An estimation of the average information content, I, or the complexity, H, of a linguistic text or a metabolic pathway based on the *cellese-humanese isomorphism* thesis and the simplified version of Shannon's formula, Eq. (4.3). The cellese is postulated to consist of two sub-languages – DNese and proteinese

Language	Letters in alphabet (a)	Letters in a word (b)	Words in a sentence (c)	Sentences in a text (d)	Complexity[a] of a text (H or I, in bits)
English	26	~10	~10	~10	$\sim 4.7 \times 10^3$
DNese	~60 (nucleotide triplets)	~100 (genes)	~10 (genes co-expressed)	~10 (genes working as a pathway)	$\sim 5.9 \times 10^4$
Proteinese	20 (amino acids)	~100 (polypeptide)	~10 (complexes/ metabolons)	~10 (metabolic pathways)	$\sim 4.3 \times 10^4$

[a]The complexity of a linguistic system (viewed from the perspective of the message source) is measured in terms of Shannon's entropy, H, that is, Eq. (4.3), which is equivalent to information, I, when viewed from the receiver's point of view (Seife 2006)

one language is replaced by the other. In other words, cell and human languages may be said to belong to a linguistic symmetry group with five symmetry operators, that is, the SG(5) group.

The set of the five rules common to cell and human languages may be divided into two complementary subsets – (1) *physical laws* (to be denoted as the P set) and (2) *linguistic* or *semiotic principles* (to be denoted as the L set) (See Sect. 6.2). It is clear that PSO and MERIT belong to the P set, and that the members of the L set include the principles of triple articulation as indicated in Table 6.3, the principles of the *arbitrariness of signs* and *rule-governed creativity* that are discussed next. These results agree with the matter-symbol complementarity thesis of Pattee (1969, 2008) and the basic tenets of the semantic biology advocated by Barbieri (2003, 2008a, b).

6.1.3 The Complexities of the Cellese and the Humanese

One of the most useful results that can be derived from the *cellese-humanese isomorphism* thesis is our ability to estimate the complexity (or the information content per symbol) of the cellese based on our experience with the humanese (see Table 6.4). The maximum *complexity* (viewed from the perspective of the message source) or the maximum information content (viewed from the receiver's perspective) (Seife 2006) of an English text can be estimated using the simplified version of Shannon's formula (see Eq. 43), that is,

$$I = cbd \log_2 a \tag{6.13}$$

where a is the number of letter in an alphabet, b is the number of letters in a word, c is the number of words in a sentence, and d is the number of sentences in a text.

In other words, Eq. 6.13 is based on the *principle of triple articulations* (PTA), denoted as 1, 2, and 3 as shown in Scheme (6.14):

$$\textbf{Letters} \overset{1}{\rightarrow} \textbf{Words} \overset{2}{\rightarrow} \textbf{Sentences} \overset{3}{\rightarrow} \textbf{Texts} \tag{6.14}$$

The *cellese hypothesis* (Ji 1997a, 1999b) assumes that PTA, Eq. 6.14, applies to the molecular processes occurring in the living cell and identifies the three levels of articulations of the cellese as shown in Scheme (6.15):

$$\textbf{Monomers} \overset{1}{\rightarrow} \textbf{Biopolymers} \overset{2}{\rightarrow} \textbf{Compexes} \overset{3}{\rightarrow} \textbf{Networks} \tag{6.15}$$

We will refer to Scheme (6.15) as the principle of the *triple articulations of the cellese* (TAC).

It is interesting to note that the complexities of linguistic and molecular texts (see the last column of Table 6.4) are the same within one order of magnitude. The *cellese* can be viewed as the *formal* aspect of the living cell whereas the set of physicochemical principles and laws embodied in "biocybernetics" (Ji 1991) represents the *physical* (i.e., energetic/material) aspect of the living cell. In other words, it may be stated that

> The *cell language theory* (Ji 1991, 1999b) and *biocybernetics* (Ji 1991) are the complementary aspects of the Bhopalator, the molecular model of the living cell. (6.16)

6.1.4 *Double Articulation, Arbitrariness of Signs, and Rule-Governed Creativity*

Of the 13 design features of human language described by Hockett (1960), three of them stand out in terms of their possible application to biology. These are (1) *double articulation* (extended to the triple articulation described in Table 6.3, (2) *arbitrariness of signs,* and (3) *rule-governed creativity* (see Table 6.6). It will be shown below that these features have molecular counterparts in cell language and may be necessary to maximize the channel capacity of biological communication systems (Ji 1997a), thereby facilitating biological evolution itself.

In Table 6.3, cell and human languages are compared from a formal (i.e., linguistic) point of view. In contrast, Table 6.5 compares cell and human languages from a physical point of view.

One of the design features of the human language, *arbitrariness of signs*, states that there is *no inevitable link* between the signifier (also called signs or representamen) (see Fig. 6.2) and the signified (object or referent) (Lyons 1993, p. 71). The arbitrary nature of signs in human language contributes to the flexibility and versatility of language, according to linguists. In addition, the author suggested that the arbitrariness of signs maximizes the amount of the information that can be

Table 6.5 A *physical (or material)* comparison between human and cell languages

	Human language (*Humanese*)	Cell language (*Cellese*)
1. Scale	Macroscopic	Microscopic
2. Signifier	Words	Molecules
3. Signified	Concepts	Gene-directed molecular processes
4. Rules wrought by	Social conventions	Biological evolution
5. Information transmission by	Sounds and light (i.e., sound and electromagnetic waves)	Conformons[a] & IDSs[b] (i.e., mechanical and concentration waves)
6. Maximum Information Principle made possible by	Arbitrariness of signs with respect to their objects or referents	Arbitrariness of molecular signs with respect to their target functions

[a]Conformational strains of biopolymers localized in sequence-specific sites (Chap. 8)
[b]Intracellular dissipative structures such as gradients of ions, metabolites, proteins, etc. inside the cell (Chap. 9)

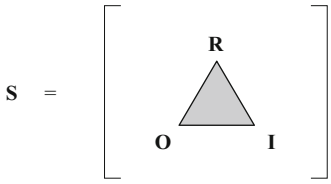


Fig. 6.2 A diagrammatic representation of the *Peircean sign triad*

transmitted by a sign, the idea being referred to as the *Maximum Information Principle* (Ji 1997a, pp. 36–37). Since cell language is isomorphic with human language, both belonging to the symmetry group, SG(5) (see Sect. 6.1.2), the *arbitrariness of signs* should apply to molecular signs in cell language, leading to the following inference:

> Just as the link between signs and their objects is arbitrary in human language, so the relation between molecular signs and their objects (or referents) are arbitrary, likely because such arbitrariness is necessary to maximize the amount of the information transmitted through or carried by molecular signs. (6.17)

For convenience, we will refer to Statement 6.17 as the *principle of the arbitrariness of molecular signs* (PAMS). Some experimental data supporting PAMS will be discussed in Sect. 12.10, where yeast RNAs are found to be divided into two distinct groups called the *cis*- and *trans-regulatory groups*, based on their genotypes, the former being less arbitrary (and thus carrying less genetic information) than the latter by a factor of about 3.

The *principle of arbitrariness of molecular signs* may be viewed as an aspect of the more general principle of *rule-governed creativity* (Ji 1997a). Both these principles appear to apply to multiple levels of biological organizations (as indicated in Table 6.6), from protein folding (Row 1a) to other processes on the molecular (Row 1b, 1c, and 1d) and cellular (Rows 2 and 3) levels.

Table 6.6 The principles of the arbitrariness of molecular signs, rule-governed creativity, and constrained freedom in action at various levels of living systems

Levels		Sign (rule, constraints)	Object/function (creativity, freedom)
1. Molecules	(a) Protein folding	Amino acid sequences	3-D shapes or folds
	(b) Catalysis	Protein shape	Chemical reaction catalyzed
	(c) Allostery	Allosteric ligand	Chemical reaction regulated
	(d) Binding	Transcription factor	Structural genes expressed
2. Cell–extracellular interactions		Intercellular messengers	Signal transduction pathways
3. Cell–intracellular interactions		Genome	Morphology, physiology

The arbitrary relation between amino acid sequence and the 3-D shape of a protein (see Row 1a in Table 6.6), which in turn determines its function, has already been pointed out in Tables 6.1 and 6.2 and is further discussed in Sect. 11.1. But protein folds are not entirely independent of amino acid sequences or completely dependent on them either, which may therefore be more accurately described as "quasi-deterministic" (Ji et al. 2009b). Although point mutations have been demonstrated to alter the shapes and functions of some proteins (but not all), it has also been found that an identical amino acid sequence can lead to more than one dominant conformations or folds, depending on the environmental conditions under which proteins fold. In fact, the Anfinsen's classic experiments with ribonuclease A carried out in 1954 clearly demonstrate how sensitively dependent ribonuclease A conformations are on the environmental conditions under which it folded. The refolding of the denatured ribonuclease A induced by the removal of urea followed by the removal of 2-mercaptoethanol led to the native conformation of the enzyme with the 100% recovery of its enzymic activity but, when the refolding was induced by removing the denaturants in the reverse order, that is, removing 2-mercaptoethanol first followed by the removal of urea, the enzyme folded into nonnative conformations with only 1% of its enzymic activity recovered. Thus, the Anfinsen experiment of 1954 supports the notion that *conformations of proteins are the functions of both* (1) *amino acid sequences* and (2) *the environmental conditions under which proteins fold*. These dual conditions for protein folding constitute the core of the *unpredictability of the 3-D protein folds* (U3DPF) (see Statement 6.1). Thus the principle of arbitrariness of molecular signs (PAMS), Statement 6.17, may best regarded as reflecting an aspect of the molecular version of the principle of *rule-governed creativity* (*RGC*), another of the 13 design features of human language (Hockett 1960). RGC states that native speakers are able to produce an indefinitely large number of novel sentences based on finite sets of words and grammatical (or syntactic) rules and that these sentences can be understood by others in the linguistic community even though they never encountered them before (Lyons 1992,

pp. 228–231; Harris 1993, pp. 57–58, 99–100). A *molecular version* of RGC may be stated as follows:

> Just as humans can produce an indefinitely large number of novel and meaningful sentences based on finite sets of words and grammatical rules, so living cells have evolved to produce an indefinitely large number of novel (i.e., unpredictable) functional molecular processes based on finite sets of molecules and physicochemical principles. (6.18)

Statement 6.18 may be referred to as the principle of rule-governed productivity, the principle of constrained freedom (PCF), or the principle of rule-governed molecular creativity. The principle of constrained freedom is symmetric or isomorphic with the principle of rule-governed creativity with respect to the following transformations.

1. Replacing "rule-governed" with "constrained"
2. Replacing "creativity" with "freedom"

These mutually replaceable elements in quotation marks may be considered to form a group comparable to the permutation group of Galois in his theory of polynomial equations (http://en.wikipedia.org/wiki/Galois_theory).

Just as it is impossible to predict the 3-D folds of a protein based on its amino acid sequence, so it is suggested in Row 1b in Table 6.6 that *it would be impossible to predict the nature of the chemical reaction that is catalyzed by an enzyme based solely on the 3-D shape (also called conformers, not to be confused with conformons of Chap. 8) of the enzymes alone, because the link between protein shape and the chemical reactions it catalyzes is not deterministic but arbitrary within physicochemical constraints (and hence quasi-deterministic),* reflecting the uncertainty about the environmental conditions under which biological evolution has selected the particular enzyme-catalyzed reaction.

The arbitrariness of the link between the shape of an allosteric ligand and the enzymic reaction it regulates (Row 1c) was pointed out by J. Monod (1971) who referred to it as "gratuity." Similarly, it is suggested in Row 1d that the link between the shape of a transcription factor and the nature of the structural gene whose expression it regulates is arbitrary within physicochemical constraints (i.e., *quasi-deterministic*), presumably to maximize the efficiency of the information transfer mediated by transcription factors (Ji 1997a).

Again in analogy to the unpredictability of the 3-D protein folds from amino acid sequences alone, so it is thought to be impossible to predict a priori the nature of the signal transduction pathways being activated based on the 3-D shape of intercellular messengers (Row 2) such as hormones, cytokines, and autoinducers.

Finally, Row 3 in Table 6.6 suggests that there may be no inevitable (i.e., deterministic) link between a genome and its phenotype, including the morphology and physiological processes of the organism involved. For example, human anatomy and physiology are arbitrarily related to and hence cannot be predicted from the human genome based on the laws of physics and chemistry alone. Again, to the extent that the link between a genome and its phenotype is arbitrary in the above sense, the genome has been optimized in order to transfer information from one

generation to the next which entails information transfer in space and time. The identical twin studies of the human brain cognitive functions using functional magnetic resonance imaging (fMRI) technique (Koten Jr. et al. 2009) indicates that brain functions, such as memorizing and recognition, are partly gene-dependent and partly gene-independent, that is, quasi-deterministic with respect to genetic influence, consistent with the *principle of constrained freedom*.

6.2 Semiotics

Semiotics is the study of signs that dates back to ancient times when farmers predicted the weather from cloud patterns in the sky, or doctors diagnosed diseases based on the symptoms of patients. The American chemist-logician-philosopher Charles Sanders Peirce (1839–1914) has made a major contribution to establishing the field of modern semiotics which has been applied to a wide range of disciplines from linguistics to art, to philosophy, and to biology (Sebeok 1990; Emmeche 2002, 2003; Hoffmeyer 1996; Barbieri 2008a, b, c; Fernández 2008). Since signs can be divided into two types – macroscopic (e.g., stop signs) and microscopic (e.g., DNA) – based on their physical sizes, it would follow that semiotics itself can be divided into two branches – *macrosemiotics* and *microsemiotics* (Ji 2001, 2002a). Few biologists would deny that DNA molecules are *molecular signs,* since they encode (or refer to) RNA and protein molecules that are different from themselves. Likewise, few biologists would deny that the cell is the smallest physical system that can read and implement the genetic information/instructions encoded in DNA, leading to the following conclusions:

Molecular and cell biology constitute a part of *biosemiotics*, the study of living systems viewed as sign processors (Emmeche 2003), and since the cell is arguably the smallest DNA-based physical system that can process molecular information and perform molecular computation in the sense of Wolfram (2002) (Ji 1999a) and since the cell is the smallest unit of all living systems, *microsemiotics* constitutes the foundation of *biosemiotics*, just as *statistical mechanics* underlies *thermodynamics*.

6.2.1 The Peircean Theory of Signs

According to Peirce,

> A *sign*, . . ., is *something* which stands to *somebody* for *something* in some *respect* or *capacity*. (Buchler 1955, p. 99) (6.19)

Thus, "apple" is a sign referring to a juicy spherical fruit to someone, E, who speaks English. But "apple" is not a sign for a Korean, K, who does not understand English. For K, the sign, S, for the same object, O, is not "apple" but "sah-gwah."

So, it is evident that the definition of a sign, S, must include, in addition to O, a third element that Peirce referred to as *interpretant*, I, which is well characterized in the following paragraph quoted in (Houser et al. 1998):

> A *sign* is a thing which serves to convey knowledge of some other thing, which it is said to *stand for* or *represent*. This thing is called the *object* of the sign; the idea in the mind that the sign excites, which is a mental sign of the same object, is called an *interpretant* of the sign. (6.20)

Thus, the interpretant is the effect that S has on the mind of its interpreter or as the mechanisms or processes by which the interpreter or the processor of S is made to connect O and S. That is, in order for a sign process to occur successfully, there must be interactions among three elements, S, O, and I, within the sign processor. It was Peirce who first recognized the necessity of invoking these three elements in the definition of a sign and their actions (which he called "semiosis"). In other words, a sign, according to Peirce, is an irreducible triad of S, O, and I, which idea is often referred to as the "irreducibility of the sign triad" or the "triadicity of a sign." It is important to note that, in this definition of a sign, the term "sign" has dual roles – as a *component* of the sign triad and as the *sign triad itself*. To distinguish between these two roles, Peirce coined the term "representamen" to refer to the narrower sense of the term sign (Buchler 1955, p. 121). Thus, we may represent the Peircean definition of a sign diagrammatically as follows:

S = sign, **R** = representamen (also often called a *sign or a sign vehicle*), **O** = object, and **I** = interpretant. Unless pointed out otherwise, sign usually means **R**, a component of the irreducible sign triad. Also, it is important to note that the interpreter of **R** or the material system that process **R**, thereby implementing semiosis, is not explicitly discussed in semiotics literature but is assumed to be present. We may use the triangle itself to represent this interpreter, thus graphically distinguishing between *interpretant* (one of the three apexes or nodes) and *interpreter* (the triangle itself). It is important to note that the bracket symbolizes the *inrreducibility* of Peircean sign triad, that is, none of the three elements can be replaced by any other.

Although the study of signs can be traced back to the beginning of the human history as already pointed out, the investigation of signs as a fundamental science did not begin until the Portuguese monk John Poinsot (1589–1644) and C. S. Peirce (apparently independently of Poinsot) undertook their comprehensive and systematic studies of signs (Deely 2001).

The definition of signs that Peirce formulated can be extended to molecular biology, although Peirce probably did not know that such a possibility existed because he died about four decades before Watson and Crick discovered the DNA double helix that ushered in the era of molecular biology. Genes encoded in DNA fit the definition of the Peircean sign because they encode and stand for their complementary transcripts, RNA molecules and their functions, which are evidently distinct from the molecular structure of DNA. One plausible candidate for the *interpretant* for DNA viewed as a molecular sign is the *state of the cell*, since whether a given gene encoded in DNA is transcribed to RNA or not depends on the

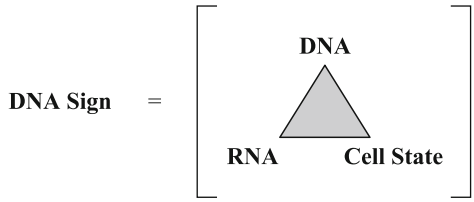


Fig. 6.3 Genes encoded in DNA as an example of Peircean signs at the molecular level. The role of interpretant is suggested to be fulfilled by *cell states*, and the interpreter of DNA is postulated to be the *cell* itself represented by the triangle. This definition seems to be consistent with the finding that only a select set of genes are expressed in cells at any given time and under any given environmental condition depending on the internal state of the cell (Nishikawa et al. 2008)

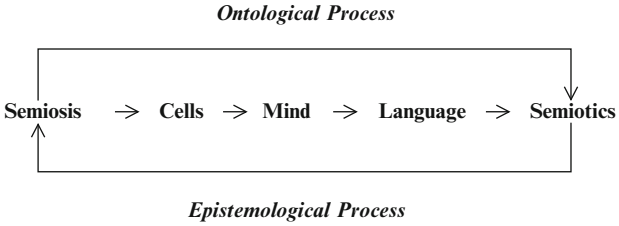


Fig. 6.4 The cyclical, or reversible, relation between *semiosis* and *semiotics*. The expression "A –> B" should be read as "B presupposes A" or "B cannot exist without A." The *upper arrow* from *left* to *right* indicates the *ontological* process in the Universe known as *evolution*, while the *lower arrow* from *right* to *left* signifies the *epistemological* causal relation resulting from the inferential activities of the human mind. It is assumed that ontological processes are independent of the human mind but epistemological processes are dependent on it. This figure is consistent with the principle of closure discussed in Sect. 6.3.2

state the cell is in, leading to the following diagrammatic representation of DNA as a sign (Ji 2002a) (Fig. 6.3).

Peirce distinguished between *semiotics* and *semiosis*. Semiotics is the systematic knowledge that human mind has created about semiosis based on empirical data, while semiosis refers to the totality of the natural and artificial processes whose occurrence requires the mediating role of signs. Thus, we may logically conclude that, *although semiotics depends on human mind, semiosis does not*. The causal relation between *semiotics* and *semiosis* may be represented diagrammatically as shown in Fig. 6.4.

6.2.2 *The Principle of Irreducible Triadicity: The Metaphysics of Peirce*

According to the metaphysics of Peirce, all phenomena, material or mental, living or nonliving, comprise three basic elements or aspects – *Firstness* (e.g., quality,

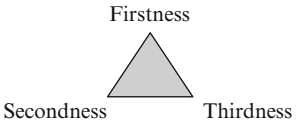


Fig. 6.5 A diagrammatic representation of the principle of irreducible triadicity of Firstness, Secondness, and Thirdness of Peirce (Goudge 1969; Hausman 1997; de Waal 2001; Sheriff 1994; Feibleman 1946)

feeling, possibilities), *Secondness* (e.g., facts, actualities, reaction, interaction, brute force), and *Thirdness* (e.g., generality, laws, habit-taking, representation, reasoning) (Fig. 6.5). For example, in logic, there are three kinds of relations; C = monadic, A = dyadic, and B = triadic relation. We may represent this principle diagrammatically as follows:

The *Threeness* plays a fundamental role in the metaphysics of Peirce, metaphysics being the study of the most general traits of reality. *Reality is the object of the conclusions one cannot help drawing*. As pointed out by Pierce, "When a mathematical demonstration is clearly apprehended, we are forced to admit the conclusion. It is evident; and we cannot think otherwise." (Goudge 1969). Metaphysics studies "the kinds of phenomena with which every man's experience is so saturated that he usually pays no particular attention to them." One way to get a feel of the three metaphysical categories of Peirce is through some of the examples that Peirce gave of these categories throughout his career. These are collected in Table 6.7, which was adopted from (Debrock 1998). It is evident that the examples are not logically tight, and, indeed, they are "vague" or "fuzzy" (Sect. 5.2.5), and even contradictory in some cases, having some overlaps here and there and missing some examples as well. Nevertheless, it is possible to recognize (1) the unmistakable family resemblances among most of the items listed within each category (i.e., within each column) and (2) distinct family characteristics present among the three categories (i.e., within each row).

6.2.3 Peircean Signs as Gnergons

One corollary of Fig. 6.4 is that the elucidation of the connection between *semiotics* and *life* would be tantamount to elucidating the principles underlying *semiosis* itself (in agreement with Sebeok 1990), and this is because life (as exemplified by cells and mind) presupposes semiosis. Based on the information-energy complementarity principle discussed in Sect. 2.3.2, we can conclude that, like all fundamental processes in nature, *semiosis* must have two complementary aspects – the *energetic/material* (e.g., computer hardware, or ATP in cells) and the *informational* (e.g., computer software or genetic information encoded in DNA). Of these two aspects,

Table 6.7 The evolution of Peirce's nomenclature of categories (Reproduced from Debrock 1998 except items 8 and 9)

	Year (*Peirce's age*)	Firstness	Secondness	Thirdness
1	1867 (*28*)	Quality	Relation	Representation
2	1891 (*52*)	First	Second	Third
3		Spontaneity	Dependence	Mediation
4		Mind	Matter	Evolution
5		Chance	Law	Tendency to take habits
6		Sporting	Heredity	Fixation of character
7		Feeling	Reaction	Mediation
8	1894 (*55*)	–	–	Learning
9		–	–	Government
10	1896 (*57*)	Quality	Fact	Law
11	1897 (*58*)	Ideas of feelings	Acts of reaction	Habits
12		Quality	Shock/vividness	–
13		Feeling	Reaction	Thought
14	1898 (*59*)	Quality	Reaction	Mediation
15		First qualities/ideas	Existence/reaction	Potential/continuity

the traditional semiotics as formulated by Peirce has emphasized primarily the *informational* aspect of semiosis, apparently ignoring the equally fundamental e*nergetic*/*material* aspect. It was only with the advances made in both *experimental* and *theoretical* branches of molecular and cell biology during the past several decades that *the essentiality of the energy*/*material aspect of semiosis has come to light* (Ji 1974a, b, 1985a, b, 1988, 1991, 1997a, b, 1999b, 2000, 2002a, b, 2004a, b). Thus it has been postulated that all self-organizing processes in the Universe, including semiosis, are driven by a complementary union *of information* and *energy,* that is, *gnergy* (Sects. 2.3.2 and 4.13) and (Ji 1991, 1995). Since information can be alternatively called "gnon" (from the Greek root *gnosis* meaning knowledge) and energy "ergon" (from Greek root *ergon* meaning work or energy), the *gnergon*, the discrete unit of *gnergy*, can be viewed as the complementary union of the *gnon* and the *ergon*:

$$\text{Gnergon} = \text{Gnon}^{\wedge}\text{Ergon} \tag{6.21}$$

where the symbol "^" denotes a *generalized complementarity relation as* defined in Sect. 2.3.3 (Ji 1991, 1995). That is, "C = A^B" reads as "A and B are complementary aspects of C," or "C is a complementary union of A and B." Since it has been postulated that Gnergy serves as the universal driving force for all self-organizing processes in this Universe (see Fig. 4.8), including molecular processes in the living cell (Ji 1991), we can interpret Fig. 6.4 as implying the following general statement:

Life results from *semiosis* driven by *gnergy*. (6.22)

Those not familiar with Peirce's (1839–1914) semiotics may think of signs as synonymous with "symbols" like stop signs and written words on printed pages.

Table 6.8 The classification of signs based on the dual trichotomies – (1) the ontological/material trichotomy (OT) (*first row*), and (2) the phenomenological/formal (PT) trichotomy (*first column*) (Ji 2002c)

	OT		
PT	Firstness (Potentiality)	Secondness (Facts)	Thirdness (Law)
Firstness (Sign)	*Qualisign*	*Sinsign*	*Legisign*
Secondness (Object)	*Icon*	*Index*	*Symbol*
Thirdness (Interpretant)	*Rheme*	*Dicent Sign*	*Argument*

Such a view is frequently referred to as "glossocentric" or "language-centered." But the concept of signs according to Peirce is much more general and includes not only linguistic symbols, but also icons (e.g., portraits, statutes, maps, electronic circuit diagrams), and indexes (e.g., smokes, laughter, fever, weathervane). The generality of signs is, in part, due to the fact that we think in signs. As someone said: *Think of an elephant; do you have an elephant in your head?* The neuronal firing patterns associated with our thoughts are signs representing their objects, whatever they may be, because neuronal firing patterns are not identical with the objects that they stand for. Peirce divides signs into a total of nine classes (Buchler 1955):

> Signs are divisible by three trichotomies; first, according as the sign itself is a mere quality ["qualisign"], is an actual existent ["sinsign"], or is a general law ["legisign"; secondly, according as the relation of the sign to its object consists in the sign's having some character in itself ('icon'), or in some existential relation to the object ["index"], or in its relation to an interpretant ["symbol"]; thirdly, according as its interpretant represents it as a sign of possibility ["rheme"] or as a sign of fact ["dicent sign"] or a sign of reason ["argument"]. (6.23)

The term "interpretant" here can be understood as the effect that a sign has on the mind of an interpreter, or as "meaning," "significance," or "more advanced sign." The above classification of signs by Peirce is summarized in Table 6.8.

Each of the nine types of signs appearing in the *interior* of Table 6.8 has dual aspects (reminiscent of the wave/particle duality of light) – (1) the *ontological* (or *material*) aspect and (2) the *phenomenological* (or *formal*) aspects, which appear on the *margins* of the table. The ontological/material aspect of a sign can be identified with *energy*/*matter* properties, while the phenomenological/formal aspect with *informational* properties. It is for this reason that the Peircean signs located in the interior of Table 6.8 can be viewed as examples of *gnergons*, the discrete units of gnergy postulated to be the ultimate cause of, or ground for, all self-organizing (or pattern-forming) processes in the Universe (Ji 1991, 1995). Since all sign processes (semiosis) can be viewed as species of self-organizing processes, ultimately driven by the free energy of exergonic chemical reactions (e.g., ATP hydrolysis or oxidation of NADH) or physical processes (e.g., heat flow, solar radiation, the Big Bang, etc.), it would follow that gnergons are the ultimate causes of semiosis (Ji 1995, 2002c) consistent with Fig. 4.8.

Complementarism, a scientific metaphysics rooted in both contemporary biology and Bohr's complementarity (Sect. 2.3.4), states that the ultimate reality consists in a complementary union of *information* and *energy*, that is, *gnergy*. Since signs are species of gnergons, it would follow that Peirce's semiotics falls within the domain of complementarism. This assertion may be supported by the following arguments:

1. Peirce's semiotics deals mainly with macroscopic signs, that is, signs with macroscopic dimensions "perfusing" the Universe; Peirce dealt mainly with *macrosemiotics*. This is not surprising because Peirce died in 1914, about four decades before the discovery of DNA double helix that ushered in the age of molecular biology and *microsemiotics* (Ji 2001, 2002a).
2. Complementarism can be applied not only to Peirce's semiotics (as suggested above) but also to molecular and cell biology, as evident in the formulation of the theory of "microsemiotics" based on the gnergy concept (Ji 2002a, c). *Microsemiotics* can be regarded as synonymous with the twin theories of the living systems known as *biocybernetics* (Ji 1991) and *cell language theory* (Ji 1997a). Thus the following relation suggests itself:

$$\begin{aligned}\text{Complementarism} &= \textit{Macrosemiotics} + \textit{Microsemiotics} \\ &= \text{Peirce's semiotics} + \text{Biocybernetics}/ \\ &\quad \text{Cell Language Theory}\end{aligned} \tag{6.24}$$

Consistent with Peirce's triadic ontology, the principle of *complementarity* may itself be manifested in the Universe in three distinct modes:

Firstness = **Complementarity in metaphysics** (e.g., Yin and Yang as complementary aspects of the Tao of Lao-tze; Extension and Thought as the complementary aspects of Substance of Spinoza; Body and Mind as the complementary aspects of the Flesh of Merleau-Ponty [Dillon 1997])

Secondness = **Complementarity in physics** (e.g., the wave-particle duality of light)

Thirdness = **Complementarity in life sciences** (e.g., hysterical anesthesia of William James [Stephenson 1986]), physiology (i.e., the left-right hemispheric specialization [Cook 1986]), and molecular and cell biology (e.g., the *information-energy complementarity* of *gnergy* [Ji 1991, 1995])

These ideas are schematically represented in Fig. 6.6.

If the ideas expressed in Fig. 6.6 are correct, the separation and divergence of physics and metaphysics that are widely believed to have begun with Galileo's experiments with falling bodies in the seventeenth century may be expected to be reversed through the mediating role of the life sciences in the twenty-first century. In other words, the principle of information/energy complementarity manifested in *biology* (Ji 1991, 1995) may provide the theoretical framework for integrating *metaphysics* and *physics*.

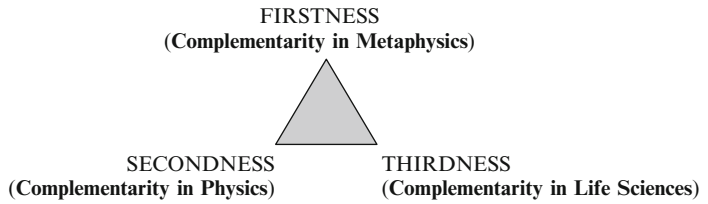


Fig. 6.6 The three modes of being of the generalized complementarity (Ji 1995). This diagram suggests the possibility that *life sciences* as Thirdness may serve as the mediator between *metaphysics* and *physics*. *Life science* may be viewed as synonymous with *cognitive sciences, since all organisms are cognizant of and interact with their environment*. The three nodes of the triangle may also be interpreted diachronically (Sect. 4.5): Firstness gave rise to Secondness, which in turn gave rise to Thirdness

6.2.4 Macrosemiotics versus Microsemiotics: The Sebeok Doctrine of Signs

As indicated in Sect. 6.2, we can divide semiotics into two branches – the *macrosemiotics* dealing with macroscopic signs such as written words and texts, and the *microsemiotics* concerned with molecular signs such as DNA, cytokines, and neurotransmitters, etc. Peirce did not have access to the empirical evidence that came to light only in the mid-twentieth century, that semiotic processes are not confined to the macroscopic world (*macrosemiosis*) but also occur on the molecular level (*microsemiosis*). The possibility of extending Peircean semiotics from macroscale to microscale was clearly foreseen by Sebeok in 1968 when he wrote (as cited in Deely 2001):

> . . .the genetic code must be regarded as the most fundamental of all semiotic networks and therefore as the prototype for all other signaling systems used by animals, including man. From this point of view, molecules that are quantum systems, acting as stable physical information carriers, zoosemiotic systems, and, finally, cultural systems, comprehending language, constitute a natural sequel of stages of ever more complex energy levels in a single universal evolution. It is possible, therefore, to describe language as well as living systems from unified cybernetic standpoint . . . A mutual appreciation of genetics, animal communication studies, and linguistics may lead to a full understanding of the dynamics of semiotics, and this may, in the last analysis, turn out to be no less than the definition of life. (6.25)

Elsewhere (Ji 2001), it was suggested that Statement 6.25 be referred to as the *Sebeok doctrine of signs* for convenience of reference.

The first full-length paper on microsemiotics was published in (Ji 2002a). Despite the enormous difference in the sizes of the sign processors involved in macro- and microsemiosis (see Table 6.9 below), it is surprising that there exists a

Table 6.9 A comparison between the physical dimensions of the *macrosemiotic* and *microsemiotic agents*. Notice that the linear dimension of the human body is about five orders of magnitude greater than that of the cell (Adapted from Ji 2001)

Parameters	Macrosemiotics	Microsemiotics
1. *Sign processor or agent*	Human body	Cell
2. *Size*	Macroscopic	Microscopic
Linear size (m)	~1	$\sim 10^{-5}$
Volume (m^3)	~1	$\sim 10^{-15}$
3. *Number of cells involved*	$\sim 10^{13}$	1
4. *Signs used for communication*	Words and sentences	Molecules
Linear size (m)	$\sim 10^{-3}$	$\sim 10^{-8}$
Volume (m^3)	$\sim 10^{-9}$	$\sim 10^{-24}$
5. *Mechanics obeyed*	Classical	Classical and quantum
6. *Thermal stability at ~25°C*	Yes (i.e., rigid)	No (i.e., thermally fluctuating)
7. *Powered (or driven) by*	Chemical reactions	Chemical reactions

set of principles that is common to the semiotic processes on both these levels as evidenced by the isomorphism found between human and cell languages (see Table 6.3) (Ji 1997a, b, 1999b, 2001, 2002a). This unexpected finding may be rationalized if we can assume that semiosis, the process of handling *information*, is scale-free, just as the process of handling *energy* are scale-free as evidenced by the universal applicability of the laws of energy and entropy to all structures and processes in the Universe from the microscopic to the cosmological, another evidence supporting *the information-energy complementarity* principle discussed in Sect. 2.3.2.

6.2.5 *Three Aspects of Molecular Signs: Iconic, Indexical, and Symbolic*

If *macrosemiotics* and *microsemiotics* are isomorphic as asserted by the cell language theory (Ji 1997a, 2001), it may be inferred that the triadic aspects of macrosigns (i.e., signs with macroscopic sizes, Table 6.9), namely, the iconic, indexical, and symbolic aspects (Table 6.8), may also be found in microsigns (or molecular signs). As already indicated in Sects. 6.2.1 and 6.2.3, (1) a *sign* stands for something (called *object or signified*) to someone (interpreter, receiver, or sign processor) in some context (environmental contingencies), and (2) there are three kinds of signs – *iconic* signs (e.g., a statute) related to their objects by *similarity*, *indexical* signs (e.g., smoke) related to their objects by *causality*, and *symbolic* signs (e.g., words) related to their objects by *convention, rules,* and *codes* which are *arbitrary* from the standpoint of the laws of physics and chemistry.

Applying these concepts and definitions to the molecular information processing systems in the living cell, it may be conjectured (1) that DNA serves as the sign for RNA to cells during the transcription step catalyzed by *transcriptosomes*, RNA in

turn serving as the sign for proteins during the translation step catalyzed by *ribosomes*, (2) that the relation between DNA and RNA during transcription is primarily iconic (due to Watson-Crick base paring) and indexical (requiring the mechanical energy stored in DNA as *conformons* (Ji 2000) to power orderly molecular motions), and (3) the relation between mRNA and protein synthesized during translation is *iconic* (owing to the complementary shapes of codons and anticodons), *indexical* (requiring *conformons* in the ribosome to drive the orderly movement, or *translation*, of aminoacyl tRNA molecules along the mRNA track), and *symbolic* (due to the *arbitrariness of the relation* between the codons of mRNA and the corresponding amino acids carried by tRNA, i.e., the arbitrariness of the genetic code) (Barbieri 2003, 2008c).

If these conjectures prove to be correct in principle, it would be logical to conclude that biological information processing in the cell cannot be completely characterized in terms of the *laws* of physics and chemistry alone but requires, in addition, the *rules* (e.g., genetic codes) engendered by biological evolution, thus supporting the *von Neumann–Pattee principle of matter-sign complementarity* as applied to biological systems (Pattee 2001, 2008; Ji 1999a, b). In other words, biology is best viewed not as an autonomous science separate from physics and chemistry as some evolutionary biologists assert but a *triadic* science based on *physics, chemistry,* and *semiotics* on equal footings.

6.2.6 Human and Cell Languages as Manifestations of Cosmolanguage

The proposition that the cell possesses its own language, "the cell language," seems almost tautological in view of the fact that cells communicate, since *no communication would be possible without a language*. The natural question that then arises concerns the relation between human language and cell languages. There may be three possibilities:

1. Human language has evolved from cell language.
2. Both cell and human languages are different manifestations of a third language that exists independent of, and serves as the source of, them.
3. Possibilities (1) and (2) are not mutually exclusive but represent the *diachronic* and the *synchronic* manifestations, respectively, of the fundamental characteristics of the Universe we inhabit, namely, that *the final cause of our Universe is to know itself through Homo sapiens*. (Such a Universe was named *the Self-Knowing Universe* or *Universum sapiens* in Ji [1991].)

The author is inclined to accept the third possibility. If this view is true, we are living in the *Self-Knowing Universe* where both cell and human languages exist as diachronic manifestations of a third language which may be referred to as the Cosmological language (or *Cosmolanguage*, for short). By invoking the existence

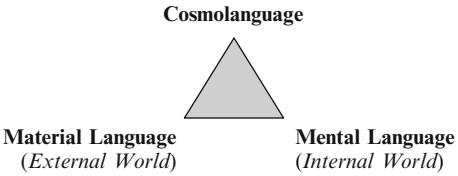


Fig. 6.7 The postulate that the cosmolanguage is manifest in two ways – externally as material language (including cell language) and internally as mental language (exclusive to *Homo sapiens*?)

of the cosmolanguage, I am in effect postulating that the *language principle* (or more generally *semiotic principles*) applies to all phenomena in the Universe. In Ji (2002a), I expressed the same conclusion as follows:

> *. . . the principles of language (and associated semiotic principles of Peirce, including rule-governed creativity and double articulation) are manifested* at two levels – at the material level in the external world as well as at the mental level in the internal world. We may refer to this phenomenon as the "principle of the dual manifestations of language or semiosic principles", or the "language duality" for short. Like the wave/particle duality in physics, this matter/mind duality may be a reflection of a deep-lying complementarity which may be identified with the following triad. . .: (6.26)

Figure 6.7 can be read in two ways – diachronically (or ontologically) as indicating the evolution of the mental and material languages from the cosmolanguage, and synchronically (or epistemologically) as indicating that the material and mental languages are complementary aspects of the cosmolanguage. Both these interpretations are consistent with the model of the Universe called the Shillongator proposed in (Ji 1991). Figure 6.7 may be consistent with Wolfram's *Principle of Computational Equivalence* (Sect. 5.2.1) if we view language, communication, and computation as fundamentally related.

6.2.7 Semiotics and Life Sciences

S*emiotics* and the *science of life* (i.e., biology, agricultural science, and medicine) have had a long and venerable history of interactions (e.g., ancient physicians in both East and West diagnosed the diseases of patients based on symptoms; farmers used cloud patterns to predict weather, etc.), but the connection between *semiotics* and *life sciences* in general may have undergone a significant weakening when the reductionist scientific methodologies were imported into life sciences from physics and chemistry around the nineteenth century. The reductionist trend in physics began with the birth of the mathematically oriented physics following the successful experiments with falling bodies performed by Galileo in the seventeenth century. After over three centuries of domination of physical and biological

sciences by reductionism, a new trend seems to be emerging in physics and life sciences that emphasizes *integration* and *holism*, without necessarily denying the fundamental importance of *reductionism* (Elsasser 1998; von Baeyer 2004; Emmeche 2002; Hoffmeyer 1996, 2008; Fernández 2008). As a concrete example of such a new trend, we may cite the isomorphism found between the cell language and the human language (see Table 6.3). One of the major goals of this book is to reveal the deep connection that exists between *life* and *semiosis*, thereby laying the foundation for a *semiotic theory of life*, or organisms viewed as systems of *molecular signs* and *sign processes* (Hoffmeyer 1996).

6.2.8 Semiotics and Information Theory

The study of information may not be successfully carried out without the aid of *semiotics*. This is because information is carried by *signs* (without signs, no information can be generated, transformed, stored, or transmitted) and the study of signs in general is the domain of *semiotics*. Nauta (1972) states a similar view in greater details:

> . . .Much work has been done in the field of pure information theory, but the problems concerning the meaning (i.e., semantics vis-à-vis syntactic; my addition) and application (i.e., pragmatics: my addition) of information have largely been neglected. In our opinion, these important problems can be tackled only from a semiotic point of view. The key to these problems will be the analysis of signals, signs and symbols. (Nauta 1972, p. 29) (6.27)

> Semiotics, divided into transmission theory, syntactics, semantics and pragmatics, and subdivided into pure, descriptive, and applied semiotics, offers a general framework for the study of information processes and for the development of a universal theory of information. In its generalized form, semiotics encompasses the following fields: Logistics (artificial symbols) Linguistics (symbols) Semiotics in a narrower sense (signs) Automatics, the study of automatic processes and pre-coded representations and mechanisms (signals). (Nauta 1972, pp. 61–62) (6.28)

Nauta distinguishes three information carriers – "signals," "signs," and "symbols" (Table 6.10). He defines signals as carriers of *form* but not *meaning* or *function*; signs as carriers of form and meaning but not of function; symbols as carriers of form, meaning, and functions. This contrasts with Peirce's division of signs into "iconic signs," "indexical signs," and "symbolic signs," each of which can have form, meaning, and function (Table 6.10).

It is not clear to me why Nauta invoked his triad of information carriers rather than using Peirce's original sign triad, but it may be possible to represent Nauta's information carriers as linear combinations of Peirce's triadic signs. Writing Nauta's information carriers with capital letters and Peirce's signs with lowercase letters, we may construct a set of algebraic equations as shown below, where

Table 6.10 Definition of signals, signs, and symbols according to Nauta (1972, p. 159)

	Form	Meaning	Function
Signals	+	−	−
Signs	+	+	−
Symbols	+	+	+

doubly indexed coefficients, a_{ij}, indicate the degree of contribution of Peircean signs to a given information carrier (IC) of Nauta:

$$\begin{aligned} \text{Signal} = \text{IC}_1 &= a_{11}\,\text{icon} + a_{12}\,\text{index} + a_{13}\,\text{symbol} \\ \text{Sign} = \text{IC}_2 &= a_{21}\,\text{icon} + a_{22}\,\text{index} + a_{23}\,\text{symbol} \\ \text{Symbol} = \text{IC}_3 &= a_{31}\,\text{icon} + a_{32}\,\text{index} + a_{33}\,\text{symbol} \end{aligned} \tag{6.29}$$

In general, we may write:

$$\mathbf{A}x = b \tag{6.30}$$

with

$$A = \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix}, \quad x = \begin{bmatrix} \text{icon} \\ \text{index} \\ \text{symbol} \end{bmatrix}, \quad \text{and} \quad b = \begin{bmatrix} \text{IC}_1 \\ \text{IC}_2 \\ \text{IC}_3 \end{bmatrix}$$

Equation 6.30 may be viewed as an algebraic expression for the relation between *information theory* (as represented by b) and semiotics (as represented by x) and **A** as the rule of transforming the Peircean semiotics to the information theory according to Nauta (1972).

More recently, Debrock (1998, pp. 79–89) proposed a novel theory of information viewing information as *events* rather than as *entities* and suggested that such a dynamic approach to information may be consistent with the Peirce's theory of signs. Debrock's suggestion seems consistent with the postulate that Peircean signs are gnergons, the source of energy and information to drive all self-organizing processes, including informed events (see Sect. 6.2.3).

6.2.9 The Cell as the Atom of Semiosis

The following statement is often made as a useful metaphor:

The cell is the atom of life. (6.31)

In addition, it is asserted here that :

The cell is the atom of semiosis. (6.32)

The term "semiosis" is defined as any physicochemical processes that are mediated by *signs* such as *communication*, *computation,* and DNA-directed *construction.* This triad of processes was referred to as *the C-triad* in (Ji and Ciobanu 2003).

One consequence of combining Statements 6.31 and 6.32 is the corollary that the *cell provides the physical basis and mechanisms for both living processes and semiosis*. A theoretical model of the cell, capable of achieving both these functions, was first proposed in 1983 in an international conference on the Living State held in Bhopal, India, and hence was named the *Bhopalator* (Fig. 2.11) (Ji 1985a, b, 2002b). One of the basic principles underlying the Bhopalator is that of *information-energy complementarity* as manifested in two ways – as *conformons* (conformational strains of biopolymers harboring mechanical energy in sequence-specific sites; see Chap. 8) and as *IDSs* (intracellular dissipative structures such as cytosolic calcium ion gradient; see Chap. 9).

6.2.10 The Origin of Information Suggested by Peircean Metaphysics

In this section, the general problem of the origin of information (including biological and nonbiological) is discussed based on Peirce's metaphysics (Sect. 6.2.2). As is evident in the following quotations, Peirce made a clear distinction between *possibility*, Firstness, and actuality, Secondness (see Table 6.7):

> Possibility implies a relation to what exists. (Hartshorne and Weiss 1931–1935, paragraph #531)
>
> . . .a possibility remains possible when it is not actual (Hartshorne and Weiss 1932, paragraph #42)
>
> . . .possibility evolves the actuality (Hartshorne and Weiss 1932, paragraph #453)
>
> In order to represent to our minds the relation between the universe of possibilities and the universe of actual existent facts, if we are going to think of the latter as a surface, we must think of the former as three-dimensional space in which any surface would represent all the facts that might exist in one existential universe. (Hartshorne and Weiss 1933, paragraph #514)

Feibleman (1946) summarized the essence of Peirce's' distinction between *possibility* and *actuality* as follows:

> Not all *possibles* can exist: *actuality* is a selection of them.

When I read this statement, especially the term "selection," it occurred to me that Peirce's metaphysics might provide a philosophical foundation for the *origin of information* in this Universe, since information can be broadly defined as resulting from the *selection* of a set of objects, events, or entities from a larger set of them. The formalism is very simple. Let us designate the number of all possibilities (or *possibles* of Peirce) out of which this Universe originated as p, and the number of actual existents (which may be called "actuals") as a. Then the primordial

information associated with (or imparted on) this Universe, to be designated as I_C, where C means "cosmological," may be expressed simply as the binary logarithm of the ratio between these two numbers (assuming for simplicity that all *possibles* have equal probabilities of being actualized):

$$I_C = \log_2 (p/a) \text{ bits} \tag{6.33}$$

Although it is almost impossible to measure or determine p and a (and hence I_C), the mere fact that we can write down a mathematical expression relating these two quantities to the information content of the Universe may be significant.

Equation 6.33 describes only the informational aspect of the origin of the Universe. The energy aspect of the origin of the Universe appears adequately described by the Big Bang theory in physics. That is, the energy requirement for the selection process implicated in Eq. 6.33 is met by the dissipation of free energy (or entropy production in this case, since the Universe is isolated) attending the expansion of the Universe:

$$p \xrightarrow{\text{Entropy Production}} a \tag{6.34}$$

where the arrow indicates that a actuals have been selected out of p possibles (i.e., $p > a$). In Ji (1991), it was suggested that p might be identified with (all possible) *superstrings*, and hence a may now be identified with a subset of p reified into elementary particles constituting all the material entities extant in this Universe. The total number of particles in this Universe has been estimated to be approximately 10^{80}, which is known as the Eddington number (Barrow and Tipler 1986, p. 225). These a actuals are thought to possess sufficient *information* and *energy* (i.e., *gnergy*) to evolve higher-order structures such as atoms and molecules, stars, planets, galaxies, the biosphere, and organisms including humans, under appropriate conditions emergent at specific epochs in the history of the Universe (see Fig. 15.12). It is interesting to note that a similar view was recently put forward by a group of cosmologists (Kane et al. 2000). The biological information encoded in living systems may be viewed as ultimately derived from the Cosmological Information, I_C, through a series of information *transductions*, similar to the well-studied phenomenon of signal transductions occurring in the living cell (Sect. 12.16). If this view of the origin of information is correct, a set of interesting inferences could be made:

1. What happens in this Universe cannot be completely random, including biological evolution. That is, biological evolution may be constrained (or directed) by the cosmological information, I_C, encoded in nonliving material entities (i.e., abiotic matter).
2. All information associated with this Universe may be continuous with (or traced back to) the origin of the cosmological information at the time of and prior to the Big Bang.

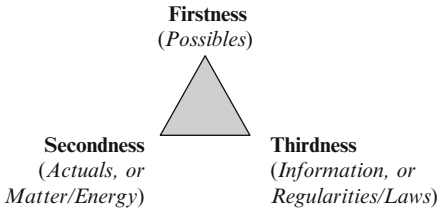


Fig. 6.8 A postulated evolution (or reification) of *possibles* into *actuals* and associated *information* (*and laws*). The nodes are read in the counter clock-wise direction starting from the top node

3. *Possibles*, *Actuals*, and *Information* may reflect the ontological triad of Peirce.

The similarity between Figs. 6.8 and 4.5 may be significant. The similarity may be transformed into an identity simply by equating the Gnergy with the Possibles of Peircean metaphysics, leading to the following conclusions:

Gnergy is the source of possibles out of which all actuals in the Universe are derived. (6.35)

6.2.11 The Triadic Model of Function

The notion of the *structure-function correlation* is widely discussed in biology. In fact, biology may be defined as the scientific study of the correlations between *structure* and *function* of living systems at multiple levels of organization, from molecules to the human body and brain (Polanyi 1968; Bernstein 1967; Kelso and Zanone 2002). The concept of *function* is not dichotomous or dyadic as the familiar phrase "structure-function correlation" may suggest but is here postulated to be *triadic* in the sense that a function involves three essential elements – *structure*, *processes*, and *mechanisms*, *all organized within an appropriate boundary or an environmental condition that constrains the processes to perform a function*. M. Polanyi (1891–1976) clearly realized the fundamental role played by boundary conditions in effectuating living processes at the molecular, cellular, and higher levels (Polanyi 1968). A similar idea was expressed by N. Bernstein (1967) at the level of human body movement. Polanyi's and Bernstein's ideas may be expressed in the language of information theory:

$$I_X = \log_2(w_0/w_x) \text{ bits} \tag{6.36}$$

where I_X is the Shannon information (Sect. 4.3) associated with Function X, w_0 is the number of all possible processes allowed for by the laws of physics and chemistry, and w_x is the number of processes actually selected by the boundary conditions to perform Function X. Equation 6.36 quantitatively expresses the idea that functions are processes selected (or constrained) by appropriate boundary

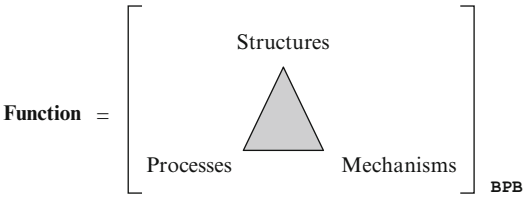


Fig. 6.9 A diagrammatic representation of the triadic conception of function in biology. This diagram presents function as an irreducible triad *of structures*, *processes*, and *mechanisms*. BPB stands for Bernstein-Polanyi boundaries. The boundary-sensitive mechanisms are thought to select only those dissipative structures that perform a desired function out of all possible processes permitted by the laws of physics and chemistry

conditions to perform Function X at a given level of biological organization. For the convenience of discussion, it is suggested that the boundary conditions that constrain and enable Function X to appear from the processes allowed for by the laws of physics and chemistry be referred to as the *Bernstein-Polanyi boundaries* and the information, I_X, embodied in (or needed to specify) such boundaries be referred to as the *Bernstein-Polanyi information*. The Bernstein-Polanyi boundaries (BPBs) reduce the degree of freedom of the components of the system so that they have no choice or freedom but to perform the motions or movements that constitute a function at a given level of organization. Thus, boundaries, constraints, and reduced degrees of freedom are all synonymous terms referring to a function (Polanyi 1968; Bernstein 1967). The triadic conception of function can then be diagrammatically represented as shown in Fig. 6.9:

One advantage of Fig. 6.9 is that it provides a geometric template to organize the four terms that are obviously related with one another, that is, *function*, *structure*, *process,* and *mechanism*. It may be significant that the triadic definition of a function given in Fig. 6.9 is isomorphic with the triadic definition of a sign given by Peirce (1839–1914) (see Fig. 6.2) and consistent with his metaphysics that all phenomena comprise three basic elements (Sect. 6.2). Table 6.11 lists various examples of functions in biology and their triadic components.

6.2.12 The Principle of Prescinding

The term "prescinding" refers to our mental capacity (or tendency) to focus on some aspect of a phenomenon, process, or structure in exclusion of other aspects for the convenience of thought. For example, according to the diagram shown in Fig. 6.10, "function" comprises three irreducible aspects, "structure," "process," and "mechanism." However, it is often convenient to focus on one of these aspects of function and discuss the structure-function, the process-function, or the mechanism-function correlation for the purpose of convenient analysis and communication. Which of these

Table 6.11 Examples of various functions and their elements in biology

Function	Structure	Process	Mechanism
1. Transcription	DNA template	RNA polymerization	RNA polymerase driven by conformons[a]
2. Translation	mRNA, tRNA, rRNA	Peptidyl transfer reaction	Directed movement of the ribosome components driven by conformons
3. Amino acyl tRNA synthesis	tRNA anticodons	Amino acylation of tRNA	Allosteric control of amino acylation by tRNA anticodon
4. Protein folding	Amino acid sequence	Rate of translation	Environment-sensitive protein conformation
5. Enzymic catalysis	Protein folds	Chemical reactions	Conformon-driven regulation of the activation energy barrier
6. Semiosis	Representamen (or signifier, sign vehicle)	Object (or signified, referent)	Interpretant (or codemaking, mapping, habit-forming, evolution)

[a]Conformons are the mechanical energy stored in sequence-specific sites within biopolymers that are generated from exergonic chemical reactions and drive all orderly molecular motions inside the cell including enzymic catalysis, molecular motors, pumps, rotors, and chromatin remodeling (see Sect. 8.1)

Epistemology

‖

[**Innate Knowledge** encoded in **Cell Language**]

↓

[**External Knowledge** expressed in **Human Language**]

Fig. 6.10 Epistemology as the study of the rules governing the conversion of cell-linguistic texts into human-linguistic texts, and as a cell language-based interpretation of Socrates' doctrine of *anamnesis* and of the theory of *pre-reflective experience* of Merleau-Ponty (Dillon 1997, pp. 1–2)

correlations is chosen for discussion would depend on the context of the discourse at hand and on the perspectives of the discussants involved. Peirce (1868) views "prescision" as a form of "abstraction" (Colapietro 1993) and characterizes it in connection with the related terms "discrimination" and "dissociation" as follows:

> The terms "prescision" and "abstraction," which were formerly applied to every kind of separation, are now limited, not merely to mental separation, but to that which arises from attention to one element and neglect of the other. Exclusive attention consists in a definite conception or supposition of one part of an object, without any supposition of the other. Abstraction or prescision ought to be carefully distinguished from two other modes of mental separation, which may be termed discrimination and dissociation. Discrimination has to do merely with the senses of terms, and only draws a distinction in meaning. Dissociation is that separation which, in the absence of a constant association, is permitted by the law of association of images. It is the consciousness of one thing, without the necessary simultaneous consciousness of the other. Abstraction or prescision, therefore,

supposes a greater separation than discrimination, but a less separation than dissociation. Thus I can discriminate red from blue, space from color, and color from space, but not red from color. I can prescind red from blue, and space from color (as is manifest from the fact that I actually believe there is an uncolored space between my face and the wall); but I cannot prescind color from space, nor red from color. I can dissociate red from blue, but not space from color, color from space, nor red from color.

6.3 Philosophy

6.3.1 The "Five Causes Doctrine"

The *Four Causes Doctrine* of Aristotle (384–322 B.C.) consists of the first four items listed below but lacks the last cause which is here thought to be essential to be taken into account in view of the fundamental discoveries made in evolutionary and developmental biology since Darwin (Waddington 1957; Gerhart and Kirschner 1997; West-Eberhard 2003; Carroll 2006; Jablonka 2006, 2009). I elected to refer to this new addition to Aristotle's list of the four causes as the "original" cause but it could as well be referred to as a "historical" cause:

1. The *material cause* (What is it made out of?)
2. The *efficient cause* (How does it work?)
3. The *formal cause* (What is it?)
4. The *final cause* (What is it for?)
5. The *original cause* (Where does it come from? How did it originate?)

The five causes doctrine asserts that no structure, process, or phenomenon can be said to be completely known or understood until and unless the associated five causes have been determined and described. In other words, no theory, especially biological ones, would be deemed complete unless the five causes described above are fully detailed.

It may be objected that it is not necessary to invoke the fifth cause because it can be viewed as a part of the efficient cause. I would agree to such an opinion under one condition – recognizing two kinds of the efficient causes – (1) rapid and (2) slow. The *rapid efficient cause* takes effect in times shorter than the lifetime (or cycling time) of the system under consideration, and the *slow efficient cause* act over times much longer than the lifetimes of individual systems. The former may be referred to as the *synchronic* efficient cause and the latter as the *diachronic* efficient cause (see related discussions in Sects. 4.5 and 6.3.2). Alternatively, we can adopt the five causes and associate the efficient cause with the synchronicity (and developmental biology) and the fifth cause with diachronicity (and evolutionary biology).

The Four Causes Doctrine of Aristotle was formulated over 2,000 years ago based on abstractions from everyday human experiences in the macroscopic world. Since then two major developments have taken place in human knowledge – (1) the development of the theory of biological evolution formulated by Darwin in 1859 and (2) the development of quantum mechanics that began with the discovery of quanta by M. Planck in 1900. Therefore, it would not be too surprising if it is found

that the Four Causes Doctrine cannot be extended to the contemporary biological sciences and physics without updating. The addition of the fifth cause to the *Five Causes Doctrine* may be viewed as a natural consequence of taking into account of the modern theory of biological evolution, and a further modification may be necessary in order to take cognizance of the quantum revolution of the twentieth century. In what form this predicted modification of the Four Causes Doctrine should take is not yet clear.

6.3.2 The Principle of Closure

When two entities, A and B, need each other for their own existence, so that without A, B cannot exist or function, or vice versa, A and B can be said to exhibit or embody the *principle of closure*.

Semantic Closure. *The principle of closure* defined above was inspired by, and is a generalization of, the concept of "semantic closure" or "semiotic closure" formulated by H. Pattee (1995, 2001) who characterized *semantic closure* as follows:

> . . .this complex interrelationship of strong and weak bonds. . . that allows the realization of von Neumann's quiescent *symbolic description* and *dynamic material construction*.

The Principle of Ontological and Epistemic Closure. Before the cell can read DNA, an *epistemic* act, the cell must have been endowed with such a capability through evolution, an *ontological* process. Before the human brain can know anything, an *epistemic* act, it must have been endowed with the knowing capability through biological evolution, an *ontological* act. These statements are consistent with the pre-fit hypothesis of ligand–protein interactions, including enzymic catalysis (Sect. 7.1.3), which in fact may provide the molecular rationale for their validity. As will be discussed in Sect. 7.1.3, the pre-fit hypothesis is rooted in the generalized Franck–Condon principle imported from quantum physics and well supported by recent experimental findings in molecular biology Kurakin (2009). It seems to me that there is a real possibility that the pre-fit hypothesis can rationalize, in molecular terms, Kant's *Copernican Revolution in Philosophy (CRP)*, namely, the claim that objects conform to our knowledge rather than the other way around (http://en.wikipedia.org/wiki/Copernican_Revolution_(metaphor). That is, our *knowledge* is pre-fit to *objects* just as *enzyme active sites* are pre-fit to their *substrates and products* (see Fig. 7.2). We may refer to this idea as the *Copernican Revolution (CRB) in Biology* and suggest that *CRB and CRP belong to the same category of paradigm shifts* and further that *CRB underlies CRP*.

The Diachronic and Synchronic Closure. Although humans can use a language without knowing its past history which is related to the *synchronicity* emphasized by Saussure (Culler 1991), a language cannot be effective as a means of communication among members of a community without its long history of development and evolution (*diachronicity*). Biologists can describe all the physics, chemistry, and biochemistry of the living cell (*synchronicity*), but it would be impossible for them

to understand the workings of the cell without taking into account the long history of biological evolution (*diachronicity*). *This is because the synchronic properties of the cell* (e.g., ligand–receptor interactions, cell cycle, chemotaxis, etc.) *are needed for its evolution and the evolutionary process is needed for the emergence of such synchronic properties endowed with genetic information.*

The Closure Relation Between Boundary Conditions and the Dynamics of Physical Systems. It is clear that no physical laws can describe any observable properties without *there* being specific boundary conditions. In other words, the equation of motion describing a physical system, which embodies laws of physics, cannot be solved without the initial and boundary conditions applicable to that system (Pattee 1995).

6.3.3 The Anthropic Principle

Cosmologists have found that the numerical values of the fundamental physical constants such as c (speed of light), G (gravitational constant), h (Planck constant), e (electronic charge), m_e (electron mass), and m_n (neutron mass) must be precisely what they are in order for our Universe to evolve to contain those elements (e.g., carbon, nitrogen, iron, etc.) that are essential for life to exist on this planet (Barrow and Tipler 1986; Kane et al. 2000). Deviations by even a few percent from these values have been found to lead to alternate model universes devoid of carbon atoms, for example. Therefore, it is clear that there is a *closure relation* between the existence of life (A) in this Universe and the numerical values of the key physical constants (B) that characterize the structure of this Universe: that is, Without B, no A; or A presupposes B. In this view, the anthropic principle is a species of the principle of closure (Sect. 6.3.2).

6.3.4 The Table Theory

It appears that we acquire our knowledge about an unfamiliar object only in terms of what we already know, reminiscent of the biological principle that organisms derive from preceding organisms (except when life first originated), and ligands bind only to those receptors that are pre-fit to their shapes (Sect. 7.1.3). We may state this idea as follows:

> Our knowledge about an unknown object can be increased only in terms of the properties of an already familiar object. (6.37)

Statement 6.37 may be related to Socrates' (ca. 470–399 B.C.) *doctrine of recollection*, or *anamnesis*, according to which knowledge can only come from recollection. A similar idea was advanced by the French phenomenologist Maurice Merleau-Ponty (1907–1961) in his theory of "pre-reflective experience": (Dillon 1997, pp. 1–2). An intriguing possibility to account for the phenomenon of

Table 6.12 A formalization of the "table theory" or an analogical inference. *Internal* and *external relations* may also be referred to as "intra-" and "inter-system" relations

Parameters	**F** (familiar)	**U** (unfamiliar)
1. Components: $f_1, f_2, f_3, \ldots, f_n$		***AR***
$u_1, u_2, u_3, \ldots, u_n$		$\mathbf{f_1}$ <——> $\mathbf{u_1}$
2. Relations:	***IR***	↕ ↕
↕: Internal (or intra-system) Relation (***IR***)		$\mathbf{f_2}$ <——> $\mathbf{u_2}$
<——>: Analogical (or inter-system)		↕ ↕ (?)
Relation (***AR***)		$\mathbf{f_3}$ <——> $\mathbf{u_3}$
3. The "Table Symmetry Principle":		↕ ↕
(1) If **F** and **U** are *isomorphic*,		. .
(2) if ***IR***(f_i, f_{i+1}) is known,		. .
(3) if ***AR***(f_i, u_i) is known, and		. .
(4) if ***AR***(f_{i+1}, u_{i+1}) is known, then		↕ ↕
(5) ***IR***$(u_i, u_{i+1}) =$ ***IR***(f_i, f_{i+1})		$\mathbf{f_n}$ <——> $\mathbf{u_n}$

anamnesis may be opened up by the postulated isomorphism between cell and human languages (Table 6.3). Because we are made up of cells which are in turn made up of material entities originating in nature, we may already *know* how cells and nature work by virtue of the communication mediated by cell language between the human brain and its constituent cells, although we may not be able to express this knowledge for the purpose of communication among humans because it is not encoded in human language. To do so, we must convert our *innate* (or *internal*) knowledge encoded in cell language (which may be identified with "pre-reflective experience" of Merleau-Ponty) into what may be called the *external* or *objective* knowledge expressed in human language, and this postulated process of *cell-human language transduction* (or *translation*) may constitute the heart of epistemology. The language mediating the communication between cells (C) and humans (H) may be referred to as *the CH language*, distinct from human language (which may be called *the HH language*) and cell language (*the CC language*). Through CH language, humans may be able to communicate with the Universe itself, since cells are the embodiment of the laws of nature and the historical record of the Universe. We may represent this series of ideas diagrammatically as shown in Fig. 6.10.

In Ji (1991), the essence of the above ideas was formalized under the rubric of "table theory." The term "table" is employed here, because the theory utilizes a 2-D table as an essential graphical tool for comparing the properties of a familiar (F) object with those of an unknown or unfamiliar (U) object. The *table theory* has three key elements – (1) sets of components or nodes for F or U; (2) two kinds of relations, internal relation (IR) and analogical relation (AR) (IR and AR may also be referred to as "intrasystem" and "intersystem" relations, respectively); and (3) the principle of *table symmetry* stating that, if F and U are isomorphic (i.e., obey a common set of principles), IR of U can be inferred from the IR of F given that AR exists between the components of F and U. These ideas are summarized in Table 6.12. The main objective of comparing two objects, F and U, is to discover the *relations* among the components of U (i.e., the vertical arrows among the u's;

see the question mark next to the vertical double arrow by using the relations among the components of F based on the assumption that a set of similarity relations (see the horizontal arrows) holds between components of F and the corresponding components of U.

The cell language theory (see Table 6.3) formulated on the basis of the similarity between the properties of living cells and those of human language may be viewed as one of the most detailed examples of the application of the "table theory."

6.3.5 *The Principle of Mőbius Relations*

The Möbius strip is "a one-sided surface that is constructed from rectangle by holding one end fixed, rotating the opposite end through 180°, and applying it to the first end" [*Webster's Ninth New College Dictionary*]. The essential geometric properties of the Möbius strip may be characterized in terms of the following two propositions:

> The Möbius strip consists of two opposite surfaces, A and B, when viewed locally. (6.38)

> Surfaces, A and B, merge into one another when viewed globally. (6.39)

Statements 6.38 and 6.39 may be combined into one:

> Locally A **or** B; globally A **and** B. (6.40)

Statement 6.40 may be viewed as an alternative expression of what is referred to as the *global–local complementarity* (or the *forest-tree complementarity*). In all these statements, the terms "local" and "global" may be replaced with "synchronic" and "diachronic," respectively. For the definitions of "synchronicity" and "diachronicity," see Sects. 4.5 and 6.3.2.

6.3.6 *The Pragmatic Maxim of Peirce*

According to Peirce, the meaning of a word or a concept can be equated with the totality of the practical effects or consequences that the word has in life:

> In order to ascertain the meaning of an intellectual conception one should consider what practical consequences might conceivably result by necessity from the truth of that conception; and the sum of these consequences will constitute the entire meaning of the conception. (Goudge 1969, p. 153) (6.41)

This maxim will become useful in defining the meaning of life in Sect. 16.1.

6.3.7 *A New Architectonics Based on the Principle of Information-Energy Complementarity*

Architectonics is the science of systematizing all knowledge. We can recognize three distinct types of sciences. By "science" is meant a system of human knowledge organized according to some rules. Also I am including matter within the concept of energy, since energy and matter are interconnected and interconvertible through $E = mc^2$ (Shadowitz 1968).

1. "Energy science" or *energetics*, the study of energy transformation, transmission, and storage in the Universe, for example, physics, chemistry, quantum mechanics, thermodynamics, chemical kinetics, Newtonian mechanics, statistical mechanics, etc.,
2. "Information science" or *informatics*, the study of information transduction, transfer, and storage, for example, linguistics, computer science, informatics, logic, mathematics, etc., and
3. "Energy-Information science" or *gnergetics*, the study of goal-directed or teleonomic processes driven by gnergy, for example, cosmology, biology, cognitive science, philosophy, and religion.

According to complementarism (see Sect. 2.3.4), all irreconcilable opposites can be viewed as complementary aspects of a third which transcends the level where the opposites are recognized or have meanings. Thus, if we view information and energy as irreconcilable opposites, then there must be a third for which energy and information are complementary aspects. This third entity was given the name "gnergy" in the mid-1980s. We can express the same ideas algebraically thus:

$$\text{Ontology} : \text{Gnergy} = \text{Gnon}^{\wedge}\text{Ergon} \tag{6.42}$$

$$\text{Epistemology} : \text{Gnergetics} = \text{Gnonics}^{\wedge}\text{Ergonics} \tag{6.43}$$

where the symbol, ^, denotes the *complementary relation* of Bohr, generalized in complementarism in terms of three complementarian logical criteria (see Sect. 2.3.3).

Equations 6.42 and 6.43 provide the logical basis for equating "Energy-Information science" with gnergetics, or gnergy science, in (3) above. We can summarize all these ideas in the form of a diagram (Fig. 6.11):

The tree types of sciences described in (1) through (3) above and those described in Fig. 6.11 are related as follows:

Energy Science = Energetics (or Ergonics)
Information science = Informatics (or Gnonics)
Energy-Information Science = Gnergetics (or Gnergonics)

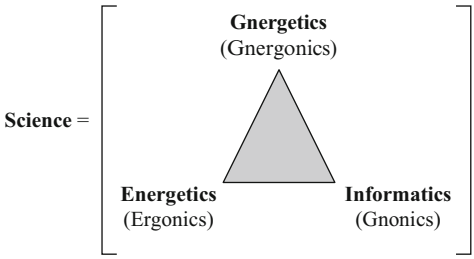


Fig. 6.11 The trichotomization of sciences based on the metaphysics of complementarism (Sect. 2.3.4). Gnegons, ergons, and gnons are discrete units of gnergy, energy, and information, respectively

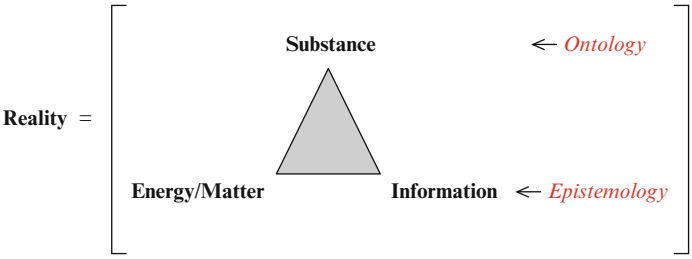


Fig. 6.12 The "triadic theory of reality" (TTR). TTR organizes seven fundamental concepts in physics and metaphysics (i.e., *energy*, *matter*, *information*, *epistemology*, and *ontology*, *Substance*, and *Reality*) within a coherent conceptual framework or network rooted in the Peircean theory of signs as depicted in Fig. 6.2 (see Sect. 6.2.1)

This is the systematization (or the architectonics) of knowledge suggested by the information/energy complementarity principle (Sect. 2.3.2).

6.3.8 The Triadic Theory of Reality

Wheeler (1998) presupposes the existence of the questioner or questioners who ask a series of binary questions, the answers to which are thought to constitute knowledge or science. Since the questioner came after the Universe and there must have been something to question about, it seems logical to infer that ontology precedes epistemology. Both Wheeler (1998) and Bohr (1933, 1958; Murdoch 1987; Pais 1991) seem to be concerned primarily with *epistemology*, taking ontology for granted.

If this analysis is right, it may be necessary to go beyond Wheeler and Bohr by extending the Bohr's principle of complementarity to *ontology*, and one way to do this may be to integrate all the major concepts discussed in philosophy into a logically coherent system using the triadic diagram discussed in Sect. 6.2.1.

TTR shown in Fig. 6.12 may be regarded as the periodic table of philosophy and a geometrical version of complementarism, according to which the ultimate reality is the complementary union of irreconcilable opposites. It should be noted that there are three kinds of complementarities embedded in Fig. 6.12.

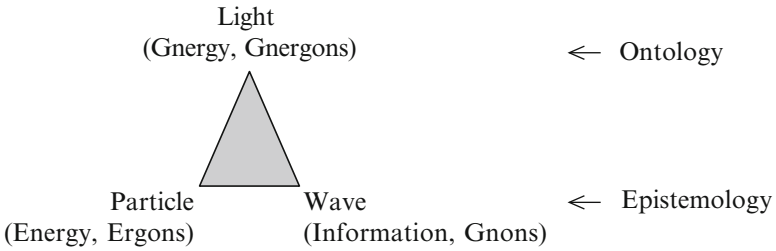


Fig. 6.13 Light as gnergy or the complementary union of information (gn-) and energy (−ergy). Gnergons are defined as discrete units of gnergy; ergons are discrete units of energy; and gnons are discrete units of information. The double labeling of each node is necessitated by the continuity-discontinuity complementarity

1. The "horizontal complementarity" = Energy/Matter and Information (or Life-Information, Liformation; see Table 2.6) as the complementary aspects of Substance.
2. The "vertical complementarity" = Ontology and Epistemology as complementary aspects of Reality.
3. The "complementarity of complementarities" = The "horizontal" and "vertical" complementarities as complementary aspects of Reality.

TTR described in Fig. 6.12 suggests that Wheeler is primarily concerned with what is here called the *horizontal complementarity* without acknowledging the third term, *Substance*, and Bohr may have glimpsed both the *horizontal* and *vertical* complementarities when he stated that "Contraries are complementary," since this statement can be shown to be recursive on the concept of complementarity (Ji 2008b).

TTR may shed a new light on the long-lasting debate between Bohr and Einstein on the interpretation of quantum mechanics (Murdoch 1987; Petruccioli 1993; Cushing 1994; Johansson 2007). For example, the reason that we observe the wave property (interference patterns) and particle property (photoelectric effects) of light (and other quantum entities generally referred to as quons [Herbert 1987]) depending on the measuring apparatus used may be because

Light is BOTH waves and particles even before it is measured. (6.44)

In my lexicon, light as directly observed by the human eye (before measurement) corresponds to gnergy which appears as either waves or particles depending on which measuring apparatus light has gone through. This situation can be described diagrammatically as shown in Fig. 6.13:

Two observations seem to support the triadic interpretation of light:

1. A stream of electrons arriving at a screen past a hole one at a time produces *the Airy pattern* characterized by a set of dots that form concentric circles, the dots

reflecting the particle property and the circular patterns indicating the wave property of the electron wave (Herbert 1987, p. 62)

2. The de Broglie equation quantitatively relates the wave property (wavelength) and particle property (momentum) of a quon:

$$(\text{Wavelength}) = (\text{Planck constant})/(\text{Momentum}) \tag{6.45}$$

One simple interpretation of both the Airy pattern and de Broglie equation is to assume that light (or quons) is both waves and particles at the same time, as Bohm has been advocating throughout his career following de Broglie's idea.

If the above analysis is correct, *the Bohr-Einstein* and *Bohr-Bohm* debates may have a possible solution:

> Both Bohr and his opponents are right in one sense and wrong in another, because their arguments are on two separate levels of reality – Bohr on the epistemological level and his opponents on the ontological level. To the extent that Bohr (his opponents) confined his (their) argument(s) to the epistemological (ontological) level, Bohr's (his opponents') argument(s) is (are) valid. To the extent that Bohr (his opponents) asserted the validity of his (their) argument(s) beyond the epistemological (ontological) level, his (their) argument (s) loses legitimacy. (6.46)

6.3.9 The Type-Token Distinction

Philosophers distinguish between *types* and *tokens*. A type is an abstract object that does not exist anywhere but tokens are concrete realizations of a type that exist physically somewhere at some time. For example, the living cell is a type but the cells constituting my body are tokens of the living cell. At least two examples illustrating the type-token distinction appear in this book. *Gnergy* is a type and *gnergons* are its tokens (Sect. 2.3.2). *MAPK* is a type and its tokens include *JNK, ERK1/2,* and *RK* proteins in the MAPK signaling cascade discussed in Sect. 12.16. Seger and Kreebs (1995) refer to MAPK as a "generic name" while JNK, ERK ½, and RK as "specific names" (see the margins of the table shown in Fig. 12.35).

Part II
Theories, Molecular Mechanisms, and Models

Chapter 7
Molecular Mechanisms: From Enzymes to Evolution

7.1 Molecular Mechanisms of Ligand–Protein Interactions

7.1.1 Thermodynamics and Kinetics of Ligand–Protein Interactions

Binding is prerequisite for practically all molecular processes occurring inside the cell, including *messenger (or molecular) recognition*, *enzymic catalysis, transport processes, and control of gene expression*. Furthermore, *binding* must be followed by *de-binding* if molecular machines are to work more than one cycle. Otherwise, molecular machines will get stuck in a substrate- or a product-bound state and not be able to move on to the next state to perform molecular work in continuous cycles. Molecular machines stuck in either a substrate- or a product-bound state is akin to the gear shift of a car stuck in either the drive or the neutral position. To emphasize the importance of this basic feature of molecular machines, it may be justified to formulate Statement 7.1 to be referred to as the *Principle of the Binding and De-binding Requirement of Molecular Machines* (PBDRMM):

> All molecular machines must perform at least one cycle of *binding and debinding* of molecules in order to carry out their functions more than once. (7.1)

The simplest form of ligand–protein interactions can be represented as shown in Scheme 7.2:

$$\begin{array}{ccccc} \mathrm{L}+\mathrm{P} & \leftrightarrow & [\mathrm{L}^{*}\cdot\mathrm{P}^{*}] & \leftrightarrow & \mathrm{L'}\cdot\mathrm{P'} \\ \text{Initial} & & \text{Transisiton} & & \text{Final} \\ \text{State} & & \text{State} & & \text{State} \end{array} \tag{7.2}$$

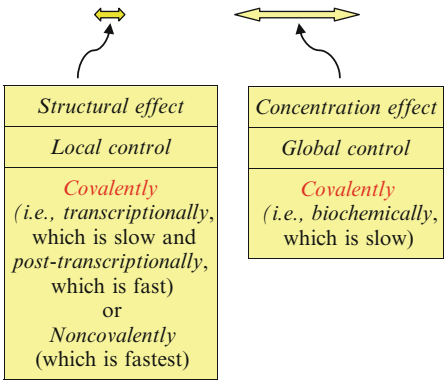
where L = ligand (including proteins, RNA, and DNA); P = proteins; L* = the ligand in the transition-state conformation; P* = the protein in the transition-state conformation; [. . .] = the transition state of the ligand-protein complex; L' = the

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_7,

ligand in the bound-state conformation; and P' = the protein in the bound-state conformation.

There are two aspects to Scheme 7.2 – (1) the *thermodynamic aspect* that determines whether or not the binding process as written will take place under a given experimental condition and, if so, to what extent, and (2) the *kinetic aspect* that determines the rate or speed of the binding process. The thermodynamics of ligand binding under most biological conditions (i.e., constant pressure and temperature) is determined by the Gibbs free energy change, $\Delta G = G_{final} - G_{initial}$, namely, the difference in Gibbs free energy levels between the initial and final states of the system under consideration. Gibbs free energy is defined by Eq. 2.1. Any binding process accompanied by a decrease in Gibbs free energy (i.e., $\Delta G < 0$) will occur spontaneously. In contrast, if the binding free energy change is positive, that is, $\Delta G > 0$, the binding process will not occur spontaneously unless and until coupled to (or driven by) another process accompanied by a sufficiently large negative Gibbs free energy change so that the combined Gibbs free energy change becomes negative. In other words, all spontaneous binding processes, either simple or coupled, are associated with negative Gibbs free energy changes. More generally, the relation between the concentrations of the chemical species involved in a binding process and the accompanying Gibbs free energy change is given by Eq. 7.3, using Scheme 7.2 as an example (Kondepudi and Prigogine 1998, pp. 235–237):

$$\Delta G = \Delta G^0 + RT \log([L' \cdot P']/[L][P]) \tag{7.3}$$



where ΔG^0 is *the standard Gibbs free energy change* (i.e., the Gibbs free energy change under the standard condition of the unit concentrations of the chemical species involved), R is the gas constant, T is the absolute temperature, and [L'P'] and[L][P] are the concentrations (or *activities,* more precisely speaking; Sect. 3.1.7). Evidently, Eq. 7.3 is consistent with the Le Chatelier's principle (which states that, when a system at equilibrium is perturbed, the system will readjust itself in the

direction of reducing the perturbation), since, if L and P are increased in Scheme 7.2, the perturbation will shift the equilibrium from left to right and the quotient, [L'·P']/[L][P], in Eq. 7.3 will decrease making ΔG more negative (or less positive).

The binding process in Scheme in 7.2 can be altered in two distinct ways:

1. By changing the concentrations of the interacting molecules, that is, L, P, and L'·P', and
2. By changing the structures of the interacting molecules thereby changing their binding affinities for ligands as reflected in the standard Gibbs free energy change, ΔG^0.

The first mechanism of changing binding equilibria may be referred to as the "concentration effect" (which is global affecting all interacting molecules more or less simultaneously and the second mechanism as the "structure effect") (which can be localized to individual molecules). The concentration effect will be manifested through the quotient term in Eq. 7.3, and the structure effect will be exerted through the changes in the standard Gibbs free energy levels, ΔG^0, of interacting molecules.

At equilibrium, $\Delta G = 0$. So, Eq. 7.3 can be rewritten as

$$\Delta G^0 = - RT \log K \tag{7.4}$$

$$K = e^{-\Delta G0/RT} \tag{7.5}$$

where K is the equilibrium constant defined as [L'·P']/([L][P]). Equation 7.5 indicates that the equilibrium constant of a ligand-binding process is the exponential function of the standard Gibbs free energy change associated with that process.

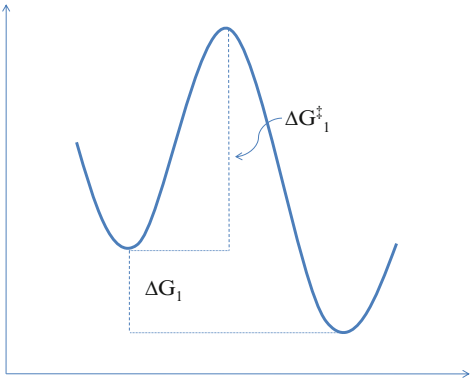
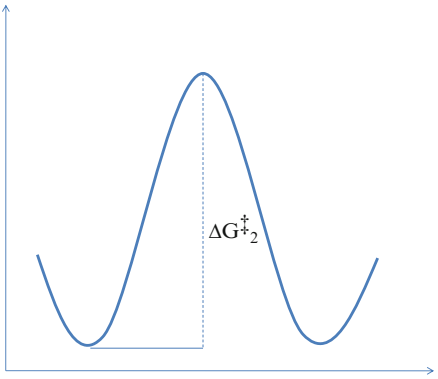
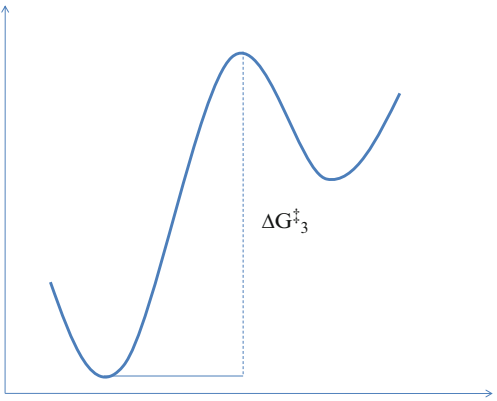
As evident in Eq. 7.3, ΔG and ΔG^0 can become equal when [L'·P'], [L] and [P] are unity (e.g., 1 mol/L). Thus, ΔG^0 can be experimentally determined by measuring ΔG while keeping the concentrations of L·'P', L, and P at 1 mol/L. Similarly, the kinetics (i.e., rate) of the ligand-binding process, Scheme 7.2, is determined by both the concentrations of the chemical species involved, that is, [L] and [P], and the Gibbs free energy change, $\Delta G^{\ddagger}$, between the initial and the transition state of the system (assuming that the rate of de-binding is negligible) according to Eq. 7.6:

$$k = Ae^{-\Delta G\ddagger/RT} \tag{7.6}$$

where k is the *rate constant* (i.e., the rate at unit concentrations of chemicals involved) for the binding process, Scheme 7.2, and A is the "pre-exponential factor" that reflects the molecular motions at the transition state (Laidler 1965; Kondepudi and Prigogine 1998, pp. 237–239). Please note that Eq. 7.6 indicates that the *rate constant*, k, of binding is an exponential function of the *Gibbs free energy of activation,* $\Delta G^{\ddagger}$, whereas Eq. 7.5 indicates that *the equilibrium constant, K,* of the same process is an exponential function of the *standard Gibbs free energy change,* ΔG^0.

The Gibbs free energy changes accompanying the binding process represented by Scheme 7.2 are diagrammatically presented in Table 7.1. The *x*-axis is the

Table 7.1 The thermodynamic and kinetic requirements of ligand–protein interactions. $\Delta G =$ the Gibbs free energy change accompanying the transformation of the system under consideration from the initial to the final state, that is, $\Delta G = G_{final} - G_{initial}$; $L^* =$ the ligand in the transition-state conformation; $\Delta G^{\ddagger}$ is always positive but $\Delta G_i^{\ddagger}$ can be negative (see $i = 1$), zero (see $i = 2$), or positive (see $i = 3$). Types I, II and III bindings can be alternatively referred to as the exergonic (or downhill), equilibrium, and endergonic (uphill) bindings, respectively

Binding	$L + P \leftrightarrow [L^* \cdot P^*] \leftrightarrow L'P'$	ΔG
Type I		$\Delta G_1 < 0$
Type II		$\Delta G_2 = 0$
Type III		$\Delta G_3 > 0$

"reaction coordinate" representing the progression of the binding process (e.g., in terms of intermolecular distances), and the *y*-axis represents the Gibbs free energy level, G, of the system along the reaction coordinate. The binding processes can be divided into three classes depending on the signs of the associated Gibbs free energy changes – (1) Type I (also called *downhill* or *exergonic*) when $\Delta G < 0$, (2) Type II (also called "equilibrium") when $\Delta G = 0$, and (3) Type III (also called *uphill* or *endergonic*) when $\Delta G > 0$.

Due to the positivity (i.e., the positive sign) of ΔG, Type III binding processes cannot occur spontaneously, that is, L cannot bind to P to form L'·P' to any great extent. However, there are two ways to increase the extent of the binding process so as to increase the concentration of the L'·P' complex – (1) By utilizing the concentration effect (discussed above), that is, by increasing [L] and [P], and (2) By utilizing the structural effect, that is., by increasing the binding affinities of L and P by modifying their structures either *non-covalently* (e.g., through allosteric ligand) or *covalently* (e.g., *through transcription or posttranscriptionally* via phosphorylation or acetylation [Zhaio et al. 2010; Wang et al. 2010]).

As indicated in Eq. 7.3, the concentration effect is *global*, affecting all interacting molecules more or less simultaneously due to the rapidity of diffusion processes, whereas the structural effect can be *local* since structural changes can be made only to select molecules by enzyme catalyzed posttranscriptional modification or transcriptional activation of select genes. Because of these two mechanisms, ligand-binding processes can be regulated in two contrasting and independent ways – *local* and *global* and fast and slow – the extra degrees of freedom introduced by these processes may have played important roles in biological evolution.

What distinguishes *chemical* and *biochemical reactions* is that the former depends on *molecular collisions among reactants* while the latter depends on *molecular binding to proteins*. When two molecules A and B collide, they typically remain in physical contact only transiently (typically lasting for 10^{-13}–10^{-15} s, the periods of bond vibrations). In contrast, when a ligand bind to a protein, the ligand-protein complex can last for much longer times, depending on the geometry of the binding pocket of the protein which determines the activation free energy barrier for the de-binding of the ligand. Whether or not the colliding molecules, A and B, will undergo chemical reactions critically depends on the magnitude and the direction of the momentum changes experienced by the colliding molecules, the momentum p of a particle being defined as the mass m of the particle times its velocity v, that is, $p = mv$. When A and B collide with a sufficient momenta in the right direction, the collision can lead to chemical transformations. Whether or not the binding of a ligand L to a protein P will lead to a chemical transformation (i.e., enzymic catalysis) depends on two factors – (1) the thermodynamic factor requiring that the "binding free energy," ΔG, in Table 7.1, be negative, and (2) the kinetic factor dictating that the activation free energy, $\Delta G^{\ddagger}$, is small enough to be overcome by thermal fluctuations of enzymes (Ji 1974a, 1979).

7.1.2 *Active versus Passive Bindings*

Based on the thermodynamics of binding processes, we can divide all ligand–protein interactions into three classes designated as Types I through III in Table 7.1. Alternative names for these three types of ligand–protein interactions are also indicated in the table. Although most binding experiments focus on Type I binding, it is very likely that Types II and III also play important roles in living cells. In theory, there are two kinds of bindings – "active (also called 'downhill' or 'exergonic') binding (AB)," and "passive (also called 'uphill' or 'endergonic') binding (PB)." AB is defined as the binding process which cannot occur (due to the endergonic nature of the binding process as depicted in the third row of Table 7.1) without being coupled to some exergonic process, including PB depicted in the first row of Table 7.1. AB can occur if Type III binding is coupled to Type I such that ΔG_1 is more negative than ΔG_3 is positive so that their sum is negative, that is, $\Delta G_1 + \Delta G_3 < 0$.

As evident in Table 7.1, if binding is exergonic, de-binding must be endergonic; if binding is endergonic, the associated de-binding should be exergonic. Combining these elements, we can formulate the following general statement:

> No molecular machines can be driven by the free energy of binding alone; All molecular machines must be driven by chemical reactions. (7.7)

We may refer to Statement 7.7 as the Chemical Reaction Requirement for Molecular Machines (CRRMM).

The proteins that bind ligands actively (ABPs) are predicted to have the following properties:

1. ABPs have at least two binding sites, each specific for a unique ligand, L_1 or L_3, say, with the associated free energy of bindings ΔG_1 and ΔG_3.
2. ABPs bind L_1 avidly, that is, $\Delta G_1 < 0$.
3. ABPs do not bind L_3, that is, $\Delta G_3 > 0$.
4. However, when both L_1 and L_3 are present together, ABPs can bind L_3 as well asL_1, if $\Delta G_1 < \Delta G_3$, that is, $\Delta G_1 < \Delta G_3$.

The proteins that actively de-bind ligands, to be called the active de-binding proteins (ADP), are predicted to have the following properties:

1. ADPs have at least two binding sites, each specific for a unique ligand, L_1 or L_3, say, with the associated free energy of bindings ΔG_1 and ΔG_3.
2. ADPs bind both L_1 and L_3 avidly, that is, $\Delta G_1 < 0$ and $\Delta G_3 < 0$.
3. In the presence of L_1, ADPs bind L_3, despite the fact that $\Delta G_3 > 0$, because binding of L_1 increases the binding affinity of ADPs for L_3 if $\Delta G_1 < \Delta G_3$, that is, $\Delta G_1 < \Delta G_3$.

Active de-binding process may occur during oxidative phosphorylation as proposed by Boyer (2002).

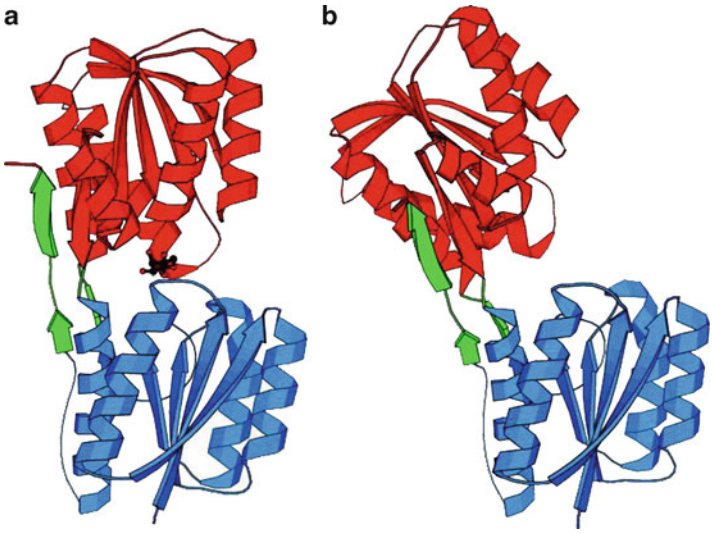


Fig. 7.1 The three-dimensional structure of the ribose-binding protein (RBP). (**a**) The closed conformation of TBP that binds ribose (as indicated by the cluster of *dark points*) between its *upper* and *lower* domains. (**b**) The open conformation of the protein showing the wide-open-binding cavity too large for the ribose molecule to be trapped. The two conformations are thought to be in thermal equilibrium, that is, they interconvert rapidly, although the probability of RBP being in the closed conformation is only 4% (Reproduced from Fig. 1, Ravindranathan et al. 2005)

7.1.3 The Kinetics of Ligand–Protein Interactions: The "Pre-fit" Mechanism Based on the Generalized Franck–Condon Principle

Binding of ligands (e.g., substrates, products, hormones, cytokines, prostaglandins, RNAs, DNAs) to proteins and nucleic acids play fundamental roles in energy and information transductions in the living cell. Binding of ligands to biopolymers (proteins, RNAs and DNAs, carbohydrates) usually cause shape or conformational changes of the molecules involved (See Fig. 7.1). For a rigorous definition of "conformation" and to differentiate between "conformation" and "configuration," readers are recommended to consult Sect. 3.2. In addition, ligand binding to biopolymers can lead to "energization" of biopolymers to drive the next elementary steps, since a part of binding free energy can be stored in them as conformational deformations called *conformons* (Chap. 8), in agreement with the *Circe* hypothesis of enzymic catalysis proposed by Jencks (1975). Conformational changes of proteins or nucleic acids can elicit two kinds of consequences – alterations in ligand-binding force (or *affinity*) and changes in the position of ligand-binding site. These will be referred to as *binding-force change* (BFC) or *transformation* and *binding-position change* (BPC) or *translocation* (to use the terms introduced by

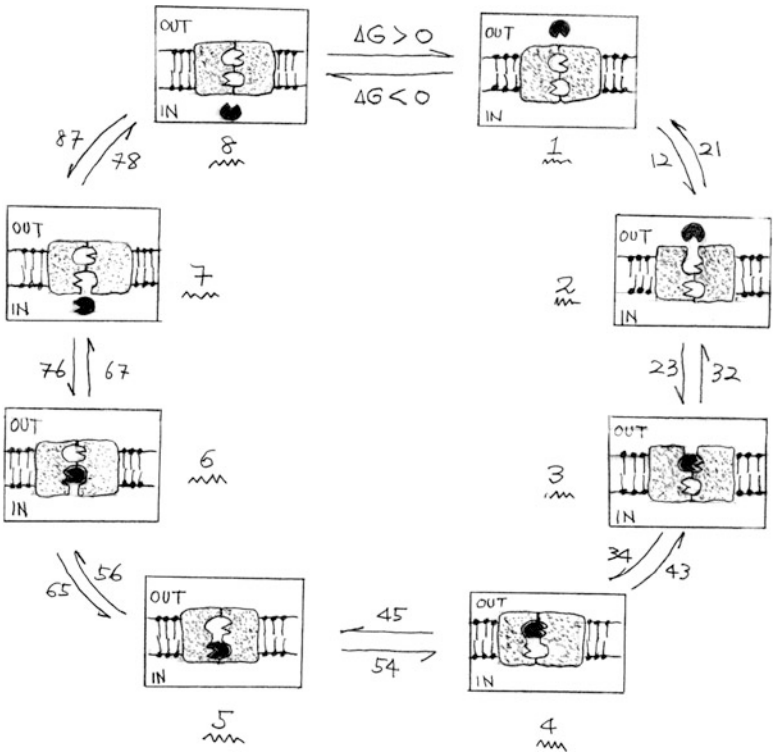


Fig. 7.2 The Franck–Condon mechanism of selective ligand uniport (i.e., the movement of one ligand across the membrane)

Stein et al. [1974]). The mechanism of action of all molecular motors and membrane pumps appear to depend on both BFC (*transformation*) and BPC (*translocation*) as depicted in Fig. 7.2.

One interesting consequence of the *Principle of Slow and Fast Processes* (PSFP), or the *generalized Franck–Condon principle* (GFCP) (see Sect. 2.2.3), as applied to enzymic catalysis, is that enzymes must undergo *conformational changes* before substrates can bind to their active sites to initiate catalysis. This conclusion is diametrically opposed to the *induced-fit hypothesis* of Koshland (1958) widely discussed in biochemistry textbooks [e.g., see Fig. 8.10 on p. 200 in (Berg et al. 2002)]. It may be convenient to refer to the PSFP-based mechanism of the substrate–enzyme interactions as the "pre-fit hypothesis" to contrast it with the *induced-fit hypothesis* of Koshland, "pre-fit" because enzymes are postulated to have been *selected* by evolution *(and hence carry genetic information)* on the basis of their ability to assume certain conformational states capable of "capturing" or binding their elusive substrates as they bump into them randomly due to Brownian motions or thermal fluctuations. These two contrasting mechanisms of binding are schematically represented in Processes 7.8 and 7.9, where L stands for a ligand,

E and E' refer to the two conformational states of the enzyme molecule in the "unbound" and "binding" conformations, respectively. The concept of *conformation*, in contrast to that of *configuration*, plays a fundamental role in my theoretical reasoning in molecular biology (Ji 1997a). As explained in Sect. 3.2, c*onformations* are three-dimensional structures of a molecule that can be altered without breaking or forming any covalent bonds. When such bonds need to be broken or formed during structural or shape changes, we are now dealing with "configurations" and not "conformations." There are two distinct mechanisms of ligand-binding processes:

$$\textit{Induced Fit Hypothesis (IFH)}: \mathrm{L} + \mathrm{E} \leftrightarrow \mathrm{L}\cdot\mathrm{E} \leftrightarrow \mathrm{L}\cdot\mathrm{E}' \tag{7.8}$$

$$\textit{Pre-Fit Hypothesis (PFH)}: \mathbf{L} + \mathbf{E} \leftrightarrow \mathbf{L} + \mathbf{E}' \leftrightarrow \mathbf{L}\cdot\mathbf{E}' \tag{7.9}$$

The following differences exist between these two mechanisms:

1. IFH predicts that E cannot assume E' without first binding L. In contrast, PFH predicts that E can assume E' in the absence of L, the probability P(E') of observing E' being dependent only on the Gibbs free energy difference, ΔG, between E and E', that is, $\Delta G = G(E') - G(E)$, obeying the Boltzmann distribution law (Moore 1963, p. 621; Andrews 1963, p. 33),

$$P(E') = P(E)e^{-\Delta G/RT} \tag{7.10}$$

   where R is the universal gas constant and T the absolute temperature.
2. The conformational change of E to E' *follows* ligand binding according to IFH, whereas it precedes ligand binding according to PFH.
3. The energy required for the conformational transition from E to E' is provided by the substrate binding energy in IFH, whereas, in PFH, it is "borrowed" *temporarily* from thermal environment to be "paid back" subsequently from the free energy of binding of L to E' rapidly enough to avoid violating the Second Law of thermodynamics (Ji 1974a, pp. 29–30) (see Sect. 2.1.4). This mechanism is consistent with the theory of enzymic catalysis proposed by Jencks (1975) based on the *Circe effect* in which a part of the free energy of substrate binding is stored in the enzyme-substrate complex as conformational deformations of the enzyme to be utilized later to lower the activation free energy barrier for catalysis.
4. Another way to describe the difference between IFH and PFH is that, in the former, L "instructs" E to change its conformation to E', while, in the latter, L "selects" E' over E which are both available to L due to the thermal equilibration between the two conformers (or conformational isomers). Thus, it can be stated that IFH is based on *instruction*, whereas PFH is based on *selection*.

An indirect evidence for PFH was recently reported by K. Ravindranathan (2005) who used X-ray crystallographic data on the *ribose-binding protein* (RBP)

to calculate the probabilities of observing the "open" and "closed" conformations of this protein in the absence of ribose (RBP is involved in the ribose transport across the plasma membrane in *E. coli*.). They found that RBP can exist in *closed* and *open* conformations in 4% and 96% of the time, respectively, in the absence of ribose (Fig. 7.1).

Most interestingly they find that ribose can bind only to the closed form, thereby shifting the equilibrium toward the closed conformation. Therefore, their findings can be represented schematically as follows:

$$\mathbf{RBP}_{\text{open}} \leftrightarrow \mathbf{RBP}_{\text{closed}} \tag{7.11}$$

$$\mathbf{Ribose} + \mathbf{RBP}_{\text{closed}} \leftrightarrow \mathbf{Ribose} \cdot \mathbf{RBP}_{\text{closed}} \tag{7.12}$$

Processes 7.11 and 7.12 can be accounted for by PFH which is based on the generalized Franck–Condon principle or the Principle of Slow and Fast Processes (PSFP) (see Sect. 2.2.3), in terms of the differential kinetic properties between RBP (i.e., *slow* conformation change) and ribose molecules (i.e., *fast* diffusion in and out of the binding pocket of RBP) secondary to their size difference, which dictates that, in order for ribose to bind to RBP, the slower conformational changes of RBP must precede the faster thermal motions (i.e., collisions) of ribose against the binding site of RBP.

Many hormones and cytokines exert their biological actions on cells by binding to their target receptors which undergo dimerization. Biologists have been assuming that hormone/cytokine binding "induces" dimerization of receptor monomers, R, most likely because of the influence of the *induced fit hypothesis* (Koshland 1958; Berg et al. 2002):

$$\mathbf{R} + \mathbf{H} \leftrightarrow \mathbf{R} \cdot \mathbf{H} + \mathbf{R} \leftrightarrow \mathbf{R} \cdot \mathbf{H} \cdot \mathbf{R} \rightarrow \mathbf{Biological\ Actions} \tag{7.13}$$

In contrast, PFH suggests the following alternative mechanism:

$$\mathbf{R} + \mathbf{R} + \mathbf{H} \leftrightarrow \mathbf{R} \cdot \mathbf{R} + \mathbf{H} \leftrightarrow \mathbf{R} \cdot \mathbf{H} \cdot \mathbf{R} \rightarrow \mathbf{Biological\ Actions} \tag{7.14}$$

In other words, PFH predicts that receptors can (and indeed must) dimerize before hormones can bind, again for the same kinetic reason as indicated above: The thermal motions of R's are so slow relative to that of H that, unless R's are already brought close enough to each other via Brownian motions, H could not be "captured" before it bounces back out from R into the surrounding medium.

The X-ray crystallographic investigations on erythropoietin receptor (EpoR) provide another evidence for PFH. EpoR is the receptor for EPO, a glycoprotein (i.e., a protein covalently linked to sugar residues) that, upon binding to EpoR, regulates the proliferation, differentiation, and maturation of red blood cells. EPOR was thought to be activated by EPO-induced dimerization, but the X-ray structural

data on the extracellular domains of EpoR, known as the EPO-binding protein (EBP), have indicated that EpoR can form a dimmer in the absence of EPO (Livnah et al. 1999), consistent with PFH, that is, Process 7.14.

The pre-fit hypothesis is supported by recent experimental results reviewed in Kurakin (2009). In particular the following statement by Kurakin accurately captures the essences of the pre-fit mechanism of ligand-protein interactions and 'info-statistical mechanics discussed in Sect. 4.9:

> . . . The latest studies addressing the structure and dynamics of various enzymes suggest that the walk of a protein structure through its conformational landscape is actually not random, but proceeds along statistically preferred routes that, strikingly enough, happen to correspond to the conformational changes observed during actual enzymic catalysis . . . In other words, a substrate-free enzyme prefers to sample the sequence of coupled conformational transitions that correspond to actual changes in its structure when the eynzyme peforms its function.

It may be stated that Kurakin's review article, along with the other experimental evidence discussed in this book, establishes the validity of the pre-fit hypothesis that was formulated a quarter of a century ago based on the generalized Franck-Condon principle (Ji 1974a, b).

7.1.4 The Franck–Condon Mechanism of Ligand–Membrane Channel Interactions

In passive transport, the ion *selectivity* is imparted by the ion channel protein, but the direction of ion *movement* is determined by the Gibbs free energy change accompanying the ion movement. In active transport, however, the transporting proteins can provide both the selectivity to ions (or other ligands) and the Gibbs free energy needed for the ligand movement across the membrane against the concentration gradient of transported ions. The pre-fit hypothesis mandates that biopolymers undergo conformational changes before a ligand can bind to its receptor as indicated above. This hypothesis was formulated on the basis of the Principle of Slow and Fast Processes (PSFP), or the *generalized Franck–Condon principle* (GFCP), according to which the slower of any two coupled processes must precede the faster one in order for the slow and fast processes to be coupled (Sect. 2.2.3).

A simplified representation of the mechanism of passive ion movement across the cell membrane based on GFCP is shown in Fig. 7.2. The ion channel (see the dotted square) is postulated to have two ligand-binding sites, which generate three *channels* (or gates) across the biological membrane (to be denoted as upper, middle, and lower gates). Each gate has two conformational states – *open* and *closed*. The ligand binds to its upper binding site only when the upper gate happens to be in the open state (see 1, 2 & 3). As the upper gate closes, the middle gate opens (see 3 & 4), all as a part of thermal fluctuations of the gate proteins. Notice that States 5 through 8 are symmetric with (or mirror images of) States 1 through 4, thereby implementing the same mechanisms entailed by GFCP.

The GFCP-based transport mechanism shown in Fig. 7.2 appears to be supported in part by the crystal structural data of the sodium-galactose transporter described in (Faham et al. 2008), which exhibit one half cycle of the opening and closing of the ion channel/gate while the ligands move through it across the membrane. Three differences are noteworthy between Fig. 7.2 and the mechanism described in (Faham et al. 2008):

1. Figure 7.2 is based on a well-known physical principle, that is, GFCP or PSFP, whereas the Fanham et al. mechanism is devoid of any principle to account for the action of the transporter.
2. Figure 7.2 has eight states of the channel protein and 16 steps underlying the selective transmembrane ligand transport, whereas the Fanham et al. mechanism shows only two states of the transporter protein.
3. Thermal fluctuations play an essential mechanistic role in the transmembrane ligand movement as depicted in Fig. 7.2, whereas thermal fluctuations are not explicitly implicated or mentioned in the Fanham et al. mechanism.

7.1.5 Scalar and Vectorial Catalyses: A Classification of Enzymes

Enzymes can be divided into two groups depending on whether or not one or more of the products of enzymic catalysis undergo any net displacement (beyond thermal fluctuations) in space – the *scalar enzymes* if the product does not undergo any net displacement, and the *vectorial enzymes* if the product produced undergoes a net displacement in space. The vectorial enzymes in turn divide into two groups – the *linear vectorial enzymes* and the *rotary vectorial enzymes*. Some examples of the enzymes belonging to these different classes are given in Table 7.2.

It is interesting to note that the minimum number of the active sites needed for the various types of catalyses are one, two, and three for *scalar*, *linear,* and *nonlinear* (or rotary or circular) catalyses, respectively, in agreement with the geometric principle that *two points* are needed to define a *line* and *three points* are needed to define a nonlinear line or a *circle*.

A clear example of the *rotary catalysis* was recently reported by Uchihashi et al. (2011; Junge and Müller 2011) who used a high-speed AFM (atomic force microscopy) to measure the propagation speed of the *conformational waves* (~ 1 s per cycle) of the β subunit around the isolated $\alpha_3\beta_3$ stator ring (see Figs. 1 and 2 in Uchihashi et al. 2011). The authors concluded that the "structural basis of the unidirectionality" of the rotary conformational waves "is programmed in the stator ring" but they did not provide any molecular mechanisms for the unidirectional wave propagation. One possible such mechanism is suggested below that is based on the *pre-fit hypothesis*, which is in turn rooted in the *generalized Franck–Condon principle* or the *Principle of Slow and Fast Processes* discussed in Sect. 7.1.3.

Table 7.2 A classification of enzymic catalysis based on mechanisms and principles

Catalysis	Minimum number of active sites	Motion of products	Examples	Mechanisms	Principles
Scalar	1 (*Basic catalysis*)	*None*	Most enzymes (e.g., histidine decarboxylase; Fig. 7.5)	*Pre-fit mechanism* (Sect. 7.1.3)	*Generalized Franck-Condon principle* (GFCP), also called the *Principle of Slow and Fast Processes* (PSFP) (Sect. 2.2.3)
Vectorial	2 (*Linear catalysis*)	*Linear* (or *translational*)	Ion channels (Fig. 7.2)	*Pre-fit mechanism*	*GFCP/PSFP*
	3 (*Rotary catalysis*)	*Circular* (or *rotary*)	F_1-ATPase	*Pre-fit mechanism*	*GFCP/PSFP*

The pre-fit mechanism of the rotary catalytic activity of the F_1-ATPase stator ring consists of the following key elements:

1. In the absence of ATP, the three β subunits of the F_1 stator exist in (or assume) only one ground-state conformation designated as **O** (from "open"), and since there are three β subunits per F_1 stator, the ground conformational state of the F_1 stator as whole can be designated as **(O/O/O),** which is characterized by the presence of an opening in its center (see Fig. 1A in Uchihashi et al. 2011). The red bold letters symbolize the conformational state of the β subunits and the slash indicates the subunit which may also undergo conformational changes but these changes are not detectable with the high-speed AFM method employed by Uchihashi et al. (2011). (*It should be noted here that the hole in the center of the F_1 stator ring disappears when two of the three β subunits bind ATP and ADP (see Fig. 1D in* Uchihashi et al. 2011*) and undergo conformational transition from the **O** to the **C** and **C'** states*.)
2. The ground-state F_1 stator is in thermal equilibrium with (or thermally fluctuate among) three different conformational states designated as **(O/C/C')**, **(C'/O/C),** and **(C/C'/O)** (see the top row in Fig. 7.3).
3. In the presence of ATP, the F_1 stator binds ATP to its β subunit in the C' conformation, ADP (produced from ATP hydrolysis) to its β subunit in the C conformation, and the third β subunit is left empty in the O conformation.
4. The structure of the ligand-bound F_1 stator has been selected by biological evolution because of its ability to select, out of all the theoretically possible conformational transitions, only those states that obey the generalized Franck–Condon principle (or the Principle of Slow and Fast Processes):
5. The essence of the pre-fit mechanism (in contrast to the induced-fit mechanism of Koshland (1958)) is that conformational transitions of enzymes precede the

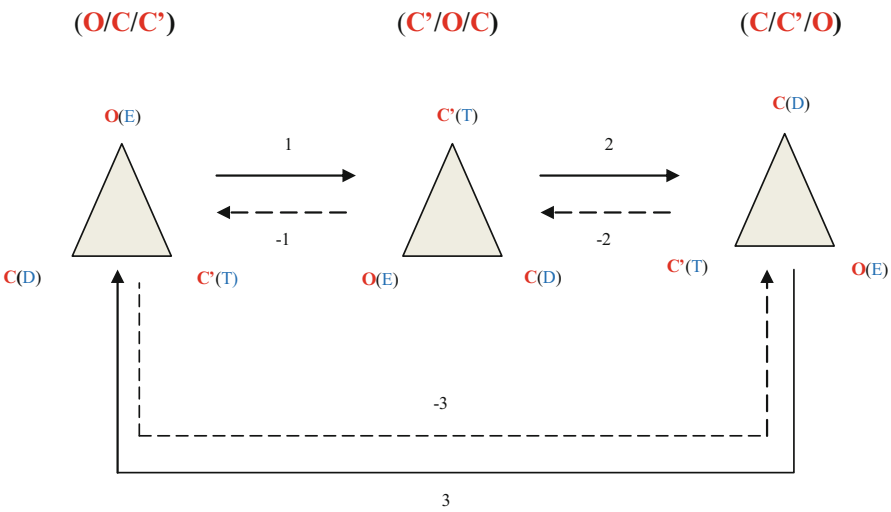


Fig. 7.3 The pre-fit mechanism of the rotary catalysis of F_1-ATPase based on the generalized Franck–Condon principle (GFCP) or the Principle of Slow and Fast Processes (PSFP). *O* = open conformation; *C* = closed conformation whose shape is complementary to that of ADP; *C'* = closed conformation whose shape is complementary to that of ATP; *E* = no ligand, that is, empty; *T* = ATP; *D* = ADP. The *filled triangle* stands for the $\alpha_3\beta_3$ stator ring (also called the F_1-ATPase stator ring) that catalyzes the hydrolysis of ATP to ADP and inorganic phosphate, P_i. Although experimentally only the O conformation could be detected by the high-speed AFM (Uchihashi et al. 2011), it is predicted here that there will be found two other conformations, designated as C and C' in this figure that circulate counter clockwise around the F_1-ATPase stator ring in phase with the O conformation. The *solid arrows* (see Steps 1, 2 and 3) indicate the direction of conformational transitions occurring in the presence of excess ATP relative to ADP in the medium, while the *dotted arrows* (see Steps -1, -2 and -3) indicate the direction of motions in the presence of excess ADP and Pi relative to ATP

associated ligand-binding events, because the former is a slower process than the latter. For example, when that F_1 stator undergoes the transition from State *1* to State *3* in Fig. 7.4, the conformations of the β subunits change from **(O/C/C')** to **(C'/O/C)** and the ligand system changes from (E/D/T) to (T/E/D). But, because the conformation changes are slower than the ligand-binding events, the transition from State *1* to State *3* cannot occur unless and until State *1* undergoes a transition to an intermediate state, State *2*, by first changing the conformational state from **(O/C/C')** to **(OC'/CO/C'C),** which is a high-energy state as indicated by the superscript double dagger and leads to the transition of the ligand-binding state from (E/D/T) to (E,T/D,E/T,D). As one can see, State *2* is intermediate between states *1* and *3* in both the *conformational states* of the proteins and the associated *ligand systems*, thus satisfying the *Principle of Microscopic Reversibility* (Sect. 3.3). From State *2*, the F_1 stator can go back to State *1* or go forward to State *3*, in which case the ligand-binding state spontaneously changes from (E,T/D,E/T,D) to (T/E/D). The mechanisms of the state transitions from *3* to *5* and from *5* to *1* as shown in Fig. 7.4 are all similar to the state transitions from

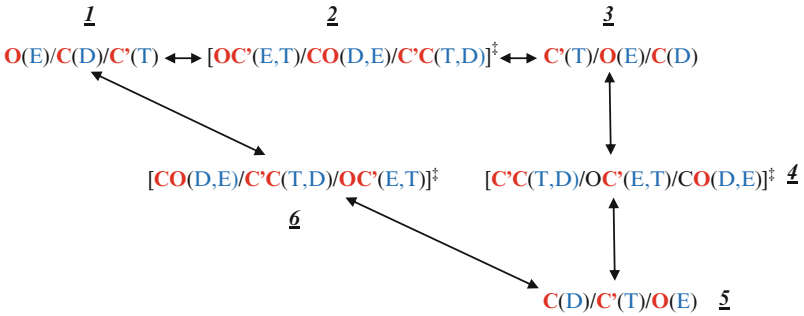


Fig. 7.4 The *pre-fit* molecular mechanism of the rotary catalysis of the F_1-ATPase (in the direction of ATP hydrolysis) based on the generalized Franck–Condon principle (GFCP) or the Principle of Slow and Fast Processes (PSFP) (Sect. 2.2). The *red bold* letters symbolize conformational states of the F_1 stator ring and the *blue* letters indicate the ligands bound to the β subunits. The *square brackets* indicate the high-energy transition state or activated states called the Franck–Condon state (Reynolds and Lumry 1966). The mechanism obeys the Principle of Microscopic Reversibility (see Sect. 3.3) so that it can be driven forward (from *left* to *right*) or backward (from *right* to *left*), depending whether the Gibbs free energy change, ΔG, accompanying ATP hydrolysis is negative or positive, respectively

1 to 3 in that they obey both the generalized Franck–Condon principle and the principle of microscopic reversibility.

7.2 Enzymic Catalysis

7.2.1 Enzymes as Molecular Machines

Chemical engineers can control chemical reactions at the macroscopic (or bulk) level, but it is only enzymes that can (or have both *energy* and *information* to) *control* chemical reactions on the microscopic (or molecular) level. Since (1) the living properties of the cell can be exhibited only if driven by exergonic (i.e., free energy-releasing) chemical reactions and (2) since most, if not all, chemical reactions inside the cell are catalyzed by enzymes, it would follow that enzymes provide the immediate mechanisms for controlling living processes in cells. So, to understand life on the most fundamental level, it is necessary first to understand how individual enzymes (as networks of atoms) work and how they work as groups (as nodes of metabolic networks) to accomplish results that are beyond the capabilities of individual enzymes (such as space- and time-dependent expressions of select genes).

Enzymes may be viewed as the most basic bionetworks whose nodes are atoms and whose links are of two principal types – *covalent bonds* and *non-covalent bonds*. The former involves sharing of one or more pairs of electrons between two atomic nuclei (with interaction energies in the range of 50–100 kcal/mol), while the latter involves much weaker bonds such as electrostatic bonds, hydrogen bonds, hydrophobic bonds, and van der Waals interactions (with interaction energies in the range of 1–3 cal/mol).

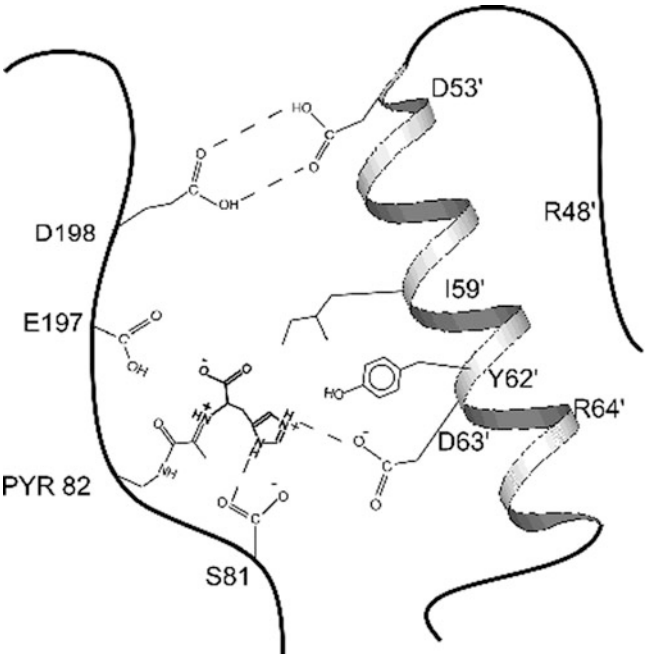


Fig. 7.5 A portion of an enzyme (histidine decarboxylase) viewed as the network of atoms of amino acid residues linked together through both *covalent* and *non-covalent* bonds. D = aspartic acid; E = glutamic acid; I = isoleucine; R = arginine; S = serine. *Solid lines* and the *ribbon* indicate *covalent* bonds, and *dotted lines* and *empty space* indicate *non-covalent* interactions (Downloaded from the web site of Jon D. Robertus, University of Texas, http://research.cm.utexas.edu/jrobertus)

As an example of an enzyme viewed as an atomic network, let us examine histidine decarboxylase (HDC), a portion of which is shown in Fig. 7.5. This enzyme catalyzes the removal of carbon dioxide from amino acid histidine:

$$\text{Hisitidine} \xrightarrow{\text{HDC}} \text{Histamine} + \text{CO}_2 \tag{7.15}$$

HDC exists as a trimer (i.e., three identical units combined to form a functional unit). Each unit consists of a linear chain of 662 amino acids (molecular weight = 74,017 Daltons). Each of the three active sites is located at the interface between two HDC molecules. Each HDC molecule can exist in two conformational states denoted as T and R. Low pH and high histidine concentration favor the R conformation which has a high affinity for histidine, while high pH favors the T conformation which has a low affinity for histidine:

$$\text{HDC}(T) + \text{H}^+ \longleftrightarrow \text{HDC}(R) \tag{7.16}$$

One active site of HDC in the R form is shown in Fig. 7.5. The active site is partially formed by helix B from a neighboring molecule. At acidic pH, two protons are trapped

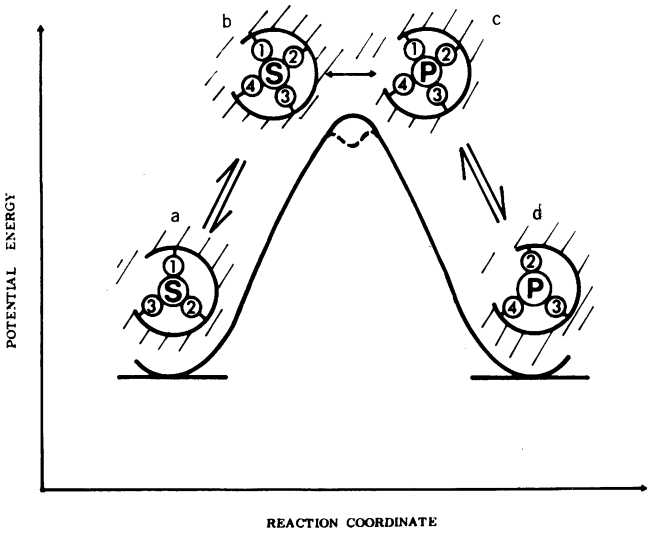


Fig. 7.6 Mechanism of enzymic catalysis based on the generalized Franck–Condon principle (GFCP) or the Principle of Slow and Fast Processes (PSFP) (Sect. 2.2.3). The conformational transitions of the active site accompanying enzymic catalysis are schematically indicated by the rearrangements of the Arabic numerals identifying different catalytic residues (Reproduced from Ji 1974a, 1979)

between two aspartic acid residues (see residues D198 and D53'), thus holding two chains close together. As HDC's product, histamine, accumulates, the pH rises and the protons are pulled off from D198 to D53', which triggers conformational changes in the B helix, leading to dissolution of the helical structure and rearrangements of catalytic residues away from the catalytic center, including D53', J59', and Y62'. In the process, residue D53' is found to be displaced by up to 5–10 Å (10^{-8} cm).

The structural information contained in Fig. 7.5 does not reveal the dynamic nature of enzymic catalysis or the geometry of the active site at the transition state (lasting no longer than perhaps 10^{-9}–10^{-12} s). Therefore, the overall dynamics of enzymic catalysis (and of bionetworks in general) must be inferred based on theoretical principles and structural and kinetic data available on the network under consideration.

The overall sequence of steps involved in an enzyme-catalyzed chemical reaction can be represented briefly as shown in Process 7.17:

$$\mathbf{S} + \mathbf{E} \leftrightarrow [\mathbf{ES} \leftrightarrow \mathbf{EP}]^{*} \leftrightarrow \mathbf{E} + \mathbf{P} \tag{7.17}$$

where S, E, and P are, respectively, the substrate, the enzyme, and the product, and ES and EP represent the enzyme-substrate and enzyme-product complexes. The symbol [. . .]* indicates the transition state (also called the Franck–Condon state) in which the E assumes such an unusual conformational state (i.e., mechanically strained state often referred to as the Franck–Condon state) that S and P becomes indistinguishable (see *b* and *c* in Fig. 7.6). Figure 7.6 schematically represents the

active site of an enzyme converting substrate S to product P within the enzyme-substrate complex (see b and c).

Notice that the substrate is bound through catalytic residues 1, 2, and 3 (see *a*), while the product is bound through catalytic resides 2, 3, and 4 (see *d*), dictated by their unique molecular shapes (not shown). Because the conformational changes necessary to rearrange catalytic residues at the active site when S is converted into P would be much slower than the electronic transitions accompanying the S to P conversion (as discussed in Sect. 2.2.3), it was postulated in (Ji 1974a) that the conformation of the active site must first change to an intermediate state between the initial and final states of the enzyme, characterized by the presence of catalytic resides 1, 2, 3, and 4 (see *b* and *c*), before S can be converted (or, in the quantum mechanical parlance, *tunnels*) to P at the transition state. This state is denoted as [ES ↔ EP]* in Process 7.17. At the transition state, S and P lose their molecular identities and exist as an intermediate (or a resonance hybrid) between S and P, which fact is symbolized by the double-headed arrow within the square bracket in Process 7.17. The transition state can either return to the initial state regenerating S or go over (or tunnel) to the final state, leading to the production of P. The height of the activation free energy barrier (i.e., the difference between the free energy levels of *a* and *b*) is postulated to be controlled by the genetic information encoded in the spatial arrangement of the catalytic residues (numbered 1 through 4) in *b* and *c* (Ji 1979) which, of course, would be influenced by the conformational state of the rest of the enzyme. Therefore, Fig. 7.6 embodies the elements of both *statistical mechanics* (related to free energy) and *information theory* (related to the geometric arrangement of the catalytic residues in the active site) and represents a concrete example of what was referred to as "info-statistical mechanics" in (Ji 2006a). The proposed mechanism of enzymic catalysis was motivated by the Franck–Condon principle imported into biology from chemical kinetics in (Ji 1974a), with the typographical errors therein corrected in Ji (1979) and generalized in (Ji 1991) into the "*generalized Franck–Condon principle (GFCP)*" or "*the principle of slow and fast processes (PSFP)*" (see Sect. 2.2.3).

7.2.2 *Enzymes as Coincidence Detectors*

The molecular mechanism of enzymic catalysis based on PSFP (Fig. 7.4) can also be viewed as the process of *coincidence detection*. A coincidence detector is defined in neurobiology as

> a computational unit that fires if the number of input spikes received within a given time bin, Δt, equals or exceeds the threshold, Θ. Mikula and Niebur 2003).

The concept of a *coincidence detector* as applied to an enzyme can be schematically represented as shown in Fig. 7.7.

Here, Brownian motions, including the thermally driven fluctuations of the catalytic residues, are considered to be much slower than the electronic transitions

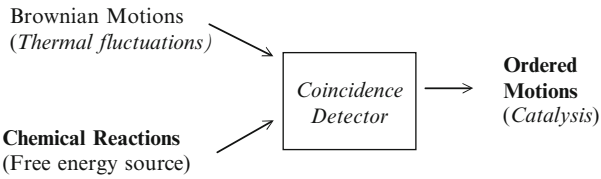


Fig. 7.7 Enzymic catalysis viewed as a *coincidence-detecting event* involving the synchrony between the substrate-binding event and the event of complementary conformational alignment of catalytic residues at the binding site

involved in chemical bond-breaking or bond-forming processes within substrates, the heart of the catalytic process. Only when right Brownian motions of the catalytic residues *coincide* with the presence of the right substrates at the active site of an enzyme is the catalysis postulated to occur. Hence, catalysis can be thought of as a form of *ordered motions* of enzymes as a whole, and the free energy cost for rectifying the random Brownian motions to ordered motions is borne by the free energy-releasing chemical reaction whose occurrence is postulated to be synchronous with the ordered motions and/or by the free energy of substrate binding partially stored in enzymes as conformational strains. The latter mechanism is similar to what is referred to as the *Circe effect* by Jencks (1975).

In another sense, enzymes can be viewed as *selectors of Brownian motions* enabled or driven by chemical reactions that they catalyze *coincidentally*, the selecting actions involving a small subset of the *conformers* of the catalytic residues that are accessible through thermal fluctuations of an enzyme. Conformers are conformational isomers, not to be confused with conformons, which are conformational strains localized in sequence-specific sites within a conformer. Conformers are a *geometric* concept, whereas conformons are both a *geometric* and *energetic concept*.

The rate of the occurrence of such coincident events can be estimated from the equation derived by Mikula and Nieber (2003):

$$N_{out}(p,\ m,\ \theta;\ q=0) = \frac{1}{\Delta t}\sum_{j=0}^{m}\binom{m}{j}p^j(1-p)^{m-j} \tag{7.18}$$

where N_{out} = the output rate, firings per minute; p = the probability of a spike occurring within a time bin Δt; m = the number of input spike trains, each having n time bins; Θ = the threshold number of spikes that must be exceeded by the summed input spikes before the coincidence detector fires or is activated; q = the correlation coefficient between spike trains 1, ... , m; and j = the number of coincident spike trains.

Although Eq. 7.18 was derived based on the neuron as a model of a coincidence detector, I am assuming that the Mikula–Niebur equation can be applied to *enzymes* (as suggested in Fig. 7.7) and *protein complexes* in general. Equation 7.18 can also be extended to *assemblies of neurons* in the brain to represent an increased neuronal synchrony associated with perception (Woelbern et al. 2002; Anderson et al. 2006; Averbeck and Lee 2004).

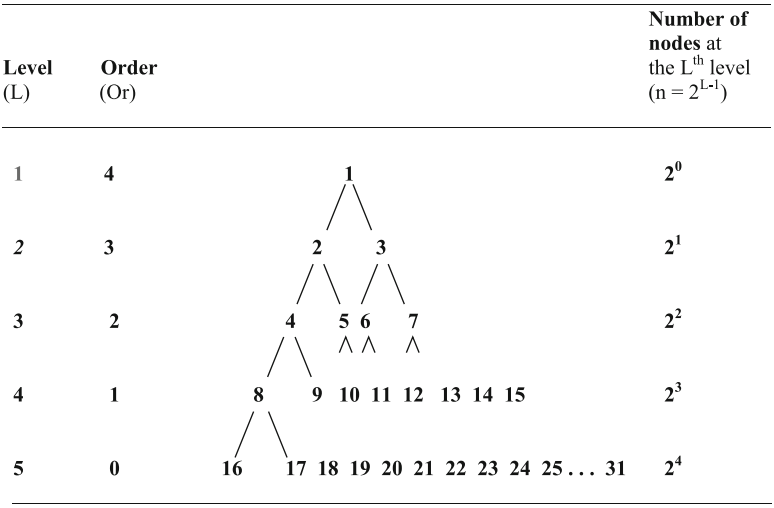


Fig. 7.8 An example of a five-level temporal hierarchy composed of a set of coincidence-detecting events (CDEs), each constructed from a set of three nodes, j-i-k, where the simultaneous occurrence of events j and k leads, causes or correlates with event i

7.2.3 *Enzymes as Building Blocks of the Temporal Structures of the Cell*

We can recognize two distinct kinds of hierarchies (or tree structures) in nature: *spatial* and *temporal*. The nodes of spatial hierarchies may be primarily associated with *equilibrium structures* (equilibrons), whereas those of temporal hierarchies with *dissipative structures* (dissipatons) of Prigogine (1977, 1980) (Sect. 3.1.5). The simplest *temporal hierarchy* is a set of n bifurcations, where n = 1 or greater. When n = 1, we have what may be called the "unit bifurcation." A unit bifurcation consists of three nodes connected thus: 1-2-3. When 1 and 3 are events whose simultaneous occurrences (within a very short time window or time bin, say, m seconds) leads to (or causes) event 2, we are dealing with what may be called the "unit temporal bifurcation (UTB).". This is equivalent to viewing 2 as a "coincidence detector" or a "coincidence-detecting event (CDE)." We can easily imagine a system of two or more CDEs coupled in such a manner as to form a tree, which may be referred to as a *temporal hierarchy* (or *temporal web*).

We can represent a *temporal hierarchy* schematically as shown in Fig. 7.8, where the "leaves" (i.e., lowest elements 16 through 31) are inputs to a system (to be defined below) observed at a given time slice, and the root of the hierarchy (i.e., element 1) is the system output at that time point. We assume that the root and the leaves are connected through a system of *coincidence detectors*, each receiving two inputs (e.g., 8 and 9 at a given time point) within a short time gap, Δt, to produce one output (e.g., 4 at the same time point) when the combined strength of the two inputs equals or exceeds a threshold value, Θ (see Eq. 7.18).

If the number of input trains carrying the leaves is m, the number of coincident input trains is j, and the probability of the input signal being in one time bin is p, we can use the Mikula–Niebur equation (7.18), to calculate the probability P of observing output 1 (Fig. 7.8) at a time point as follows:

$$\mathrm{P} = {}^{m}\mathrm{C}_{j}\mathrm{p}^{j}(1-p)^{m-j} \tag{7.19}$$

where ${}^{\mathrm{m}}\mathrm{C}_{j}$ is the binary coefficient given by m!/j!(m − j)!.

Each node in the temporal hierarchy represents an event; the higher its position in the hierarchy, the less probable or rarer is its occurrence. The probability of output P in Eq. 7.19 is a nonlinear function of three variables, m, j, and p, assuming that the correlation coefficients among the input signal trains are zero (Mikula and Niebur 2003). Therefore, there may be an optimal set of variables for maximizing the P value. If the Mikula-Niebur equation (7.18), can be applied to multiprotein complexes with r subunits divided into two groups, one group consisting of s coincidence detectors with very short Δt and the other of l (lower case L) coincidence detectors with very long Δt, so that r = s + l, then s detectors will affect P through p, and l detectors will affect P through C in Eq. 7.19.

Equation 7.19 may provide one possible rationale for the existence of multiprotein complexes. In other words, the multiplicity of the components in a multiprotein complex can enhance the probability of the rare event (i.e., node 1 in Fig. 7.6) outputted by a system of coincidence detectors (represented by all the nodes having 3° of connectivity) by either increasing C or optimizing p in Eq. 7.19.

If a temporal hierarchy consists of n levels (an example of a five-level temporal hierarchy is given in Fig. 7.8), there will be $2^{(\mathrm{L}-1)}$ nodes at the Lth level, for example, $2^4 = 16$ nodes at L = 5, that is, Nodes 16 through 31. For convenience, we will define the order of a node as (n − L), where n is the total number of the levels constituting the temporal hierarchy under consideration and L is the level of the node. We will refer to the nodes at the Lth level as the (n − L)th-order coincidence detecting events (CDEs). Thus, Nodes 16 through 31 represent the zeroth-order CDE, 8 through 15 represent the first-order CDEs, 4 through 7 represent the second-order CDEs, etc. The higher the order of a CDE, the smaller would be the probability of its occurrence in nature since its occurrence depends on the occurrences of its lower order CDEs, unless facilitated by some mechanisms driven by dissipation of free energy. In other words, we can recognize two kinds of CDEs – *passive* and *active* CDEs. The temporal hierarchy (TH) built from *passive* CDEs may be called *passive TH* and that build up of active CDEs as *active TH*. I here postulate that living systems are examples of *active THs* and *passive THs* belong to abiotic systems.

The idea that living systems embody active THs seems to be supported by both theoretical and experimental evidences:

1. Enzymes are active coincidence detectors in that the simultaneous localization of three or more catalytic residues at the active site of an enzyme at the transition state, driven by the free energy of substrate binding, leads to catalysis as indicated in Fig. 7.4.

Free Energy
Passive Temporal Hierarchies ----------> **Active Temporal Hierarchies**

Fig. 7.9 The biological evolution as the emergence of active temporal hierarchies from passive temporal hierarchies driven by free energy dissipating physicochemical processes

2. All molecular motors can be treated as coincidence detectors in that the mechanical energy stored in them results from the coincidence of the nuclear rearrangements (also called conformational or non-covalent changes) of proteins and the electronic transitions of bound ligands (e.g., ATP hydrolysis to ADP and Pi, or oxidation of AH_2 to A).
3. Bacteria can act as coincidence detectors (Mok et al. 2003).
4. Neurons of the visual cortex, auditory cortex, somatosensory cortex, hippocampus, the frontal cortex, and odor sensors act as coincidence detectors (Nase et al. 2003; Konig et al. 1996).
5. The cerebral cortex responsible for consciousness may be a high-order coincidence detector of neuronal firings (Swindale 2003), constructed ultimately from a set of enzymes acting as the lowest-order coincidence detectors.

The spatial structures of living systems (e.g., DNA double helix, 3-D structures of enzymes and biochemicals, etc.) that have been the focus of research in molecular biology for over half a century may be considered as a necessary condition but not sufficient condition for the phenomenon of life. The missing link may be identified with what may be called "temporal structures," which may act as the sufficient condition for life. In other words, *spatial structures* can lead to life if and only if they can support *temporal structures* or *active temporal hierarchies* as defined above. In this context, the biological evolution (discussed in Sect. 14) may be viewed as the natural process from which *active temporal hierarchies* emerge from *passive temporal hierarchies* through dissipation of free energy (Fig. 7.9):

The root of a temporal hierarchy with n levels (e.g., Node 1 in Fig. 7.8) can be identified with an (n – L)th-order CDE, according to the definitions introduced above. As can be seen from Fig. 7.8, an (n − 1)th-order CDE requires simultaneous occurrences or synchrony of $2^{(n-1)}$ zeroth-order CDEs (e.g., Nodes 16 through 31), since p(1) = P(2)P(3) = P(4)P(5)P(6)P(7) = P(8)P(9)P(10)P(11)P(12)P(13)P(14) P(15) = P(16)P(17) … .P(31). If the average probability of occurrence of a zeroth-order CDE is P = 0.01 and n = 5, then the probability P of the (n−1) th = fourth order CDE being realized passively (i.e., without any free energy input) would be $P^{2\wedge(n-1)} = (10^{-2})^{2\wedge(n-1)} = (10^{-2})^{16} = 10^{-32}$ which is an infinitesimally small number. If n = 3, then $P = (10^{-2})^4 = 10^{-8}$, which may be increased close to unity (i.e., increased by a factor of 10^8), if free energy can be utilized to promote the coincidence events underlying the (n − L)th = (3 − 1) th = second order CDE. Living processes (e.g., enzymic catalysis, active transport, cell cycle events, directed cell motions, etc.) appear highly improbable to us. *This may be an illusion arising from our ignorance about the precise mechanisms available to living systems or their components*, driven by free-energy dissipation,

which reduces uncertainty or, equivalently, increases the probability P arbitrarily close to unity. If these conjectures are valid, the following corollaries would follow:

> With appropriate spatial structures capable of utilizing free energy, there is no event that cannot be realized in nature with a probability arbitrarily close to unity. (7.20)

> Life is an inevitable consequence of some spontaneously occurring spatial structures capable of utilizing free energy. (7.21)

> Appropriate spatial structures and complementary free energy sources are necessary and sufficient to both originate and maintain temporal hierarchies underlying all organisms. (7.22)

We may view these statements as reflecting a principle to be called "the Principle of the Inevitability of Life (PIL)." That is, PIL may be interpreted as implying that, given the right initial conditions on the surface of the earth, the repetitive operations of the laws of physics and chemistry are bound to produce life.

Nature may have overcome the problem of joint probabilities being smaller than individual probabilities in two ways:

1. Make the simplest (or zero-order) coincidence detectors out of enzymes, whose structures are mechanically (i.e., conformationally) deformable so that ligand binding can affect their internal states, including storage of free energy.
2. Make first-, second-, third-order, etc., coincidence detectors by combining two or more zero-order coincidence detectors utilizing chemically derived free energy.

It is suggested here that these two conditions are necessary and sufficient to evolve high-order coincidence detectors which can output signals with arbitrarily large probabilities. The following justification may be offered for this conclusion. Let us consider a high-order coincidence detector composed of N subunits, where N can be as large as 50 or more (as in the case of transcriptosomes (Halle and Meisterernst 1996) of eukaryotes, enzyme complexes that catalyze the synthesis of RNA molecules using DNA as a template). Hans Frauenfelder and his coworkers (Frauenfelder 1987, Frauenfelder et al. 2001; Fenimore et al. 2005) have shown over the past several decades that proteins can exist in numerous conformational states, that is, 3D structures of biopolymers that can be altered without breaking or forming covalent bonds, which he referred to as "conformational *substates*." These conformational substates, in turn, may be closely related to what I called "virtual conformons" in (Ji 2000, p. 38). If we assume that only one of these conformational substates (or a virtual conformon selected out of many to be transformed into the corresponding "real" conformon through free energy input) can participate in detecting the coincidence event and if its probability of occurrence is P_i (where $i = 1, 2, \ldots, N$, is the identity of the protein subunit), then the total probability, P, of activating the high-order coincidence detector would be the joint probability of all the zero-order coincidence detectors needed to register the coincidence event involved:

$$P = (P_1)(P_2)(P_3)...(P_a) \tag{7.23}$$

where a is the number of the subunits acting as the necessary component coincidence detectors. Without losing generality, we can assume, for simplicity, that all P_i values are the same and equal to p. Then Eq. 7.23 reduces to

$$P = p^a \tag{7.24}$$

P can be increased while holding a constant in two ways:

1. Divide the subunits of the high-order coincidence detector into two groups "a" subunits whose activities are all necessary and "b" subunits, any one of which, working with the "a" necessary components, is sufficient to activate the high-order coincidence detector. We may refer to the former kind of subunits as *multiplicative* (a) and the latter *additive* (b) components. Again, assuming that these two kinds of subunits all have the same probability of activation, *p*, Eq. 7.24 can be transformed into a product of two terms:

$$\begin{aligned} P &= (bp)(p^a) \\ &= bp^{a+1} \end{aligned} \tag{7.25}$$

2. Make all *p*'s positively dependent on the total number, *N*, of the subunits in the high-order coincidence detector (i.e., the enzyme complex under consideration). In other words, let all the subunits, no matter where they are located within the complex, interact (i.e., constrain one another) mechanically/conformationally/allosterically in such a way that the probability of activating (through thermal fluctuations, I presume) individual subunits is directly proportional to *N*, which appears eminently feasible. We can incorporate this idea into Eq. 7.25 to obtain:

$$P = bp(N)^{(a+1)} \tag{7.26}$$

where $p(N)$ indicates that the probability p is the function of N. Equation 7.26 is rather crude at this stage but can be readily elaborated on to make it more realistic, but it is good enough for drawing qualitative conclusions about the possible biological role of subunit architecture of many enzyme complexes in the cell: To improve the probability of activating coincidence detection through thermal fluctuations, which is equivalent to increasing the probability, P, of realizing highly rare events, namely, the activation of the enzyme complex, through orderly (hence free energy-dissipating) interactions among N subunits of higher-order coincidence detectors.

Thus, if these theoretical arguments based on viewing enzymes as coincidence detectors are correct, we can conclude that it would be possible to produce any rare physicochemical processes inside the cell (e.g., activation of the expression of select genes at right loci at right times, RNA synthesis, protein synthesis, cell division, etc.) using multi-subunit enzyme complexes (i.e., SOWAWN machines or hyperstructures discussed in Sect. 2.4) consisting of N subunits (of which *a* are multiplicative and *b* are additive) by increasing *b* more rapidly than increasing *a* in Eq. 7.25.

Table 7.3 Active and passive phase transitions in physics and biology

	Physics	Biology
1. System	Physical (e.g., chemicals)	Biological (e.g., cells)
2. Homogeneity	Homogeneous	Heterogeneous
3. Observables averaged over n	$n \sim N$	$n << N$
4. Example of phase transitions	Water to ice	Enzymic catalysis
	Magnetization	Molecular motors
	Liquid crystals	Activated metabolic pathways
5. Correlation	Spatial	Temporal
6. Mode	Passive	Active
7. Key variables	Free energy	Free energy and genetic information
8. Mechanisms	Self-assembly (leading to equilibrium structures)	Self-organization (leading to dissipative structures)

7.2.4 Enzymic Catalysis as an Active Phase Transition

The concept of "phase transition" studied in statistical mechanics (Fisher 1998; Domb 1996) can be imported into molecular cell biology (being the study of cells from the molecular point of view) with great benefit. Statistical mechanics deals with random motions of a large number of molecules (in the order of Avogadro's number, N, which is 6×10^{23}/mol) belonging to a few classes that underlie macroscopically observable thermodynamic properties of physical systems. In contrast, molecular cell biology deals with both random (e.g., thermal fluctuations of enzymes) and nonrandom motions (e.g., active transport of ions) of a small number (much smaller than N) of molecules belonging to a large number (10^3–10^{50}?) of classes. Thus Elsasser (1998) referred to biological systems as "finite" and "heterogeneous" in contrast to "infinite" and "homogeneous" physical systems (see the first three rows in Table 7.3). Some examples of phase transitions (which is viewed here as synonymous with "order-disorder" or "disorder-order" transitions) in physics and biology are given in Row 4 in Table 7.3.

Enzymic catalysis can be treated as a phase transition in the sense that catalysis involves the transition of the random thermal fluctuations of an enzyme molecule into its orderly motions required by the catalytic action, paid for by the free energy of the reaction it catalyzes. Hence, we can view enzymic catalysis as an example of a *phase transition* where the correlations among events (e.g., segmental motions of proteins) in contrast to structures occur, not along the spatial dimensions alone as in physics, but also along the time dimension. In other words, the essence of enzymic catalysis may be the "freezing" of the transient conformations of the enzyme needed for catalysis for durations much longer than are allowed for by thermal motions (and the Second Law), by inputting free energy via exergonic binding interactions or electronic transitions accompanying chemical reactions. This is why we can view catalysis as an "active" (i.e., far-from-equilibrium) form of phase transition (cf. "active temporal hierarchy," Sect. 7.2.3), whereas traditional phase transitions may now be viewed as "passive" phase transitions (i.e., on the way to

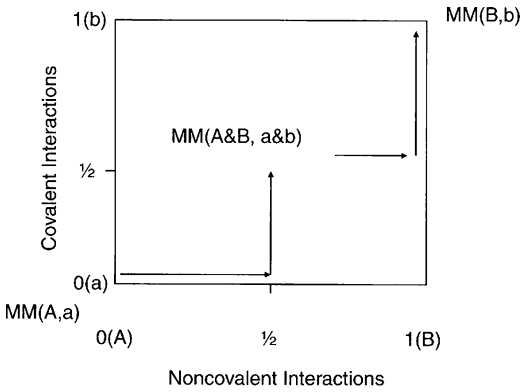


Fig. 7.10 The dynamics of enzymic catalysis represented on a two-dimensional hypercube of Kosko (1993) (reproduced from Ji 2004a). The *x*-axis represents the non-covalent changes of the enzyme conformation and the *y*-axis indicates the covalent changes of the chemical subsystem consisting of the substrate and the product bound to the enzymic active site. Also the *x*-axis encodes the conformational states of the enzyme that can assume any numerical values between 0 and 1 inclusive, and the *y*-axis encodes the quantum mechanical states of the chemical subsystem which can assume only the numerical values of 0, ½, or 1

equilibrium) (Table 7.3). One of the fundamental differences between these two classes of phase transitions is that physical phase transitions are driven by free energy, whereas biological phase transitions are driven by both *free energy* and *genetic information* that control phase transitions, thus justifying the neologism, "info-statistical mechanics" proposed (Ji 2006a) and Sect. 4.9.

7.2.5 Enzymes as Fuzzy Molecular Machines

Computer scientists distinguish between two kinds of computers – the traditional Turing machines obeying the *crisp* (also called binary, Boolean, or Aristotelian) *logic* and the fuzzy Turing machines based on the *fuzzy* (or multivalued or multivalent) *logic* (Bedregal and Figueira 2006; Peeva and Zahariev 2008). According to Wiedermann (2004), fuzzy computers have more computing power than classical Turing machines.

Although it has been widely recognized that enzymes can be treated as molecular machines (Lumry 1974, 2009; Lumry and Gregory 1986; McClare 1971, 1974; Ji 1974a, b, 1991, 2000; 2004a; Alberts 1998; Astumian 2000, 2001), little attention appears to have been given as to which of the two possible logics, crisp or fuzzy, is being obeyed by enzymes. Two observations support the notion that enzymes are fuzzy molecular machines:

1. Enzymes can be described in terms of a two-dimensional fuzzy cube of Kosko (1993) (Ji 2004a) as show in Fig. 7.10

2. Xie and his colleagues (Lu et al. 1998; Min et al. 2005) demonstrated that a single molecule of cholesterol oxidase exhibits not one but a set of over 30 rate constants under an identical experimental condition (see Fig. 11.24), which phenomenon being known as *dynamic heterogeneity* (Zwanzig 1990; Bagshaw and Cherny 2006).

Unlike a crisp machine which exists in well-defined, unambiguous internal states that can be characterized in terms of a string of N digits or, geometrically speaking, in terms of the 2^N vertices of an N-dimensional hypercube (as discussed in Sect. 5.2.5), where N is the number of variables needed to describe the machine, a fuzzy machine has many more internal states than a crisp machine of an equal dimension, because each of the N variables of a fuzzy machine can assume numerical values between 0 and 1. Thus, the internal states of a fuzzy machine can be represented by the points located in the interior of the N-dimensional hypercube (e.g., see points A and F in Fig. 5.8), which are clearly more numerous than the number of the vertices of the hypercube.

In Fig. 7.8, a simplified description of an enzymic catalysis is given utilizing a two-dimensional fuzzy cube, where the states of the enzyme and the chemical subsystem (consisting of the substrate and the product bound to enzyme active site) are represented in the x- and y-axis, respectively. The conformation of the enzyme can assume any of the states between 0 (or A) and 1 (or B), while the chemical subsystem can assume only one of the three states denoted as 0 (or a), ½ (or a & b), and 1 (or b). The combined system of the enzyme and the chemical subsystem can assume any of the states along the zigzag line that connects vertices (0, 0) and (1, 1) and hence lies in the interior of the two-dimensional hypercube, a characteristic property of a fuzzy machine.

The theoretical rationale as to why enzymes are fuzzy rather than crisp machines is not yet known. One possibility is that, due to their small physical size, enzymes cannot avoid the randomizing influence of thermal fluctuations, making it impossible for them to occupy any crisp (i.e., 0 or 1) internal states. We may refer to this concept as the *Principle of Fuzzy Molecular Machines* (PFMM) which may be stated as:

> Molecular machines cannot reside on the vertices of the N-dimensional hypercube, where N is the number of the binary questions required to characterize the internal states of the machine. (7.27)

Alternatively, PFMM may be stated as follows utilizing the concept of the Kosko entropy defined in Eq. 5.24:

> The Kosko entropy of molecular machines cannot be zero. (7.28)

Or,

> It is impossible to measure the single-molecule catalytic constant of an enzyme with an arbitrary accuracy. (7.29)

Statements 7.27–7.29 may be viewed as the different expressions of a new principle in enzymology that has emerged from single-molecule enzyme

measurements in the past decade, which may be referred to as the *Uncertainty Principle of Enzymic Catalysis* (UPEC). Thus defined, PFMM and UPEC are synonymous, that is, they refer to the same phenomenon. It may be that UPEC will be found to be the ultimate cause of the Knowledge Uncertainty Principle formulated in Sect. 5.2.7.

Chapter 8
The Conformon

Cells are examples of self-organizing chemical reaction–diffusion systems that have evolved to perform (or been selected because of their ability to perform) myriads of goal-directed (*purposive* or *teleonomic*) motions in space and time. The goal-directed molecular motions inside the living cell are carried out by biopolymers acting as molecular machines Albert (1998) Ebright, R. H. and Strick, and each molecular machine is postulated to be driven by conformons. Conformons, sequence-specific mechanical strains of biopolymers, can be generated from the binding energy of ligands as in the Circe effect of Jencks (1975) or from the free energy of chemical reactions as in stress-induced duplex destabilizations (SIDDSs) in supercoiled DNA described by Benham (1992, 1996a, b; Benham and Bi 2004). The living cell can be represented as a system of molecular machines (e.g., myosin, kinesin, dynein, dynamin, RNA polymerase, DNA polymerase, topoisomerases, and ion pumps) that are organized in space and time in various combinations in order to carry out cell functions demanded by a given environmental condition.

Since the necessary and sufficient conditions for all self-organizations in the Universe are postulated to be the combination of free *energy* and control *information* referred to as *gnergy* (see Fig. 4.8) (Ji 1991) (Sect. 2.3.2), the discrete units of which being referred to as *gnergons*, cells also must be driven by *gnergons*. Two classes of gnergons have been identified inside the cell so far that appear necessary and sufficient to account for cell functions – (1) *conformons* (packets of conformational energy generated from substrate binding and chemical reactions and confined within biopolymers) and (2) *intracellular dissipative structures* (IDSs), that is, the gradients of *translationally diffusible* chemicals such as glucose, pyruvate, ions, ATP, and RNA that reside *outside* biopolymers (Chap. 9). Using the piano as a metaphor, *conformons* can be compared to the packets of vibrational energies (or *phonons*) of strings and *IDSs* to the musical sounds generated by vibrating strings. Using the voice as another metaphor, *conformons* are akin to the vibrations of the vocal cord and *IDSs* to voice produced by vibrating vocal cord. Just as the vibrational motions of piano strings are responsible for generating sounds as the inevitable consequence of the laws of physics, so the oscillatory motions of

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_8,

biopolymers (i.e., conformons) are responsible to produce the *concentration waves* of diffusible molecular entities inside the cell, that is, IDSs as a consequence of the laws of chemistry (Ji 1985a, b). These and other analogical relations are summarized in Schemes 8.1 and 8.2 and Table 8.1, where the difference between *sheet music* and *audio music* is introduced as a metaphor to differentiate between two forms of genes (Ji 1988) – (1) the *static form* of genes identified with nucleotide sequences, called the *Watson–Crick genes,* and (2) the *dynamic form* of genes identified with conformons and IDSs, referred to as the *Prigoginian genes*:

$$\textit{Sheet Music} \xrightarrow{\text{Pianist}} \textit{Phonons}\,(\text{of Vibrating Strings}) \xrightarrow{\text{Physics}} \textit{Audio Music} \tag{8.1}$$

$$\begin{aligned}&\textit{DNA}\ (\text{Watson - Crick genes}) \xrightarrow{\text{Cell}} \textit{Conformons}\ (\text{Oscillating biopolymers;}\\ &\text{Lumry – McClare genes}) \xrightarrow{\text{Chemistry}} \textit{IDSs}\ (\text{Prigoginian genes})\end{aligned} \tag{8.2}$$

Alternatively, Process 8.2 can be expressed as follows:

$$\text{N} \xrightarrow{\text{P}} \text{C} \tag{8.3}$$

where N is the nucleotide system (including DNA and RNA) that stores the Watson-Crick form of genetic information, P is the protein system (including enzymes) that stores the Lumry-McClare form, and C is the chemical system (including IDSs) storing the Prigoginian form of genetic information, the three systems constituting the main components of the living cell. Scheme (8-3) incorporating the new concept of the Lumry-McClare form of genetic information was formulated in my 02/03/2012 email to M. Burgin, the author of *The Theory of Information: Fundamentality, Diversity and Unification* (Burgin 2010) based on my 1989 abstract submitted to the Fifth FAOB (Federation of Asian and Oceanian Biochemists) Congress held in Seoul, Korea. I have taken the liberty of attaching the email to this book (see Appendix N) for the convenience of the readers.

Statement 8.3 is consistent with the definition of genes given in Rows 3, 4, and 5 in Table 8.1.

In Table 8.1, the key analogical items are written in *italics*. Since both conformons and IDSs absolutely require free energy dissipation to exist and be maintained, they are examples of *dissipative structures* of Prigogine (see Rows 4 and 5) (also Sect. 3.1). Living cells must transmit information in both *space* (e.g., from cell membrane to the nucleus) and *time* (e.g., from a progenitor to its progeny, or from an embryo to its adult form) in order to carry out their functions both as individuals and as a member of a community. It was postulated in (Ji 1988) that (1) traditional nucleotide sequences encoding proteins and regulatory information (called the Watson–Crick genes) transmit information in time and (2) dissipative structures consisting of dynamic gradients of all sorts (referred to as the Prigoginian

Table 8.1 The relation among *genes*, *conformons*, and *IDSs* (intracellular dissipative structures) suggested by the music-life analogy

	Music	Life
1. Agent	Pianist	Cell
2. Energy source (chemical reactions)	Pianist's fingers	RNA polymerase
3. Information source (equilibrium structures)	Sheet music	Nucleotide sequences (Watson–Crick genes)
4. Periodic motions (dissipative structures)	Vibrating strings (or phonons)	Oscillating conformations of enzymes (or *conformons*), (Lumry-McClare form of genes)
5. Translational motions (dissipative structures)	Audio music	IDSs (prigoginian form of genes)
6. Evolutionary selection acts on	Audio music	IDSs

Table 8.2 The two types of the information-energy particles (or gnergons) responsible for self-organizing activities in the living cell and higher structures. Row 5 assumes that genes are not static as is widely believed but dynamic, storing both information (e.g., nucleotide sequences) and free energy (e.g., mechanical energy of supercoiled DNA). m-Dissipatons = mechanical dissipations (e.g., DNA supercoils; Sect. 8.3); c-dissipatons = concentration dissipatons (see text)

	Gnergons (or dissipatons)	
	Conformons (or m-dissipatons)	IDSs (or c-dissipatons)
1. *Energy* stored in	Proteins, RNA, DNA (this chapter)	Concentration gradients of ions, small molecules (Chap. 9)
2. *Information* stored in	Amino acid and nucleotide sequences	Chemical structures of ions and molecules and the space- and time-dependent shapes of the gradients
3. Information transmission in	*Time* (via genes, biopolymer networks, neural networks)	Space (via intracellular ion gradients, membrane potentials, action potentials, sounds)
4. Mechanism of formation	Generalized Franck–Condon mechanisms (Sect. 2.2.3)	Triadic control mechanisms (Sect. 15.3)
5. Sheet music analog	Coding and noncoding regions of DNA	Coding and noncoding regions of DNA
6. Audio music analog (types of motions)	Mechanical waves (periodic motions confined within biopolymers; local)	Concentration waves (translational motions propagating in space; global)

genes) transmit information in space (see Row 3 in Table 8.2). Row 6 in Table 8.1 indicates that, just as music lovers choose their favorite songs through audio music (and rarely through sheet music), *so organisms are selected by evolution through their IDSs* (i.e., the Prigoginian form of genes), and not through their nucleotide sequences (i.e., the Watson–Crick form of genes). This claim is in good agreement with the "phenotype first" postulate of evolution expressed by Waddington (1957) and others, including Kirschner and Gerhart (1998, 2005), West-Eberhard (1998), Jablonka (2006), and others.

As indicated in Rows 4 and 5 in Table 8.1, there are two types of dissipative structures operating in the living cell – *conformons* and *IDSs*. Any material systems that are endowed with the capacity to dissipate free energy to organize itself in space and/or time is conveniently referred to as *dissipatons* (Sect. 3.1.5). So defined, *dissipatons* are synonymous with *gnergons*, the discrete units of gnergy, and the postulated universal driving force for all self-organization in the Universe (Sect. 2.3.2) (Ji 1991). The difference between *gnergons* and *dissipatons* may be compared to the difference between *energy* and *force* in Newtonian mechanics (see Eq. 8.6), the former pair (i.e., gnergons-dissipatons) referring to organized motions and the latter pair (i.e., energy-force) referring to any motions, whether organized or not. Thus, conformons and IDSs are examples of *dissipatons*. Conformons are confined within biopolymers and IDSs propagate in space outside biopolymers. Another way to distinguish between *gnergons* and *dissipatons* is to view the former as the cause and the latter as consequences, that is,

Gnergons cause dissipatons. (8.4)

To differentiate between *conformons* and *IDSs*, the two kinds of *dissipatons* active in the living cell, the terms "mechanical dissipatons" (denoted as *m-dissipatons*) and "concentration dissipatons" (denoted as *c-dissipatons*) have been introduced in Table 8.2 (see the second row), which compares the characteristics of these two types of dissipatons.

8.1 The Definition and Historical Background

Cells are organized systems of biopolymers (proteins, RNA, DNA) and small molecules and ions. Some of these biopolymers (e.g., kinesin, dynein, myosin) have enzymic activity and act as molecular motors (Alberts 1998) moving teleonomically, driven by exergonic chemical reactions such as ATP hydrolysis that they catalyze. In order for molecular motors to move in goal-directed manner, they must be able to produce requisite conformons from either substrate binding or the chemical reactions they catalyze (Ji 1974b, 2000, 2004a). Conformons can provide the necessary and sufficient conditions for goal-directed motions of molecular machines because conformons carry both energy (to generate force) and genetic information (to control the direction of motions). The energy stored in enzymes as conformational or mechanical strains can generate forces because energy and force are quantitatively related to each other through the Second Law of Newtonian mechanics and the definition of energy as the ability to do work. According to the Second Law of mechanics, force ($\boldsymbol{F}$) equals mass (m) times acceleration ($\boldsymbol{a}$):

$$\boldsymbol{F} = m\boldsymbol{a} \tag{8.5}$$

where the bold letters are vectors having both a magnitude and a direction and regular letters indicate scalar quantities. Also, energy is equivalent to the work performed by a mass when it is moved by force $\boldsymbol{F}$ along distance L:

$$\text{Energy} = \text{Work} = \boldsymbol{FL} = (\textbf{Force})(\textbf{Displacement}) \tag{8.6}$$

Therefore, Eq. 8.6 guarantees that, given the requisite molecular mechanisms (i.e., the generalized Franck–Condon mechanism; see below), conformons can generate goal-directed molecular forces within biopolymers.

Proteins are unique among biopolymers in that they are the only macromolecules (except for some RNA molecules acting as ribozymes; see Sect. 11.4.4) that can utilize the free energy stored in chemical compounds through catalysis. That is, enzymes are the only molecules that can convert *chemical energy* into *mechanical energy* by generating molecular forces inside them. The precise molecular mechanisms by which proteins catalyze the chemical-to-mechanical energy conversion are not yet fully understood, despite intensive investigations over the past half a century. There are many competing theories to account for the so-called *force-generating mechanisms* in molecular motors and machines. These include the *molecular energy machine* theory (McClare 1971), *Brownian ratchet* hypothesis (Astumian 2000, 2001), and a *nonequilibrium statistical thermodynamic model* (Qian 2006, 2007). The conformon theory of molecular machines first proposed in (Green and Ji 1972a, b) and further developed and elaborated on the basis of the generalized Franck–Condon principle (GFCP) (Ji 1974a, b, 1985a, b, 1991, 2000) is unique among these because (1) it is the only theory providing a principled (i.e., based on GFCP) molecular and submolecular mechanism to couple chemical reactions to force generation within proteins (Ji 1974a, b, 2000, 2004a) and (2) it is consistent with and can accommodate all the other competing theories and hypotheses on the mechanisms of action of molecular machines and motors.

It is now generally accepted that molecular machines play fundamental roles in carrying out molecular processes inside the cell (Fig. 8.1) (Alberts 1998; Baker and Bell 1998). Most recent evidence indicate that at least some motions of molecular machines are driven by conformational strains of biopolymers (see "DNA scrunching" or "DNA-scrunching stress" in Kapanidis et al. (2006); Revyakin et al. (2006). However, the general mechanisms by which these molecular machines are powered and driven by exergonic (i.e., free energy-releasing) chemical reactions are not yet clear. One realistic possibility is provided by the *conformon theory of molecular machines* proposed over three decades ago (Green and Ji 1972a, b; Ji 1974b, 1991, 2000) (this chapter). The term "conformon" was coined by combining two stems, "conform-" indicating "conformations" of biopolymers and "-on" meaning a mobile, discrete material entity. Conformons are defined as follows (Green and Ji 1972a, b; Ji 1974a, 1979, 1985a, b, 1991, 2000, 2004a):

> Conformons are sequence-specific conformational strains of biopolymers that carry mechanical energy and genetic information necessary and sufficient to effectuate any goal-oriented movement of biopolymers inside the cell. (8.7)

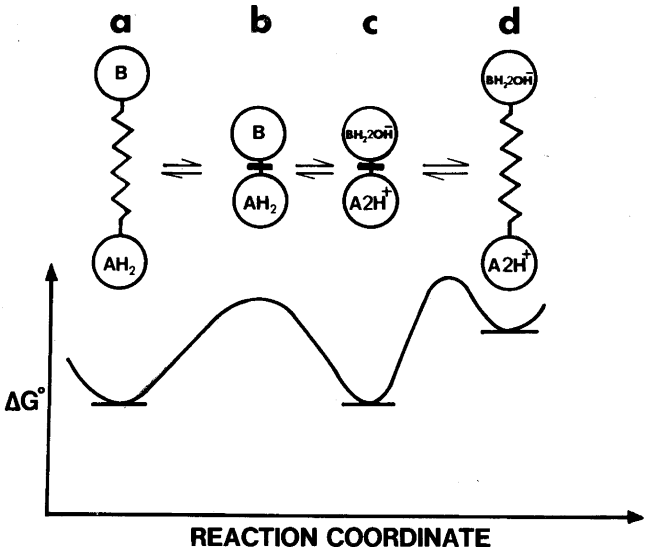


Fig. 8.1 A mechanism for converting chemical energy to mechanical energy based on the generalized Franck–Condon principle (GFCP) (Reproduced from Ji 1974b). The *spheres* symbolize enzyme active sites and the spring symbolizes the conformational deformability of enzymes. The *dumb-bell-shaped objects* are multisubunit enzymes embedded in the inner mitochondrial membrane. The first E·S complex (**a**) undergoes thermal fluctuations leading to the contraction and relaxation cycle of the "spring" (**a**, **b**). When thermal motions bring the substrate-binding sites close together at the transition state, **b**, two electrons are thought to flow (or *tunnel*) from AH_2 to B, leading to (1) generation of electrical charges and (2) the stabilization of the "cocked" or energized spring via the electrostatic attraction between separated charges. The unstabilized cocked spring in **b** corresponds to the Franck–Condon state harboring *virtual conformons*, and the stabilized cocked spring in **c** corresponds to the mechanically deformed and energized state of the enzyme harboring *real conformons*. The **c** to **d** transition exemplifies the conformon-driven work processes, which in this case is charge separation across the mitochondrial inner membrane

Although the concept of conformons was originally invoked to account for the mechanism of oxidative phosphorylation occurring in mitochondria (i.e., the coupling between the free energy-releasing oxidation of substrates and the free energy-consuming ATP synthesis from ADP and Pi; see below), the first experimental evidence for it was obtained in molecular biology, in the form of ATP-induced supercoiling of circular DNA double helix in bacteria observed under electron microscope in the mid-1960s (Stryer 1995, p. 795). The idea that biological properties of enzymes (and molecular machines, by extension) may depend on the mechanical (i.e., conformational) energy stored in proteins was first proposed by R. Lumry and others in the 1950s and 1960s (Lumry and Gregory 1986) (reviewed in Ji 1974b, 2000).

As indicated above, conformons were first invoked to explain the molecular mechanisms underlying free energy transfer from one protein (or chemical reaction) to another in mitochondria during energy-coupled process known as oxidative phosphorylation (or oxphos for short) (Ji 1974b). During oxphos, the enzyme

systems located in (and on) the inner mitochondrial membrane synthesize ATP from ADP and inorganic phosphate, P_i, using the free energy supplied by the oxidation of NADH to NAD^+. The whole process is very complex and has not yet been completely elucidated in my opinion (Ji 1979), despite the fact that biochemistry textbooks around the world accept the assumption that *chemiosmosis* (i.e., the process of converting *chemical* energy of say NADH to the *osmotic* energy of the pH gradient across the inner mitochondrial membrane) is responsible for driving the synthesis of ATP from ADP and P_i (e.g., see Figs. 21–22 on p. 545 in [Stryer 1995]). One glaring deficiency of the chemiosmotic hypothesis, for which P. Mitchell received the Nobel Prize in Chemistry in 1978, is a complete lack of any enzymologically realistic molecular mechanism that can convert chemical energy of NADH to the osmotic energy of the pH gradient and associated membrane potential. The chemiosmotic hypothesis can be represented as:

$$\mathrm{NADH} + {}^1\!/_2\,\mathrm{O_2} \xrightarrow{\textit{Mechanism (?)}} \mathrm{NAD^+} + \mathrm{H_2O} + \textit{Proton gradient} \tag{8.8}$$

$$\mathrm{ADP} + \mathrm{Pi} \xrightarrow{\textit{Proton gradient}} \mathrm{ATP} + \mathrm{H_2O} \tag{8.9}$$

To provide a chemically realistic molecular mechanisms underlying energy conversion in Processes 8.8 and 8.9, an alternative mechanism of oxphos, known as the *conformon hypothesis*, was proposed in 1972 (Green and Ji 1972a, b; Ji 1974a, b, 1976, 1977, 2000), according to which the free energy conversion involved proceeds through three main steps:

$$\mathrm{NADH} + {}^1\!/_2\mathrm{O_2} + \mathbf{ETC} \xrightarrow{\mathbf{ETC}^{\ddagger}} \mathrm{NAD^+} + \mathrm{H_2O} + \mathbf{ETC}^{*} \tag{8.10}$$

$$\mathbf{ETC}^{*} + \mathbf{TRU} \xrightarrow{(\mathbf{ETC/TRU})^{\ddagger}} \mathbf{ETC} + \mathbf{TRU}^{*} \tag{8.11}$$

$$\mathrm{ADP} + \mathrm{Pi} + \mathrm{TRU}^{*} \xrightarrow{\mathbf{TRU}^{\ddagger}} \mathrm{ATP} + \mathrm{H_2O} + \mathbf{TRU} \tag{8.12}$$

where all the macromolecular systems (i.e., molecular machines) are written in bold letters, **ETC** stands for *electron transfer complexes* (of which there are three denoted as **I**, **III**, and **IV**) located in the inner mitochondrial membrane, and **TRU** is an abbreviation for "tripartite repeating unit," the enzyme system consisting of (1) $\mathbf{F_0}$, (2) the oligomycin-sensitivity conferring protein (**OSCP**), and (3) $\mathbf{F_1}$, also called the **ATP synthase** or **Complex V** (see Fig. 1 in Ji 1976).

It is to be noted that, in each step, the enzyme system involved plays a dual role – as a carrier of free energy denoted by the superscript * and as an enzyme lowering the energy level of the transition state denoted by the superscript ‡. Thus, a significant amount of the free energy generated from the oxidation of NADH is stored in **ETC*** in Process 8.10, which is thought to be transferred to **TRU*** in

Process 8.11, which finally drives the free energy-requiring desorption of ATP from $\mathbf{F_1}$ in Process 8.12 (Boyer 2002). **ETC**‡ corresponds to the Franck–Condon state (see Sect. 2.2.3) that harbors *virtual* conformons symbolized by the superscript ‡, and **ETC*** is the energized state harboring real conformons symbolized by the superscript *. In other words, the superscripts ‡ and * denote the *virtual* and *real conformons*, respectively. *Virtual conformons are thermally derived and hence cannot be utilized to do work* (as discussed in Sect. 2.1.4), but *real* conformons are derived from free energy-releasing processes such as substrate binding or chemical reactions and hence can be utilized to do work. The conformon theory of molecular machines (Sect. 8.4) provides a reasonable and realistic mechanism for converting virtual conformons to real conformons based on the generalize Franck–Condon principle (Sect. 2.2.3).

According to the conformon hypothesis of oxidative phosphorylation, every key step in oxidative phosphorylation occurs inside the inner mitochondrial membrane and at no time is there any transmembrane proton gradient generated: *No chemiosmosis is required for oxidative phosphorylation*. However, the free energy stored in **TRU*** *can* be utilized to generate *transmembrane proton gradient,* if necessary, given appropriate experimental or physiological conditions, when the energy is transferred from **TRU*** to a hypothetical enzymic unit called the "proton transfer complex," **PTC**, yet to be discovered (Green and Ji 1972a, b; Ji 1979, 1985a, b). It has been postulated that the proton gradient formed across the inner mitochondrial membrane often observed under artificial experimental conditions is needed not for oxidative phosphorylation as assumed by Mitchell (1961, 1968) but (1) mainly for the *communication between mitochondria and the cytosol* for the purpose of monitoring the ATP needs of the cell and (2) possibly for synthesizing ATP driven by the proton gradient generated by anaerobic glycolysis during anoxia (lack of oxygen) or ischemia (lack of blood flow) (Ji 1991, pp. 60–61). It is further postulated that when this mechanism of proton-mediated intracellular communication breaks down due to the permeability transition of the inner mitochondrial membrane, the cell undergoes a programmed cell death or "apoptosis" (Crompton 1999).

8.2 The Generalized Franck–Condon-Principle-Based Mechanism of Conformon Generation

In Process 8.10 above, it was assumed that a part of the free energy released from the oxidation of NADH was stored in the enzyme system, **ETC**, that catalyzes the exergonic reaction. One plausible mechanism that can accomplish this *chemical-to-mechanical energy conversion* is schematically shown in Fig. 8.1. In passing, it should be noted that the *chemical-to-mechanical energy conversion* is synonymous with the *chemical reaction-induced force generation*, because *force* and *energy* (or work) are related through the Second Law of Newtonian mechanics as indicated

above (see Eq. 8.6). In other words, energy and force are causally related, leading to the following dictum:

Without energy no force can be generated; without force no energy can be stored. (8.13)

For convenience, we may refer to Statement 8.13 as *the molecularized Second Law of Newtonian mechanics* (MSLNM), in analogy to the *molecularized Second Law of Thermodynamics* (MSLT) formulated by McClare (1971) and discussed in Sect. 2.1.4.

Since the key theoretical principle underlying the *chemical-to-mechanical energy conversion* mechanism described below is the generalized Franck–Condon principle (GFCP) discussed in Sect. 2.2.3, the mechanism shown in Fig. 8.1 will be referred to as the *GFCP-based mechanism of conformon production*. GFCP is in turn related to (and consistent with) two other laws – MSLNM, that is, Statement 8.13, and MSLT discussed in Sect. 2.1.4. Thus, we have the following relations among the three theoretical entities implicated in the mechanism of the *chemical-to-mechanical energy conversion* to be presented.

$$\text{GFCP} \;=\; \text{MSLT} + \text{MSLNM} \tag{8.14}$$

The GFCP-based mechanism of conformon generation occurs through the following three key steps:

1. **ETC** (or any molecular machines) can exist in two conformational states – the ground state (to be denoted as **ETC** and visualized as a relaxed spring in Fig. 8.1a) and the thermally activated or excited state (denoted as $\mathbf{ETC}^{\ddagger}$ and visualized as a cocked spring in Fig. 8.1b). These two states are in thermal equilibrium, which can be represented as **ETC** <——> $\mathbf{ETC}^{\ddagger}$. Due to the constraints of the molecularized Second Law of thermodynamics discussed in Sect. 2.1.4, the lifetime of $\mathbf{ETC}^{\ddagger}$ must be shorter than τ, the turnover time of **ETC**.
2. In the ground-state **ETC**, the two substrate-binding sites are thought to be located too far apart for AH_2 to react with B or for the electrons to be transferred from AH_2 to B. In other words, AH_2 and B are prevented from reacting with each other in the ground state.
3. When the two sites on **ETC** that bind AH_2 and B are brought close together as a result of thermal fluctuations of **ETC** (see **a** —> **b** in Fig. 8.1), two electrons are postulated to be transferred from A to B (through *quantum mechanical tunneling* in one or more elementary steps), resulting in the formation of two protons in the AH_2-binding site and two hydroxyl groups in the B-binding site (see **c**), which stabilizes $\mathbf{ETC}^{\ddagger}$ to produce the energized state, **ETC***. Due to the exergonic nature of the redox reaction catalyzed by **ETC**, the lifetime of **ETC*** is no longer constrained by the Second Law of thermodynamics and can be much longer than τ.

The intramembrane electron transfer reaction involved in Fig. 8.1 can be described in greater detail as shown in Fig. 8.2, taking into account both the

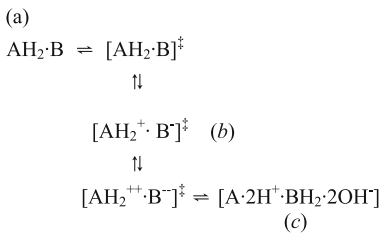


Fig. 8.2 A general mechanism of redox reaction satisfying the generalized Franck–Condon principle and the Principle of Microscopic Reversibility

generalized Franck–Condon principle (GFCP) (Sect. 2.2.3) and the principle of microscopic reversibility (PMR), which Hine (1962) describes as follows:

> . . . the mechanism of a reversible reaction is the same, in microscopic detail (except for the direction of reaction, ...), for the reaction in one direction as in the other under a given set of conditions. (8.15)

A close examination will reveal that the mechanism given in Fig. 8.2 obeys PMR. Please note that, in the Franck–Condon state, (*b*), indicated by $[\ldots]^{\ddagger}$, two electrons can be associated with either A or B with an equal probability. We assume that water molecules equilibrate rapidly within the enzyme active site, reacting with anion to form a hydroxide ion, OH^{-}, or with a cation to form a hydronium ion, H_3O^{+}, written simply as H^{+}.

8.3 Experimental Evidence for Conformons

The idea that biological properties of enzymes may depend on the mechanical (i.e., conformational) energy stored in proteins was first seriously considered by R. Lumry and others in the 1950s and 1960s (Lumry 1974, 2009; Lumry and Gregory 1986) (reviewed in Ji 1979, 2000), but the first direct experimental evidence for such a possibility did not emerge until the mid-1960s when the so-called "supercoiled" DNA was observed under electron microscope (Stryer 1995, p. 795). When a circular DNA duplex is cut through both strands and the resulting ends are twisted around the long duplex axis (called the helical axis) *n* times in the direction of increasing the distance between the paired bases (referred to as the negative direction) and then resealed, the circular form twists in space so that the helical axis itself coils into a helix, a phenomenon known as "supercoiling." To undo each helical turn, about ten hydrogen bonds must be broken between the complementary base pairs along the DNA double helix, requiring a total of about 15 kcal/mol of free energy. Thus, a circular DNA duplex which was negatively twisted around the helical axis, say, 20 times would store approximately $15 \times 20 = 300$ kcal/mol of mechanical energy in the form of conformational deformations or strains. Therefore, a supercoiled DNA duplex can be interpreted as providing *a direct experimental evidence for the concept of conformons*. That is, the supercoiled DNA duplex stores conformons.

J. H. White derived a mathematical formula (known as *White's formula*; see pp. 795–796 in Stryer 1995) that specifies the relation among three parameters – (1) the *linking number*, *Lk*, the number of times the two strands are intertwined, (2) *twist, Tw,* a number determined by the local pitch of the helix, and (3) *writhe, Wr,* a number determined by the degree of the twisting of the helical axis in space (Bauer et al. 1980):

$$Lk = Tw + Wr \tag{8.16}$$

A relaxed circular DNA duplex is characterized by the lack of any writhe, that is, $Wr = 0$, and nonzero values for the other two parameters. As described above, *writhe* can be introduced into the circular DNA duplex by first cutting the two strands of a relaxed form and by turning counter-clockwise *n* times before resealing the ends to regenerate the circular form, which can be spontaneously converted into supercoiled form. It is important to note that *Lk* can be altered only through the *cutting-twisting-resealing* operation, which are efficiently carried out by ATP-dependent enzymes known as *topoisomerases or DNA gyrase,* and that the remaining two parameters, *Tw* and *Wr*, can change in a mutually compensating manner. If the linking number of a relaxed circular DNA duplex is denoted as Lk_0 and the corresponding number for a supercoiled circular DNA duplex as *Lk*, then the *linking number difference* (symbolized as α) can be expressed as:

$$\begin{aligned} \alpha &= Lk - Lk_0 = (Tw + Wr) - (Tw_0 + Wr_0) \\ &= (Tw - Tw_0) + (Wr - Wr_0) \\ &= \Delta Tw + \Delta Wr \end{aligned} \tag{8.17}$$

Inside the cell, DNA molecules are commonly maintained by topoisomerases in negatively supercoiled states, making their linking number *Lk* smaller than their relaxed values Lk_0 so that $\alpha = Lk - Lk_0 < 0$. Therefore, α can be interpreted as a quantitative measure of *conformons* embedded in circular DNA (Ji 2000).

Linking number difference α can be viewed as a quantitative measure of the free energy stored in supercoiled DNA introduced by the *nicking-twisting-resealing* operation on the circular DNA duplexes. Interestingly, this mechanical energy can be distributed either in the twist (ΔTw) or write (ΔWr) of the supercoiled DNA duplex as indicated in Eq. 8.17. The former represents the mechanical energy stored in local deformations, while the latter indicates the same energy distributed over the whole circular DNA duplex, and these two different states of mechanical energy distributions may actually fluctuate between them due to Brownian motions, thus supporting the concept that *conformons* are mobile mechanical energy stored in biopolymers. It can be imagined that *such conformons will visit all possible local sites within a circular DNA duplex and a transcription factor will bind to DNA if and only if its resident conformons happen to "collide" with the transcription factor*. We will refer to this concept as the *transcription factor-conformon collision hypothesis* (TFCCH) *or mechanism* (TFCCM) underlying the transcription factor

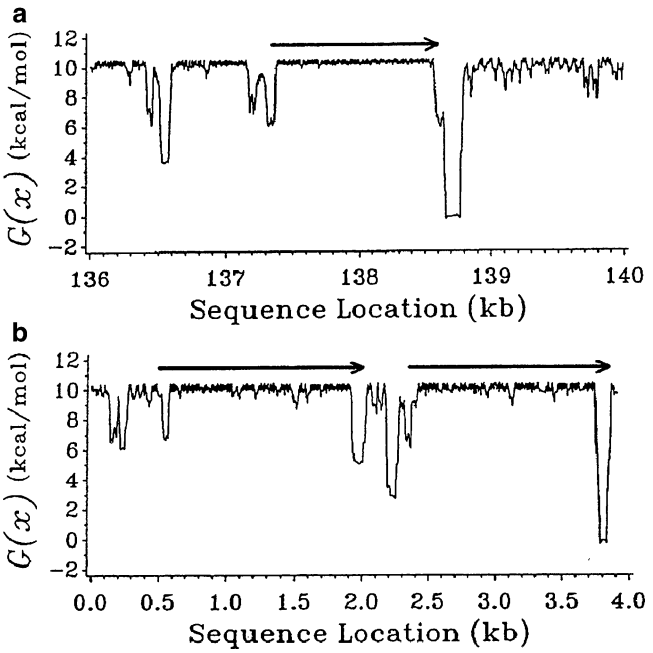


Fig. 8.3 Mechanical strains of DNA localized at sequence-specific sites within circular DNA duplexes. The *x*-axis records the nucleotide positions along the DNA duplex and the *y*-axis records the Gibbs free energy required to separate the based pairs located at position *x* along the DNA duplex chain. Notice that the base pairs located near the 3′-end (i.e., the right-hand end of the *arrow*) of some genes are already completely separated (see position 138.7 in (**a**) and 3.56 in (**b**))

binding–induced gene expression. Similar ideas have been proposed by others (Volkov 1996; Hisakado 1997; Cuevas et al. 2004; Alvarez et al. 2006). The TFCC hypothesis provides a rational explanation for the well-known phenomenon that a circular DNA duplex must exist in a supercoiled state before its genes can be transcribed or replicated (Benham 1996a, b).

In the early 1990s, C. Benham developed a statistical mechanical equation to describe the dynamics of the mechanical strains introduced in circular DNA duplexes (Benham 1996a, b; Benham and Bi 2004). His computational results indicated that the so-called stress-induced duplex destabilizations (SIDDs) (equivalent to $\alpha < 0$) were not randomly distributed along the circular DNA duplex but were localized mainly to the 5′ and 3′ ends of RNA coding regions. Three examples of SIDDs are shown in Fig. 8.3 (see the directed arrows), where the downward deflections indicate the decrease in the Gibbs free energy needed for strand separation due to the localized destabilization induced by mechanical strains. Thus, both the *sequence-specificity* and the *mechanical energy* stored in DNA make SIDDs excellent examples of the more general notion of *conformons* invoked two decades earlier and restated in Statement 8.7 (Green and Ji 1972a, b; Ji 1974b, 2000).

A more direct experimental evidence for the production of conformons from ATP hydrolysis was recently reported by Uchihashi et al. (2011; Junge and Müller

2011) who visualized the propagation of the conformational waves of the β subunits around the isolated F_1-ATPase stator ring (see Sect. 7.1.5).

Functional (as compared to non-functional) DNA molecules carry not only genetic information but also mechanical energy in the form of supercoils. The mechanical energy stored in supercoiled DNA is known to be essential for transcriptional activities in *Escherichia coli* (Benham 1996a, b), leading to the conclusion that *conformons are necessary for DNA functions*. More recently, Ebright and his coworkers (Revyakin et al. 2006; Kapanidis et al. 2006) provided direct molecular dynamics evidence, obtained using a fluorescence resonance energy transfer (FRET) technique, that conformational strain energies stored in deformed DNA strands (called "DNA scrunching" (Cheetham and Steitz 1999)) may play a critical role in transcription initiation in bacterial RNA polymerase. What these authors call *DNA scrunches* can be identified with the *conformon of* Green and Ji (1972a, b) and Ji (2000), and the *SIDDs* of Benham (1996a, b).

8.4 Conformons as Force Generators of Molecular Machines

It is the basic postulate of the conformon theory that all molecular machines are driven by conformons. The sarcoplasmic/endoplasmic reticulum calcium ion pump (i.e., the SE Ca^{++} ATPase) is one of the simplest molecular machines known with a molecular weight of 110,000 Daltons and 994 amino acid residues (Toyoshima et al. 2000). This protein can catalyze the hydrolysis of ATP and use the free energy of this reaction to transport two calcium ions across sarcoplasmic/endoplasmic reticulum membranes (Myung and Jencks 1995; MacLennan and Green 2000). The three-dimensional structure of this ion pump was determined by X-ray crystallography by Toyoshima et al. (2000). Their structure is reproduced in Fig. 8.4.

In Fig. 8.4, the first three domains of the calcium ion pump are on the cytoplasmic side of the membrane and the **M** domain (with its ten transmembrane helixes symbolized as M1 through M10) spans the membrane. ATP bound to the **N** domain donates a phosphoryl group to aspartic residue 351 located on the P domain, across a distance of about 25 Å. Two calcium ions are bound to two separate binding sites (see the two circles side by side in the membrane domain) located in parallel at about the mid-section of the membrane, separated by 5.7 Å from each other. One of the two calcium ion-binding sites is surrounded by helixes M5, M6, and M8, while the other site is associated mainly with helix M4. The distance between the aspartic acid residue 351 in the **N** domain that is phosphorylated by ATP and the calcium-binding sites in the **M** domain is estimated to be about 50 Å (Toyoshima et al. 2000).

The X-ray structure of Ca^{++} ATPase determined by Toyoshima et al. (2000) provides new information that complement the dynamic properties of the pump determined by biochemical and kinetic experiments carried out over more than four decades since the enzyme was discovered in 1962 (Toyoshima et al. 2000; MacLennan and Green 2000). The new X-ray structural data, combined with the

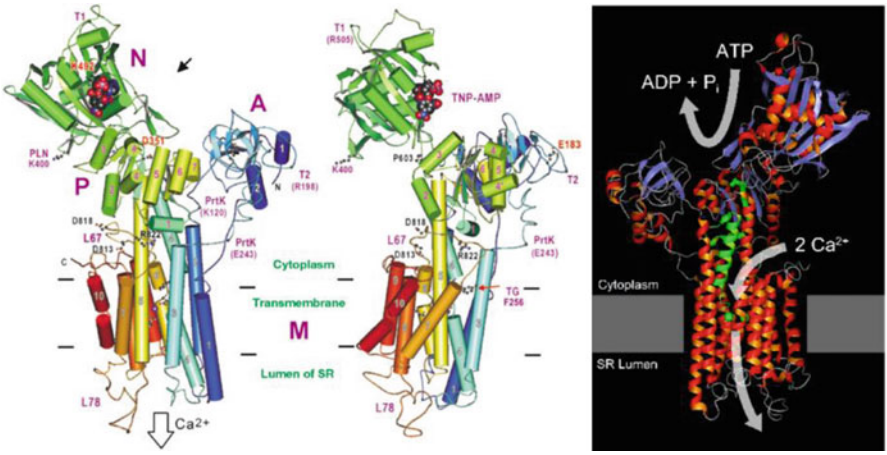


Fig. 8.4 The three-dimensional Ca^{++} ATPase of muscle sarcoplasmic reticulum determined by X-ray crystallography at 2.6 Å resolution (Toyoshima et al. 2000). (*Left*) The enzyme has four structural domains – (1) the nucleotide-binding domain denoted by **N**, (2) the phosphorylation site-containing domain, **P**, (3) the actuator domain, **A**, and (4) the calcium-binding **M** domain. Blue indicates the N terminus and red the C terminus. Transmembrane helix M5 is parallel to the plane of the paper. The model on the *right* is rotated by 50° around M5 (*Right* Reproduced by permission of Andreas Barth from http://w3.dbb.su.se/~barth/Struktur/atpase.jpg**,** which regenerated the ion pump shown in the *left panel* using the program **MolMol**)

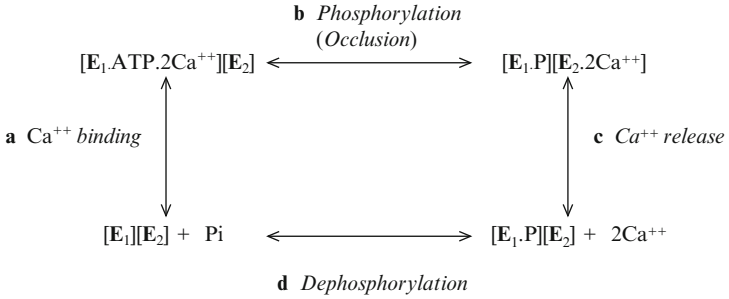


Fig. 8.5 The conformon-based mechanism of action of the sarcoplasmic/endoplasmic reticulum Ca^{++} ion pump. The ion pump proteins are written in bold letters. This mechanism has many features that have been adopted from the models of Ca^{++} ion pump proposed by MacLennan and Green (2000) and by Myung and Jencks (1995) but is distinct from these models in several important ways as explained in the text

related biochemical and kinetic data summarized by Myung and Jencks (1995) and by MacLennan and Green (2000), can be integrated with the theoretical concept of the conformon (Sects. 8.1 and 8.2) to construct a detailed and molecularly realistic mechanism of the action of the Ca^{++} ion pump as shown in Fig. 8.5.

The mechanism in Fig. 8.5 postulates that the ion pump can be divided into two structural domains, denoted as $\mathbf{E}_1$ and $\mathbf{E}_2$, both enclosed in a square bracket marking their boundaries. $\mathbf{E}_1$ has a high affinity for Ca^{++} and is accessible only from the cytosplasmic side of the membrane, and $\mathbf{E}_2$ has a low Ca^{++} affinity and is accessible only from the luminal side. In step **a**, two calcium ions and one molecule of ATP bind to $\mathbf{E}_1$ from the cytoplasmic side. In step **b**, $\mathbf{E}_1$ is phosphorylated causing it to be occluded from the cytoplasmic side and the two Ca^{++} ions are postulated to be translocated from $\mathbf{E}_1$ to $\mathbf{E}_2$ domains (probably involving a decrease in the Ca^{++}-binding affinity of $\mathbf{E}_1$ and an increase in that of $\mathbf{E}_2$, driven by appropriate conformons). In step **c**, $\mathbf{E}_2$ opens toward the luminal side and the Ca^{++}-binding affinity of $\mathbf{E}_2$ decreases (again presumed to be driven by conformons), thus releasing Ca^{++} ions into the lumen. In step **d**, $\mathbf{E}_1$ is dephosphorylated to regenerate the original $\mathbf{E}_1$ and $\mathbf{E}_2$. It should be pointed out that the $[\mathbf{E}_1.P][\mathbf{E}_2.2Ca^{++}]$ state is thought to be ADP-sensitive (i.e., this complex can transfer the phosphoryl group to ADP added from the cytoplasmic side, leading to the formation of ATP), which is consistent with the observations made by Myung and Jencks [1995], but the $[\mathbf{E}_1.P][\mathbf{E}_2]$ state is not.

There are three main features that are unique to the mechanism proposed in Fig. 8.5:

1. The Ca^{++}-binding affinity of the $\mathbf{E}_2$ domain is not constant but depends on the structural state of the ion pump as a whole (including the $\mathbf{E}_1$ domain). That is, the model assumes that the binding affinity of the Ca^{++}-binding sites in the $\mathbf{E}_2$ domain undergoes transitions among three states – high (H), intermediate (I), and low (L).
2. The accessibility of the Ca^{++}-binding sites in the $\mathbf{E}_2$ domain is also not constant but depends on the structural state of the ion pump as a whole. There are three possible accessibilities – open to the cytoplasmic (C) side only, occluded from both the cytoplasmic and luminal (L) sides, and open to the luminal side only.
3. The two calcium-binding sites are postulated to be positioned vertically relative to the plane of the membrane, separated by less than 40–50 Å, the thickness of the membrane. The X-ray crystal structure of Toyoshima et al. (2000) indicates that the two Ca^{++} ion binding sites are located side by side horizontally in the interior of the membrane contrary to what is postulated here. The reasons for this discrepancy is not clear but may include the possibility that the horizontal arrangement of the Ca^{++} ions seen by Toyoshima et al. (2000) is an artifact of protein crystallization.

Characteristic features (1) and (2) are combined and represented as in Scheme 8.18:

$$\mathbf{H}\ (\text{Open to C side}) \quad \leftrightarrow \quad \mathbf{I}\ (\text{Occluded}) \quad \leftrightarrow \quad \mathbf{L}\ (\text{Open to L side}) \tag{8.18}$$

All of the three characteristics of the proposed mechanisms of the Ca^{++} ion pump can be visualized as shown in Fig. 8.6. The formation of the occluded state is probably coincident with the phosphorylation of the C domain.

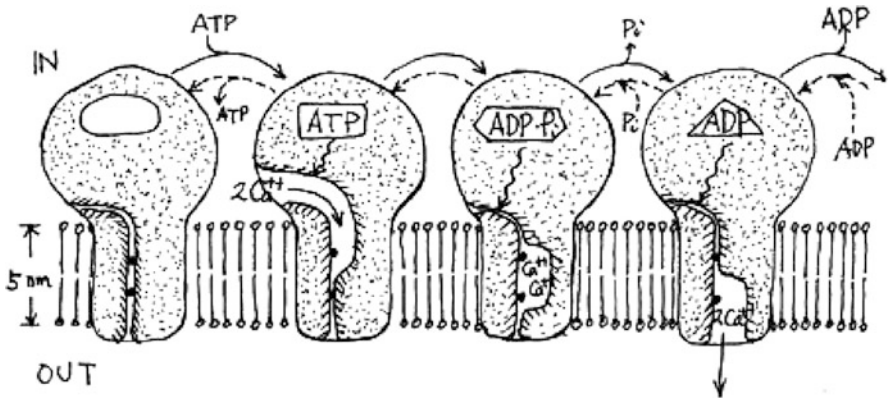


Fig. 8.6 A proposed mechanism of the action of the Ca^{++} pump based on the conformon theory of molecular machines (Ji 1974b, 1979, 2000). The model assumes that the pump molecule can be divided into two domains — the catalytic or **C** (also called $\mathbf{E}_1$) domain (see the upper portion of the pump molecule) and the transport or **T** (also called $\mathbf{E}_2$) domain (see the channel in the lower portion of the pump). Both the **C** and **T** domains undergo coordinated conformational changes amidst thermal fluctuations as schematized in the form of the changing shapes of the domains. Conformons can drive any directional motions (including Ca^{++} movement across the membrane) because they carry both *free energy* (in the form of conformational strains which act as the force generator) and *genetic information* (associated with the local amino acid sequences entrapping conformational strains). Conformons are thought to be generated in the **C** domain and "effectively" (i.e., directly or indirectly) transported to the **T** domain as symbolized by the wiggly arrows connecting the **C** and **T** domains, obeying the generalized Franck–Condon principle or the *pre-fit mechanisms* as discussed in Sect. 2.2.3. Molecular mechanisms to generate and transport conformons in enzymes have been presented Fig. 8.1 and in Ji (1974b, 1979, 2000)

8.5 A Bionetwork Representation of the Mechanisms of the Ca^{++} Ion Pump

The mechanism of the operation of the calcium ion pump proposed in Fig. 8.5 can be represented using the language of bionetwork as shown in Fig. 8.7. The two domains of the Ca^{++} ion pump are represented as **C**(. . .) and **T**(. . .) connected by **~**, which symbolizes the structures that couple these two domains mechanically (see Figs. 8.6 and 8.7). Each domain is divided into two compartments separated by a backward slash, /. The **C** domain has the ATP (or ADP) and Pi-binding sites, and the **T** domain has two calcium ion-biding sites whose accessibility to, and binding affinity for, calcium ions obey a set of rules. The pump system is postulated to exist in four distinct states denoted by **I** through **IV**:

1. In State **I**, both the **C** and **T** domains are close to their ligands.
2. In State **II**, the adenine nucleotide-binding site in **C** is accessible from the cytoplasmic side and the Ca^{++}-binding site in **T** binds Ca^{++} with high affinity.

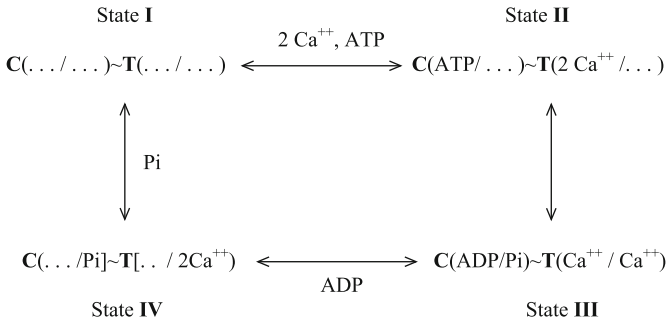


Fig. 8.7 The molecular mechanism of the action of the ATP-driven calcium ion pump of sarcoplasmic reticulum represented as a *bionetwork* consisting of four nodes and four edges. The nodes of the network represents the structural and chemical states of the **C** and **T** domains of the pump (that are mechanically coupled as indicated by ~) and the edges represent the state transitions and associated movements of ligands in and out of their binding sites

3. In State **III**, the **C** domain is phosphorylated and the Ca^{++}-binding site becomes inaccessible from either the cytoplasmic or luminal side and the calcium-binding affinity of the **T** domain decreases.
4. In State **IV**, the **C** domain releases ADP leaving the phosphoryl group covalently bound to **C** while the **T** domain opens toward the luminal side, releasing Ca^{++} by lowering its Ca^{++}-binding affinity.

There are two basic factors operating in Fig. 8.7 that control the activity of the calcium ion pump (and all other molecular machines for that matter). One is the *thermodynamic* factor that determines the direction of the net ion movement across the membrane, from a high free energy to the low free energy states, leading to a net free energy decrease, and the other is the *kinetic* factors controlling the activation free energy barriers that ions must overcome in order to move through the membrane and hence the rates of transmembrane ion movement. Either factors alone are insufficient to drive the ion movement; both conditions must be satisfied for ion movement (or the motion of any goal-directed or purposive molecular machines). We may refer to the first as the "thermodynamic requirement" and the second as the "kinetic requirement." It is postulated here that the *thermodynamic* requirement is met by the Gibbs free energy associated with the concentration gradients of ATP or Ca^{++} ion and the *kinetic* requirement is satisfied by the *conformon-driven structural changes* of the Ca^{++} ATPase that modulate the local activation energy barriers for catalysis in **C** domain and ion transport through the **T** domain. This view can be stated as follows:

> The direction of ion movement is determined by global thermodynamics of the exergonic chemical reactions or physical processes, and the rate of ion movement is determined by conformons generated in enzymes locally through ligand-binding processes. (8.19)

Statement 8.19 is consistent with the view that the primary role of enzymes and molecular machines is to control *timing* or to effect *temporal structures* (see Sect. 7.2.3). For future references, we may refer to Statement 8.19 as the "Dual Control Hypothesis of Active Transport." It is possible to generalize Statement 8.19 so that

it can be applied to both a machine (viewed as a network of the components of a machine) as well as to the network of molecular machines themselves. Thus, we may formulate what may be referred to more generally as the "Dual Control Hypothesis of Molecular Machines" (DCHMM) as follows:

> The direction of movement of molecular machines (or their components) is determined by thermodynamics through free energy changes and their speed or timing by kinetics implemented by conformons. (8.20)

Statement 8.20 may be represented using the concept of vectors. There are three key elements in Statement 8.20 – (1) molecular machines, (2) the direction of motion of the machines, and (3) the speed or timing of machine motions. We may compare (1) with the coordinates of the origins of vectors, (2) with the angle of the vectors, and (3) with the lengths of vectors.

8.6 Ion Pumps as Coincidence Detectors

Since enzymes can be viewed as coincidence detectors (see Sect. 7.2.2) and since the Ca^{++} ATPase is an enzyme, it is natural to view the ATP-driven active transport of Ca^{++} ion, shown in Fig. 8.6, as an example of an enzyme-catalyzed coincidence-detecting event as explained in Fig. 8.8.

Here, we identify the chemical processes of ATP hydrolysis within the **C** domain and the physical processes of Ca^{++} ion movement across the membrane through the **T** domain as the two events that are *synchronized* or *correlated* by the ion pump, and the set of all the space- and time-ordered motions of the molecular entities necessary to couple the **C** domain and **T** domain is treated as the coincident events or long-range molecular correlations (to use the terminology of the physics of critical phenomena [Domb 1996]). The calcium ion pump, being a *coincidence detector*, is postulated to execute an orderly movement of catalytic amino acid residues located in the **C** and **T** domains in such a manner as to hydrolyze ATP if and only if Ca^{++} ions move through the requisite binding sites in the **T** domain in the right direction, namely, from the cytoplasmic to the luminal side when the ATP

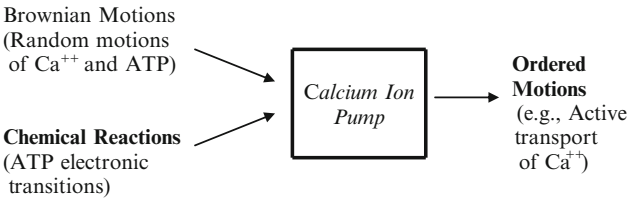


Fig. 8.8 Conformon-driven calcium ion pumping viewed as a coincidence-detecting event catalyzed by the Ca^{++} ATPase. This figure represent the application of the general enzymic mechanisms, Fig. 7.6, to the case of the calcium ion pump. See text for details

in the cytosol provides the thermodynamic driving force and in the reverse direction when the high luminal Ca^{++} ion concentration relative to that in the cytosolic side provides the thermodynamic driving force.

The essence of the model shown in Figs. 8.7 and 8.8 is the *synchronization* (or long-range correlations) of the fast ATP hydrolytic electronic transitions occurring in the **C** domain with the slow Ca^{++} ion positional changes that occur within the **T** domain separated from the **C** domain by at least 40–50 Å (Toyoshima et al. 2000). One way to avoid the *action-at-a-distance* problem that plagued Newtonian mechanics is to postulate that these two events are coupled through the *transfer of conformons* from the ATP processing sites in the **C** domain to the Ca^{++}-binding sites in the **T** domain through the structural link that connects these two domains (symbolized by "~" in Fig. 8.7), again obeying the generalized Franck–Condon principle implemented by the *pre-fit mechanisms* (Sect. 7.1.3). In other words, the two domains of the calcium ion pump are correlated or coupled via conformon exchanges just as quarks in hadrons (i.e., protons, neutrons and pions) are coupled through the exchange of gluons (Han 1999). Conformons can be generated in the Ca^{++}-binding sites in the **T** domain which are then transferred to the ATP-processing sites in the **C** domain, when the thermodynamic driving force is provided by the Ca^{++} ion gradient, high in the luminal side and low in the cytosolic side. This conclusion is mandated by the principle of microscopic reversibility, Statement 8.15 (Hine 1962).

8.7 The Conformon Hypothesis of Energy-Coupled Processes in the Cell

The cell is composed of three main classes of material entities – *biopolymers* (i.e., DNA, RNA proteins, etc.), *metabolites* (e.g., glucose, pyruvate, NADH, ATP, O_2, CO_2, H_2O, and etc.) and *inorganic ions* (e.g., H^+, Na^+, K^+, Ca^{++}, etc.). The interior space of the cell is so crowded with these molecular entities that changing the concentration of any one component at a given locus within the cell may affect the chemical activities of other components in distant locations due to the so-called crowding effects or macromolecular crowding effects (Minton 2001; Pielak 2005; McGuffee and Elcock 2010) (see Figs. 12–28).

All these intracellular molecular entities are in constant motions under physiological temperatures, and these motions can be divided into three categories – (1) *up-hill motions,* also called energy-requiring or *endergonic processes* (e.g., ion pumping, molecular motor movement, synthesis of ATP); (2) *down-hill motions*, also called energy-dissipating or *exergonic processes* (e.g., diffusion of ions across a membrane along their concentration gradients, ATP hydrolysis under physiological conditions); and (3) *random* (or *stochastic*) *motions* (e.g., thermal fluctuations or Brownian motions of biopolymers and collisions among molecules). Random motions lack any regularity but stochastic motions can exhibit regularities although

(Chemical Reactions) ⟶ (Conformons) ⟶ (Coupled Processes)

Fig. 8.9 The conformon hypothesis of coupled processes in the cell

they are not predictable. In order for the cell to carry out its functions such as growth, chemotaxis, cell cycle, cell differentiation, and apoptosis (i.e., programed cell death) in interaction with its environment through its various receptors (both membrane-bound and cytosolic), many up-hill reactions must be carried out (driven by conjugate down-hill reactions resulting in nonrandom motions) in thermally fluctuating environment without violating the laws of thermodynamics. Such coupled processes are often referred to as "energy-coupled" processes, meaning that the free energy released from the down-hill reaction is partially "transferred" to the coupled up-hill reaction in such a manner that the net free energy change accompanying the overall process remains negative. Examples of energy-coupled processes include respiration-driven ATP synthesis (i.e., *oxidative phosphorylation*), ATP- or respiration-driven active transport of protons across the mitochondrial inner membrane, and ATP-driven molecular motors and rotors, and the formation and destruction of hyperstructure or SOWAWN machines (Sect. 2.4.3). The conformon theory of molecular machines (Green and Ji 1972a, b; Ji 1974b, 2000) maintains that all such coupled processes proceed through the production and consumption of *conformons* (the mechanical energy stored in sequence-specific sites within biopolymers that acts as force generator). This idea can be represented schematically as shown in Fig. 8.9.

The coupled processes include (1) oxidative phosphorylation, (2) active transport, (3) muscle contraction, (4) intracellular molecular trafficking, (5) signal transduction, (6) gene expression, (7) DNA repair, (8) cell cycle, (9) space- and time-dependent production and destruction of hyperstructures or SOWAWN machines, (10) intercellular communication, (11) cell migration, and (12) cell shape changes.

When the mechanistic scheme shown in Fig. 8.9 is applied to mitochondria which carry out at least two coupled processes, namely, respiration-driven ATP synthesis (i.e., oxidative phosphorylation) and respiration-driven proton extrusion, we can construct the following scheme:

As will be discussed in Sect. 11.6, the chemiosmotic hypothesis of P. Mitchell (1961, 1968) assumes that respiration directly generates the proton gradient across the mitochondrial inner membrane, which subsequently drives the synthesis of ATP from ADP and Pi. In contrast, the conformon hypothesis, shown in Fig. 8.10, assumes that respiration first produce conformons (via the detailed mechanism discussed in Sects. 8.2 and 11.5), which then drives either the synthesis of ATP from ADP and Pi or the extrusion of protons from the matrix to the cytosolic space. Since the chemiosmotic mechanism absolutely depends on the presence of biomembrane, it cannot mediate the coupling of nonmembrane-dependent processes such as gene expression, muscle contraction, and molecular trafficking in the cytosol. Of the 12 coupled processes cited above that can be driven by

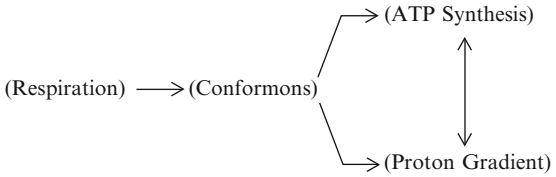


Fig. 8.10 The conformon-based mechanisms of mitochondrial energy coupling (Ji 1974b, 1979). The *double-headed vertical arrow* symbolizes both the ATP-driven proton extrusion from the matrix to the cytosol and the proton gradient-driven ATP synthesis

conformons, only Process 2 (and possibly Process 1) are membrane-dependent and hence can be driven by the chemiosmotic mechanism of P. Mitchell. Thus, it appears that the conformon mechanism is superior to the chemiosmotic mechanism on two counts – (1) the universality (i.e., applicable to both membrane-dependent and nonmembranous processes), and (2) the realistic mechanism of generating conformons from chemical reactions based on the generalized Franck–Condon principle (Sect. 2.2.3).

8.8 The von Neumann Questions and the Conformon Theory

In an article entitled "The Physics of Symbols: Bridging the Epistemic Cut," published in (Pattee 2001), Pattee discussed the seemingly unbridgeable gap (called "epistemic cut") between *symbolic structures* and *dynamic laws* implicated in all self-replicating systems, from cellular automata to living cells. Pattee was particularly interested in answering the questions raised by J. von Neumann (1966):

> . . . By axiomatizing automata in this manner one has thrown half the problem out the window and it may be the more important half. One has resigned oneself not to explain how these parts are made up of real things, specifically, how these parts are made up of actual elementary particles, or even of higher chemical molecules. One does not ask the most intriguing, exciting, and important question of
>
> 1. Why the molecules or aggregates which in nature really occur in these parts are the sort of thing they are?
> 2. Why they are essentially very large molecules in some cases but large aggregates in other cases?
> 3. Why they always lie in a range beginning at a few microns and ending at a few decimeter?
>
> This is a very peculiar range for an elementary object, since it is, even on a linear scale, at least five powers of ten away from the sizes of really elementary entities. (*The rearrangement into a set of numbered questions is my addition.*) (8.21)

It appears that Pattee's theoretical work did not address these size-related questions raised by von Neumann. Possible answers to these questions may be suggested on the basis of the *conformon theory* of molecular machines

(Sect. 8.4). Some of the key ideas generated from the *conformon theory* are described below:

1. The ability for cells to self-replicate is encoded in a set of genes numbering in the hundreds, if not thousands. It should be recalled that the human cell contains approximately 25,000 structural genes constituting only less than 3% of the total DNA mass. The timing of the expression of these genes are controlled by regulatory genes postulated to reside in "noncoding" regions of DNA that constitute more than 90% of the DNA mass in the human genome (Ji 1999b, 2002b).
2. The cell can be viewed as a "supramolecular machine" that is constructed out of a set of n molecular machines, mostly enzymes, but including DNA and RNA (where $n = 10^6$–10^9), each having a diameter about 10^5 times as large as the diameter of atoms. Interestingly, the diameter of the cell itself is about 10^5 times as small as the diameter of the human body, suggesting that the cell may possess the right physical size to mediate the world of atoms and that of the human body.
3. For the cell to be able to self-replicate, it must (1) utilize the free energy provided by chemical reactions which do not proceed inside the cell spontaneously without catalysis performed by molecular machines (also called enzymes) and (2) control the utilization of free energy in accordance with the genetic information stored in DNA and the information received from its environment.
4. Molecular machines are capable of carrying out both the *utilization* of the free energy generated from chemical reactions (called "rate-dependent dynamics" by Pattee) and the *control* of free energy utilization based on genetic information (called "rate-independent genetic symbols" by Pattee), ultimately because

   (a) Biopolymers possess the right physical sizes/dimensions to be thermally deformed, thereby transiently storing thermally derived kinetic and potential energies in the form of conformational strains, called "virtual conformons" (Ji 2000) or "conformational substates" (Frauenfelder 1987).
   (b) The genetic information encoded in the internal structures of biopolymers provide the necessary constraints to synchronize (or control the timing of) the *entrapping* of virtual conformons at sequence-specific loci and the catalysis triggered by the virtual conformons, leading to the dissipation of the requisite chemical-free energy into heat, thus paying back the thermal energy borrowed from the environment (in the form of virtual conformons) quickly enough to avoid violating the second law (Ji 1979, 2000) (Sect. 2.1.2).

The combination of the synchronized partial processes (a) and (b) is necessary and sufficient to convert *virtual* conformons into *real* conformons. As long as this conversion is completed within the cycling time τ of the molecular machine, no laws of thermodynamics is violated (Sect. 2.1.2) (McClare 1971; Ji 2004a). It should be pointed out that realistic molecular mechanisms for synchronizing processes (a) and (b) were proposed almost three decades ago based on the "generalized Franck–Condon principle" (Sect. 2.2.3) (Ji 1974b, 2000). The critical

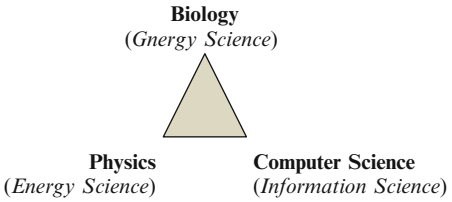


Fig. 8.11 A suggested complementarity between *physics* and *computer science*, or more generally between *energy science* and *information science*

role that thermal noise (also called thermal activations, fluctuations or Brownian motions) must play in the workings of molecular motors is now widely recognized (Astumian 2000, 2001). Thus, the conformon theory of molecular machines formulated between 1972 and 1985 may provide reasonable answers to the three von Neumann questions listed in Statement 8.21.

As pointed out by Pattee (1996), we can view the von Neumann questions as being related to the problem of the *epistemic cut* between symbolic control/computation and dynamic laws, between rate-independent boundary conditions and rate-dependent dynamics, between the subject and the object, and between symbol (or sign) and matter. To this list of complementary pairs, we may add another pair that embodies an epistemic cut – *computer science* and *physics*, or more generally *information science* and *energy science*. This gap may be bridged by biology, the science of conformons (or more generally the science of "gnergy," the complementary union of *information* and *energy* (Sect. 2.3.2) (Fig. 8.11):

Since complementarity between A and B presupposes the existence of a third term C (because A and B must be complementary aspects of something) (Sect. 2.3.3), there must exist the C term serving as the source or the ground for physics (viewed as A) and computer science (B). Biology, being the science of gnergy, seems to be ideally suited to be the C term. It is hoped that the introduction of the third term C (e.g., Gnergy) into the contemporary discourses in physics, biology, computer science, and philosophy will help clarify controversial issues involving dichotomous pairs such as *boundary conditions* versus *dynamic laws*, the *subject* versus the *object*, the *mind* versus the *body*, etc.

Chapter 9
Intracellular Dissipative Structures (IDSs)

9.1 Experimental Evidence for IDSs

According to I. Prigogine (1917–2003) (1977, 1980), there are two fundamental classes of structures in nature – *equilibrium structures* that can exist without any dissipation of free energy (e.g., crystals, a stick of candle, purified proteins) and *dissipative structures* whose maintenance requires free energy dissipation (Sect. 3.1) (Kondepudi and Prigogine 1998; Babloyantz 1986; Kondepudi 2008). For convenience, the former has been referred to as *equilibrons* and the latter as *dissipatons* (Sect. 3.1.5). The Bhopalator model of the living cell (Ji 1985a, b, 2002b) (to be discussed in Sect. 10.1) postulates that the dissipative structures present inside the living cell (hence called IDSs, or Intracellular Dissipative Structures) play a fundamental role in determining cell functions. The first direct evidence supporting this postulate was provided by the intracellular calcium ion waves observed in chemotaxing human neutrophils using a calcium ion-sensitive fluorescent dye (Sawyer et al. 1985) (see Fig. 3.2 in Sect. 3.1.2).

The most recent evidence for IDSs is supplied by the genome-wide RNA (i.e., transcript) levels measured with DNA microarrays invented in the mid-1990s (Pease et al. 1994; Schena et al. 1995; Watson and Akil 1999). Using this technique, Garcia-Martinez et al. (2004) measured simultaneously both the transcript levels (TL) and transcription rates (TR) of more than 6,000 genes in budding yeast undergoing glucose-galactose shift. The nucleotide sequence structures of genes coding for transcripts are examples of *equilibrons* and the patterns of time-varying transcript levels are examples of *dissipatons*. Not distinguishing between these two types of structures can lead to Type I (false positive) and Type II (false negative) in analyzing DNA array data (Ji et al. 2009a).

The data reported by Garcia-Martinez et al. (2004) indicate (1) that the maintenance of the concentration levels of most of the mRNAs of the yeast cells is dependent on energy supply since they decreased toward zero levels when yeast cells are deprived of their energy source (see Fig. 9.1 below), and (2) that mRNA levels of yeast cells are function-dependent so that, upon replacing glucose with galactose,

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_9,

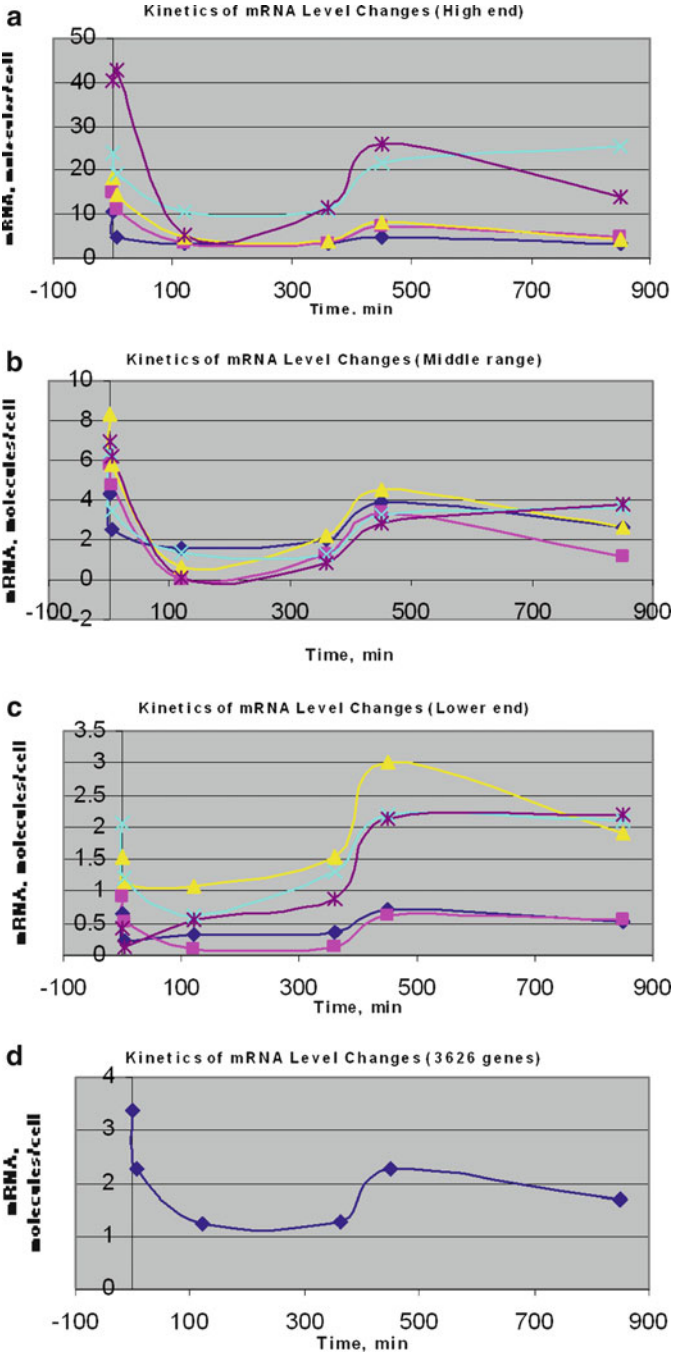


Fig. 9.1 The time series of mRNA levels of budding yeast measured with DNA arrays after switching glucose to galactose (Garcia-Martinez et al. 2004). (**a**–**c**) Individual examples randomly selected from 3,626 genes with no missing values. (**d**) The average kinetic behavior of the 3,626 transcript levels (Data from Ji et al. 2009a)

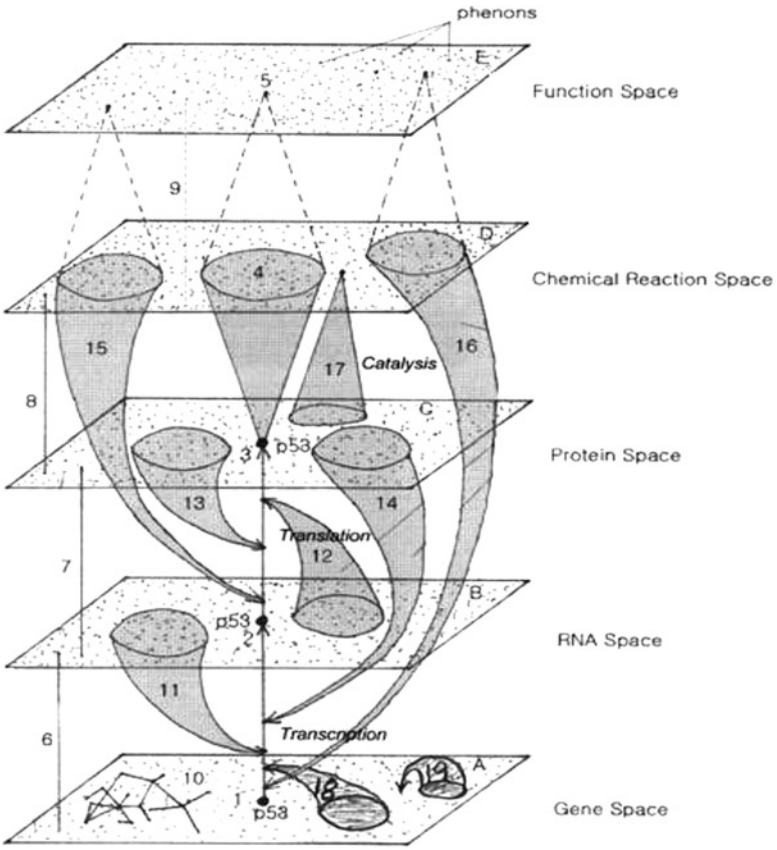


Fig. 9.2 An eight-dimensional representation of the "cell hypernetwork" or "cell interactome" that focuses on p53. The figure consists of five spaces or five traditional networks (depicted as *planes*) each consisting of elements (denoted by *dots*) that belong to the five classes of the entities indicated on the *right-hand-side* of the figure. *Dissipatons* = dissipative structures (Sect. 3.1); *equilibrons* = equilibrium structures; *phenons* = phenotypes

the levels of the mRNA molecules encoding the enzymes needed to catalyze glycolysis (converting glucose to ethanol) decline while those of the mRNA molecules encoding the enzymes needed to catalyze respiration (converting ethanol to carbon dioxide and water) and galactose metabolism increase (see Figs. 9.2 and 12.4). The first observation supports the notion that mRNA levels are *dissipatons,* since their maintenance requires free energy supply, and the second observation supports the concept that the *patterns of the changes in* (or *trajectories of*) *mRNA levels* reflect (or can be identified with) cell functions as postulated in the Bhopalator model of the cell (Sect. 10.1) (Ji 1985a, b, 2002b).

Any concentration gradients present inside the cell qualify to be called *dissipatons* or *dissipative structures*. Since there are many chemical species in the cell, small molecules such as ATP, inorganic phosphate, and various ions and macromolecules

such as proteins, RNA, and DNA that can form gradients, it would be necessary to distinguish their dissipatons with appropriate adjectives. Thus, the *X dissipaton* (e.g., RNA dissipatons) will denote the *dissipaton* consisting of the concentration gradient of X. An X dissipaton comprises two aspects – (1) the *static* structure of X which is an equilibrium structure, and (2) the *dynamic* aspect of X which is a process derived from or rooted in (1). These two aspects of X form the two of the three elements constituting a function, the third element being the mechanism of producing dynamic processes from static structures (see Fig. 6.9). Furthermore, it is here recommended that, whenever convenient, the term "ribons" be used to refer to *RNA dissipatons, the term "ribons" being derived from "ribonucleic acid*." Unlike *equilibrons* (e.g., genes defined as sequences of nucleotides), which are stable enough to be isolated, purified, and sequenced, *dissipatons* are dynamic and ephemeral in the sense that, whenever attempts are made to isolate them, they disappear, just as the flame of a candle disappears if attempts are made to capture it. The main objective of this section is to describe and use the software known as ViDaExpert to characterize and classify *RNA dissipatons* or *ribons* in cells. The computational method presented in this book (see Chaps. 18 1nd 19) should be applicable to studying other kinds of *dissipatons*, including pericellular and extracellular concentration gradients (e.g., gradients of morphogens and cheomoattractants in tissues and hormones in blood), EEG patterns, and many other time-series data, since they are undoubtedly instances of dissipative structures (or dissipatons), their existence being dependent on free energy dissipation.

The software *ViDaExpert* was developed in (Zinovyev 2001; Gorban and Zinovyev 2004, 2005) and is freely available at http://bioinfo-out.curie.fr/projects/vidaexpert/.

The term ViDaExpert derives from "the **vi**sualization of multidimensional **da**ta **Expert**" program. It is a tool for visualizing high-dimensional data on a lower-dimensional space for easy visual examination and analysis of their spatio-temporal patterns and regularities. The main technique implemented in ViDaExpert is the method of elastic maps, an advanced analog of the method of self-organizing maps. In addition, it embodies many other methods of data analysis such as principal component analysis, various clustering methods, linear discriminate analysis, and linear regression methods (Gorban and Zinovyev 2004, 2005).

The RNA kinetic data can be displayed in an abstract six-dimensional mathematical space wherein each point is associated with six numbers, each representing the concentration of an RNA molecule (or RNA equilibron) measured at one of the six time points 0, 5, 120, 360, 450, and 850 min measured after switching glucose to galactose (Garcia-Martinez et al. 2004). ViDaExpert was used to visualize the six-dimensional kinetic data of the genome-wide RNA levels of budding yeast on a two-dimensional principal grid with n^2 nodes where n is the dimensionality of the grid which was varied from 2 to 15. The elastic coefficients, that is, stretching coefficient λ and bending coefficient μ, were also varied from 0 to 50, but, having found no significant improvement in clustering behaviors of the data points, these elastic coefficients were kept constant at 0 for most analysis.

In the presence of glucose, budding yeast turns on those genes coding for the enzymes needed to convert glucose to ethanol (a phenomenon known as *glucose induction*) and turns off those genes needed for galactose metabolism (known as *glucose repression*) (Kuhn et al. 2001; Johnston 1999; Ashe et al. 2000; Jona et al. 2000). The detailed molecular mechanisms underlying these phenomena are incompletely understood at present and under intensive studies (Gasch 2002; Winderickx et al. 2002). When glucose is depleted, *Saccharomyces cerevisiae* increases its rate of metabolism of ethanol to produce ATP via the Krebs cycle and mitochondrial respiration (Gasch 2002; Ronne 1995). This metabolic control is exerted by reversing (or dis-inhibiting) the glucose repression of the genes encoding the enzymes required for respiration (i.e., oxidative phosphorylation), and this process is known as *glucose de-repression* (Gasch 2002). The glucose-galactose shift caused massive metabolic changes in budding yeast characterized by rapid decreases in most RNA levels within the first 5 min, continuing to decrease up to about 2 h after which they generally increased (Fig. 9.1), presumably due to the induction of enzymes capable of metabolizing galactose to generate ATP (see Fig. 12.3). The kinetic behaviors of the yeast transcripts under this nutritional shift are complex in detail (see Fig. 9.1a–c) but reveal a set of regular patterns, including the fact that the average glycolytic transcripts decreased between 5 and 360 min, whereas the average respiratory transcripts increased in the same time period (Fig. 12.2a). These opposite changes reflect the anticipated metabolic transitions from glycolysis (i.e., fermentation) to respiration induced by the glucose removal (leading to *glucose de-repression* mentioned above). This observation provides a concrete evidence to support the hypothesis that the dynamic patterns of the changes in RNA levels (i.e., *RNA dissipatons,* RNA trajectories, or RNA waves) in living cells can serve as indicators or molecular markers for cell functions (see the IDS-Cell Function Identity Hypothesis described in Sect. 10.2).

9.2 The p53 Network as a Multidimensional "Hypernetwork"

Just as atoms consist of two types of particles, *hadrons* (i.e., heavy particles including protons and neutrons) and *leptons* (i.e., light particles including electrons), so the cell can be viewed as consisting of two types of physical objects – *equilibrium structures* or *equilibrons* (e.g., ground-state molecules such as ATP, proteins, RNA, and DNA, and their complexes) and *dissipative structures* or *dissipatons* (e.g., ion gradients across the cytosol or cell membranes, mechanical stress gradients in supercoiled DNA and the cytoskeleton, and cyclically turning-over molecular machines). It appears reasonable to conclude that the interactions among select sets of *equilibrons* and *dissipatons* that are organized in space and time can account for all cellular functions (i.e., phenotypes), just as the interactions among hadrons and leptons are known to account for all atomic structures and their properties in physics (except perhaps the phenomenon of entanglement (Albert and Galchen 2009)). We may refer to these phenotypes (e.g., chemotaxis, morphogenesis, cell cycling) as "phenons" to go with

"equilibrons" and "dissipatons." Employing these new terms, we can describe the cell in two distinct ways – (1) *phenomenologically* as a set of phenons, or (2) *mechanistically* as a set of spatiotemporally organized *equilibrons* and *dissipatons*. The phenomenological method of describing the living cell represents the traditional cell biology that prevailed before the emergence of the Mendelian gene as a unit of inheritance and before the mechanism-based way of describing the cell began to appear in the early decades of the twentieth century, especially after the discovery of the double helical structure of DNA by Watson and Crick in 1953. Interestingly, the concepts of *equilibrons* and *dissipatons* that are postulated to be the building blocks of all molecular mechanisms underlying life appear to be closely related to what Darden (2006) refers to as "entities" and "activities" in her dualistic theory of biological mechanisms.

The abstract concepts of *equilibrons* and *dissipatons* introduced in this book can be given some concreteness by illustrating their roles in the mechanism of action of p53. The p53 protein was discovered in 1979 but its function was not established until 1989. It suppresses tumors under normal conditions, and when mutated, loses its ability to suppress tumors, leading to cancer (Vogelstein et al. 2000). About one-half of all human tumors are known to be caused by (or associated with) mutated p53. In the so-called p53 network described by Vogelstein et al. (2000), the p53 protein plays the role of a *hub* having at least 5 incoming links and 18 outgoing ones. Additionally, the synthesis of p53 protein requires a set of other proteins to catalyze the translation step and the presence of p53 mRNA as the template. The synthesis of p53 mRNA in turn requires another set of about 50 proteins (in the form of a *transcriptosome*, a term coined by Halle and Meisterernst [1996]) to catalyze transcription and transcript processing using the p53 gene as the template. Finally, the p53 protein acts as a transcription factor for several dozens of genes by binding to specific sequences in DNA, thereby activating the transcription of target genes (Vogelstein et al. 2000).

To represent all these complex mechanisms of interactions of p53 with other ligands (DNA, RNA, proteins, and most likely some inorganic ions) and its biological functions, it is almost mandatory to use the *language of networks* (Barabasi 2002). Vogelstein et al. (2000) used a two-dimensional network for this purpose, but it became obvious to me that the dimensionality of the network should be expanded to at least eight. The eight dimensions include the traditional space and time coordinates (x, y, z , and t) for localizing p53 molecule inside the cell at time t, three network-related dimensions of *n*, *l,* and *f* (where *n* stands for *nodes*, *l* for *links* or *edges*, and *f* (or p) for *functions* (or *properties*)) (Sect. 2.4.1), and the eighth dimension to characterize the higher-order organization (here called "stacking") of the five traditional networks to form what may be referred to as a "hypernetwork" or cell "interactome," the term "interactome" being defined here as the totality of molecular interactions in living systems (cf. Wikipedia.org/wiki/Interactome). Thus, the eight-dimensional hypernetwork (or *interactome*) of p53 can be graphically represented in terms of the following elements and procedures (see Fig. 9.2):

1. The two-dimensional network of genes (denoted by dots on the planes and the edges omitted for simplicity) centered on the p53 *gene* acting as a hub (see 1 on Plane A or the Gene Space).

2. The two-dimensional network of mRNA molecules (denoted by dots) centered on the *p53-coding mRNA* acting as the hub (see 2 on Plane B, the RNA Space)
3. The two-dimensional network of proteins (denoted by dots) centered on the *p53* protein acting as the hub (see 3 on Plane C, the Protein Space)
4. The two-dimensional network of chemical reactions (denoted as dots in Plane D or the Chemical Space) catalyzed by one or more proteins (e.g., see the inverted circular cone labeled 17 that connects the Protein Space and the Chemical Reaction Space)
5. The network of *functions* (denoted as dots) associated with one or more proteins including the p53-mediated functions (see 5 on Plane E or the Function Space)
6. Stacking of the above five two-dimensional networks into a three-dimensional network at each time point, t, to form "hypernetworks" or "supernetworks"

The gray circular cones in Fig. 9.2, both straight and curved, represent the biochemical analog of "renormalization" in condensed matter physics (Sect. 2.4) (Domb 1996) and hence may be referred to as "renormalization cones." A renormalization cone can be viewed as a geometric representation of a group of biological entities (be they genes, RNA, proteins, or chemical reactions) located on the base of the cone acting as a unit to catalyze a process (represented by the apex of the cone).

Most of the dots in each plane in Fig. 9.2 are probably linked to form networks, one of which is explicitly shown as a small network in the Gene Space (see 10). The best known example of such in-plane networks is the protein–protein interaction network known as the protein interactome (Ito et al. 2001; Stumpf et al. 2008; Suter et al. 2008).

There are two kinds of links (depicted as straight lines) in Fig. 9.2 – the *horizontal* links belonging to a plane (e.g., network 10) and *vertical* links spanning two or more spaces (see lines labeled 6, 7, 8, and 9). All the points in one space should be connected to their counter parts in adjacent spaces via vertical lines, if one gene codes for one RNA (see line 6), which in turn codes for one protein (line 7), which catalyzes one reaction (line 8). It is well known that a group of about 50 proteins acts as a unit to catalyze the transcription process in eukaryotes (which is indicated by Cone labeled 14), and another group of a similar size catalyzes translation (see Cone 13). As indicated above, such a process of grouping of a set of proteins into a functional unit (called a SOWAWN machine or a hyperstructure) is reminiscent of "renormalization" in statistical mechanics (Sect. 2.4.4) (Fisher 1998; Barabasi 2002; Domb 1996). Abundant experimental data indicate that some RNA molecules participate in regulating not only transcription and translation, as represented by Cones labeled 11 and 12, but also transcript degradation (not shown) (Mattick 2003, 2004; Hannon and Rossi 2004) are represented by Cones labeled 11 and 12. As indicated by Cones 15 and 16, chemical reactions can influence the rates of transcription and translation, for example, *directly* by covalently modifying DNA and RNA or *indirectly* by changing the pH, metal ion concentrations, or membrane potentials of the microenvironment inside the cell. Thus, Cones 15 and 16 can provide molecular mechanisms for epigenetic phenomena which are emerging as important topics in both developmental and evolutionary biology (West-Eberhard 1998; 2003; Riddihough and Zahn 2010; Bonasio et al. 2010).

Whereas Cones 11, 12, 13, 14, 15, 16, and 17 involve many-to-one renormalizations, we have to invoke a renormalization that involves a one-to-many transitions as well (see Cone 4) to represent the fact that p53 proteins participate in numerous functions (Vogelstein et al. 2000).

Cone18 represents all the DNA regions that affect transcription and replication by acting either as templates (i.e., as "structural genes") or as regulatory regions (i.e., as promoters, enhancers, or silencers). As discussed in Sect. 12.11, we have recently obtained the microarray evidence that some structural genes in budding yeast can co-regulate their own transcript levels in conjunction with regulatory genes (Ji et al. 2009c). Cone 18 in Fig. 9.2 was not present in my original drawing of the figure but was later added at the suggestion of one of my undergraduate students at Rutgers, Julie Bianchini, and hence is referred to as the *Bianchini cone*.

Cone 19 indicates self-replication. The existence of Cone 19 is supported by the simple fact that DNA acts as the template for DNA synthesis catalyzed by DNA polymerase which makes a physical contact with the original DNA. The concept of Cone 19 is also consistent with the hypothesis that the DNA molecule as a whole can be viewed as a gene (called the d-gene in Sect. 11.2.4). It is important to note that d-genes carry not only *genetic information* but also *mechanical energy* in the form of SIDDSs (stress-induced duplex destabilizations) (see Sect. 8.3) or conformons (Chap. 8), thus enabling d-genes to act as *molecular machines to perform goal-directed molecular motions* such as strand separations or chromatin remodeling, very similar to protein molecular machines (Sect. 7.2.1). Since genes constitute parts of a DNA molecule, and since genes appear to act as molecular machines (Ji et al. 2009c), it is probably inevitable that a DNA molecule itself should act as a molecular machine. Also, since according to the conformon theory, all molecular machines are driven by conformons (Chap. 8) (Ji 2000), the following general statement may be made:

DNA is a coformon-driven molecular machine. (9.1)

Statement 9.1 will be referred to the "DNA-as- Molecular-Machine (DMM) Hypothesis."

There are two types of networks in general – *equilibrium* and *dissipative*. *Equilibrium networks* are those molecular systems that are at equilibrium, requiring no dissipation of any free energy, whereas *dissipative networks* are those molecular systems whose nodes can interact with one another if and only if requisite free energy is available and dissipated (as in SOWAWN machines; see Sect. 2.4.4). Examples of the former would include aggregates of heterogeneous proteins in the cytosol or protein-DNA complexes constituting chromatins in the nucleus, and those of the latter include sets of activated proteins catalyzing a metabolic process such as glycolysis, respiration, or gene expression which are destroyed without continuous dissipation of free energy through, for example, phosphorylation and dephosphorylation reactions catalyzed by kinases and phosphoprotein phosphatases.

There are two types of connections in Fig. 9.2 that link one plane to another – (1) *catalysis* where a set of objects in one plane cooperates (or acts as a unit) to catalyze the coupling between one plane and another (as exemplified by Cones 4 and 11 through 17)

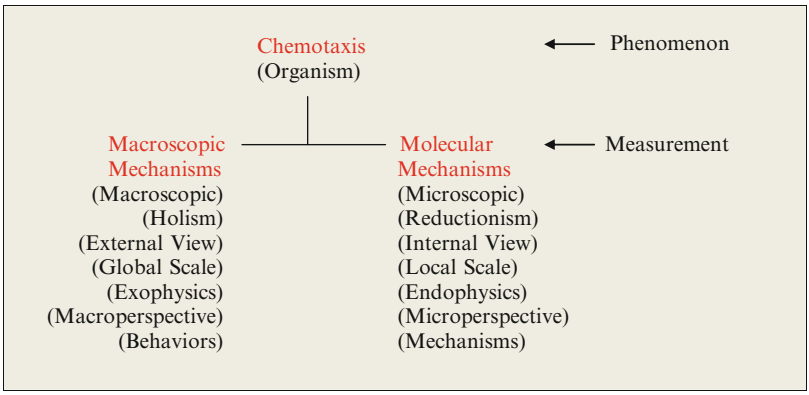


Fig. 9.3 A diagrammatic representation of the postulated *identity relation* between *chemotaxis* and its underlying *mechanisms*

and (2) what may be called *identity* as exemplified by the networks in the Chemical Reaction Space which are deemed *identical* with corresponding dots on the function plane (e.g., see apex 5 of the dotted cone whose base is labeled 4 in the Chemical Reaction Space). In *catalysis*, something A allows, something else B to happen and hence A can be said to *cause B*. In contrast, when two entities A and B are connected by an *identity* relation, they represent two different manifestations of one and the same entity and so no causal relations can be found between A and B. Thus, *chemotaxis* in the Function Space is a phenotype or a *phenon* exhibited by a living cell under certain environmental conditions, whereas the set of intricate molecular mechanisms underlying chemotaxis that has so far been characterized on the levels of chemical reactions (Chemical Reaction Space), protein dynamics (Protein Space), gene expression (RNA Space), and genetic mutations (Gene Space) represent the inner workings of the cell that performs chemotaxis. We may represent the *identity relation* between chemotaxis and its molecular mechanisms graphically as shown in Fig. 9.3 Because it is believed that the identity relation can be thought of as belonging to the relation type known as *supplementarity*, symbolized as in Sect. 2.3.1, this symbol is employed here to represent the identity relation.

The key point of Fig. 9.3 is that the *phenomenon* of chemotaxis can be *observed* (or measured) in two contrasting ways – from *outside* of the organism on a macroscopic or mesoscopic scale and from *inside the organism* at the microscopic one (e.g., by artificially separating the working components of the organism and studying them in isolation at the molecular level). The results of the measurements so obtained are very different, giving rise to various dichotomous pairs descriptive of their differences, including *holism* versus *reductionism*, *external* (or exo) versus *internal (or endo)* views, *global* versus *local* views, *exophysics* versus *endophysics*, macroviews versus *microviews*, and *behaviors* versus *mechanisms*, etc. The identity relation symbolized as an inverted T in Fig. 9.3 (as compared to the complementarity relation symbolized by ^ in Eq. 2.32) may be viewed as an example of the *supplementarity relation* discussed by Bohr (1958) and in Sect. 2.3.1 in the sense

Table 9.1 The cell interactome as a five-dimensional hypernetwork. Cis-interactions occur through direct physical contact between interacting entities, whereas trans-interactions occur through the mediation of diffusible molecules

d	n (node)	e (edge)	f (function)
1	Genes	cis-Interactions trans-Interactions	Preservation and evolution of genetic information
2	RNAs	cis-Interactions	Transfer of information from DNA to proteins
		trans-Interactions	Complexification of genetic information
3	Proteins	cis-Interactions trans-Interactions	Execution of genetic information by catalyzing those chemical reactions selected by genetic information
4	Chemical reactions	cis-Interactions trans-Interactions	Source of free energy needed for life Mediators of trans-interactions
5	Functions	trans-Interactions	Survival Evolution

that it is an *additive* relation (i.e., the top node of the inverted T is equal to the sum of the two lower nodes) unlike the complementarity relation which is *nonadditive* (Ji 1995). Thus, just as when a large number of quanta is concentrated into a small volume matter emerges, so when a large number of molecular mechanisms (which can be viewed as examples of "dissipatons" since their operations require dissipating free energy) are spatiotemporally organized inside the cell through the mechanism of evolution (i.e., a complex of coupled processes between the variation of genotypes and the selection of the fittest phenotypes by environmental conditions), living processes (including chemotaxis) emerge. If this interpretation is correct, emergence of living processes from molecular mechanisms (i.e., material processes) can be viewed as a *token* of the supplementarity relation viewed as a *type* reified over the spatiotemporal scales appropriate for the *biological evolution*. In a similar manner, the emergence of the collective properties of matter such as rigidity, fluidity, superconductivity, superfluidity, etc. of nonliving matter may be looked upon as a *token* of the supplementarity relation *type* that has been instantiated or reified over the spatiotemporal scales appropriate for macroscopic and cosmological processes.

In Sect. 2.4.1, a biological network (or bionetwork) was defined in terms of three parameters, that is, nodes (n), edges (e), and functions or emergent properties (f) (see Eq. 2.56). The complexity of the structure and function of the living cell as depicted in Fig. 9.3 entails expanding the definition of a bionetwork given by Eq. 2.56 by including two more parameters, namely, the dimensionality, d, of the network and the level, l, of the of the hypernetwork under consideration:

$$\mathrm{BN} = (\mathrm{n},\ \mathrm{e},\ \mathrm{d},\ \mathrm{l},\ \mathrm{f}) \tag{9.2}$$

The *cell hypernetwork* characterized in Eq. 9.2 as a five-dimensional hypernetwork is further detailed in Table 9.1. As indicated in Table 9.1, the *cell hypernetwork* can be alternatively referred to as the *cell interactome* which highlights the complex molecular interactions underlying the cell hypernetwork.

9.3 Interactomes, Bionetworks, and IDSs

Since the yeast two-hybrid (Y2H) method of measuring protein–protein interactions was introduced by Fields and Song (1989), a variety of derivative methods has been devised to study protein–protein and protein–drug interactions in many different species of organisms, leading to the emergence of the field of *interactomes* (Ito et al. 2001; Suter et al. 2008). The term *interactome* was coined by French scientists Bernard Jacq and his colleagues in 1999 to indicate the whole set of molecular interactions that go on in living cells. The term is a natural extension of *genome* (the whole set of genes in an organism), *transcriptome* (the whole set of RNAs encoded in a genome), *proteome* (the whole set of proteins encoded in a genome), *chemoreactome* (the whole set of chemical reactions catalyzed by enzymes in a cell), and *phenome* (the whole set of phenotypes exhibited by a cell). Since the cell is a hierarchically organized system of genome, transcriptome, proteome, chemoreactome, and phenome, we can represent the cell interactome algebraically as:

$$\begin{aligned}\textbf{Interactome} = {} & \textbf{Genome} + \textbf{Transcriptome} + \textbf{Proteome} \\ & + \textbf{Chemoactome} + \textbf{Phenome}\end{aligned} \tag{9.3}$$

Of the five subcellular interactomes appearing in Eq. 9.3, the protein interactome (also called *interative proteome*) has been best studied because of the availability of the Y2H method that allows biologists to measure protein–protein interactions directly. Table 9.2 summarizes the current knowledge of the protein–protein interactomes from several species (Stumpf et al. 2008).

The cell interactome can be graphically represented as a multilayered hypernetwork such as the p53 hypernetwork shown in Fig. 9.2. "Interactome" defined as the totality of molecular interactions in cells (http://en.wikipedia.org/wiki/Interactome) and higher organisms has a significant overlap in meanings with bionetworks (Sect. 2.4.1). Bionetworks emphasizes the *static connections* among the nodes while interactomes focus on the *dynamic interactions* among nodes. The relation between *bionetworks* and *interactomes* may be akin to the relation between *kinematics* and *dynamics* in physics (Sect. 2.3.5) and hence Bohr's kinematics-dynamics complementarity may be applicable to both physics and biology as indicated in Table 9.3. In other words,

Table 9.2 The estimated protein–protein interactome sizes of various organisms (Stumpf et al. 2008)

Organisms	Nodes	Edges	Interactome size[a]
1. *Saccharomyces* cerevisiae	4,959	17,229	25,229
2. *Drosophila melanogaster*	7,451	17,226	74,336
3. *Caenorhabditis elegans*	2,638	3,970	240,544
4. *Homo sapiens*	1,085	1,346	672,918

[a] The total number of the edges of the whole protein–protein interactome theoretically predicted based on the data obtained from partial or sub-interactomes

Table 9.3 *The Bohr's principle of kinematics-dynamics complementarity* (Murdoch 1987; Plotnitsky 2006) in action in physics and biology

	Description	
	Static	Dynamic
1. Motions	*Kinematics*	*Dynamics*
2. Life	*Bionetworks* *Hyperstructures* (Norris et al., 2007a, b), *Hypernetworks, Renormalizable Bionetworks* (Sect. 2.4)	*Interactomes*, *IDSs* (Ji 1991), *SOWAWN machine* (Sect. 2.4)

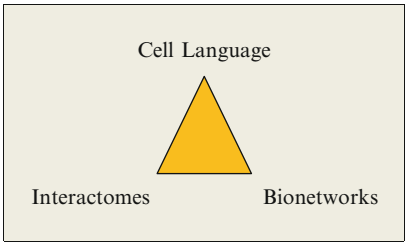


Fig. 9.4 A diagrammatic representation of the hypothesis that *cell language* is the complementary union of *interactomes* and *bionetworks* or that interactomes and bionetworks are the complementary aspects of cell language

> Bionetworks and interactomes are the complementary aspects of *life* just as kinematics and dynamics are the complementary aspects of *motion*. (9.4)

We may refer to Statement 9.4 as the *principle of the bionetwork-interactome complementarity* (PBIC), the biological counterpart of the *principle of kinematics-dynamics complementarity* in physics first articulated by N. Bohr in the 1930s to account for the wave-particle duality of light and quantum objects in general (Plotnitsky 2006). Statement 9.4 asserts that the *kinematics-dynamics complementarity principle* discovered in nonliving systems applies to living systems as well, or that biology and physics are symmetric/isomorphic with respect to the principle of the kinematics-dynamics complementarity.

It is also interesting to note that there are a set of closely related, almost synonymous terms for each of the complementary aspects of life as indicated below bionetworks and interactomes in Table 9.3. On the other hand, the *cell language theory* (Sect. 6.1.2) (Ji 1997a) cannot be readily relegated either to *bionetworks* alone or to *interacrtomes* alone but comprises both these complementary aspects, leading to the conclusion that cell language may best be viewed as the *complementary union* of bionetworks and interactomes as depicted in Fig. 9.4.

Bionetworks and *interactomes* can be classified into cellular and multicellular bionetworks and interactomes, solely based on size considerations without regard to whether or not free energy dissipation is implicated. In addition, bionetworks and interactomes can be divided into equilibrium and dissipative bionetworks and interactomes solely based on energy (or force) considerations regardless of their

Table 9.4 Examples of *equilibrial* and *dissipative* nodes and edges in bionetworks

	Equilibrial	*Dissipative*
Nodes	Proteins, RNAs, DNAs	(a) ATP hydrolysis, NADH oxidation (b) Activated G protein (c) Supercoiled circular DNA
Edges	Protein–protein, protein–RNA, protein–DNA interactions, etc. (see Table 9.5)	(a) Proton-motive force (the chemiosmotic theory), conformational energy (the conformon theory) (b) Binding to adenylate cyclase (c) Activation of select gene expressions

Table 9.5 The nine classes of interactomes in living cells predicted on the basis of the three classes of nodes

	Protein (p)	RNA (r)	DNA (d)
Protein (p)	p–p	p–r	p–d
RNA (r)	r–p	r–r	r–d
DNA (d)	d–p	d–r	d–d

sizes. The size (or geometry in general) of a network is related to *kinematics* and the energy dissipatiZon by networks is related to *dynamics*, thus providing yet another example illustrating the operation of the *principle of the kinematics-dynamics complementarity* in biology. Thus, we can divide bionetworks into *equilibrons* and *dissipatons*, depending on whether or not free energy dissipation is needed to maintain their existence. In other words, we can recognize two classes of bionetworks – "equilibrium bionetworks" and "dissipative bionetworks". The nodes and edges of equilibrium bionetworks do not dissipate free energy but those of dissipative bionetworks do (or are dissipation-dependent) (Table 9.4). That is, the nodes and edges of equilibrium bionetworks remain intact while the nodes and edges of dissipative bionetworks disappear when free energy supply is interrupted.

Another way of characterizing bionetworks or interactomes is in terms of the three fundamental building blocks of living cells, namely, proteins (p), RNA (r), and DNA (d), leading to a 3×3 table shown in Table 9.5. In the absence of clear evidence suggesting otherwise, it is here assumed that the interactions appearing in Table 9.5 are "directional" in the sense that, for example, the interaction, p-r, is not the same as the interaction r-p. In other words, Table 9.5 is asymmetric with respect to the diagonal.

Applying Prigogine's classification scheme of structures into *equilibrium* and *dissipative structures* (Sect. 3.1) to Table 9.5, we can generate a system of 18 classes of interactions as shown in Table 9.6. The examples shown in Table 9.6 for each of these 18 classes of interactions reflect my limited knowledge and may need to be replaced with better ones in the future but the structure of the table itself may remain valid, reminiscent of the periodic table in chemistry. Hence, we may refer to Table 9.6 as the *periodic table of interactomes*. A similar table was suggested for molecular machines in Sect. 11.4.4. It is interesting to note that both these tables

Table 9.6 Examples of the nine classes of interactomes predicted in Table 9.5. P = protein, r = RNA, and d = DNA

	Examples	
Interactomes	*Equilibrium*	*Dissipative*
1. p–p	Multisubunit protein complexes, e.g., hemoglobin, cytochorme C oxidase, ATP synthase	Interaction between two or more metabolic pathways, e.g., between glycolysis and oxidative phosphorylation during glucose-galctose shift (see Table 12.1)
2. p–r	RNA-binding proteins without any catalytic activity, e.g., Maxi-KH, PUF (Lee and Schedl 2011)	RNA-binding proteins with catalytic activity, e.g., DEAD/DEAH box, Zinc knuckle (Lee and Schedl 2011), RNA polymerases, RNases, spliceosomes
3. p–d	Transcription factors	DNA polymease, transposase, DNA ligase, DNA recombinase
4. r–p	Same as p–r (?)	RNA guide component of RNA-protein complex catalyzing posttranscriptional gene silencing (PTGS) (Grishok et al. 2001)
5. d–p	Mutant structural gene-protein complex	Mutant regulatory gene-protein omplex (?) DNA supercoil-induced protein binding (see the *TF-conformon collision hypothesis*, Sect. 8.3)
6. r–r	Double-stranded micro RNAs (Grishok et al. 2001)	Ribozymes (Kruger et al. 1982; Wochner et al. 2011; Tang and Breaker 2000)
7. r–d	Riboswitches without catalysis	Ribozymes
8. d–r	Same as r–d (?)	DNA supercoil-induced RNA binding or *RNA-conformon collision hypothesis* (?) akin to the *TF-conformon collision hypothesis* described in Sect. 8.3
9. d–d	Double-stranded DNA	Conformon–conformon interactions within DNA superstructures such as supercoils (?)

have 18 cells or entries, and it is not known whether the equality of the dimension of the tables is a pure coincidence or a consequence of some deep connection between *interactomes* and *molecular machines*.

Chapter 10
The Living Cell

The living cell is the unit of life. Therefore, without knowing how the cell works on the molecular level, it would be difficult to understand how embryos develop or how species evolve (Waddington 1957; Gerhart and Kirschner 1997; West-Eberhard 2003). Most experimental data on the living cell have been obtained from "dead" cells, since living cells must be destroyed in order to isolate their components for purification and analysis (Sect. 3.1.5). To determine how living cells (*dissipatons*) work based on the experimental data measured from "dead" cells (*equilibrons*), however complete, is not an easy task, just as reconstructing musical melodies from sheet music would not be easy if one does not know the rules of mapping sheet music to audio music or does not have the ability to sing from sheet music. It is probably fair to say that, despite the massive amount of experimental data on the cell that has accumulated in the literature and on the World Wide Web as of the first decade of the twenty-first century, we still do not understand how the myriad structural components of the cell interact in space and time to exhibit the dynamic phenomena we recognize as life on the cellular level. The major goal of this book is to propose, in the form of a model of the living cell called the Bhopalator (Fig. 2.11), the theoretical concepts, molecular mechanisms, and physicochemical laws and principles that may facilitate uncovering the rules that map cell structures to cell functions.

10.1 The Bhopalator: A Molecular Model of the Living Cell

Although it had been known since the mid-nineteenth century that the cell is the smallest unit of the structure and function of all living systems (Swanson 1964), it was apparently not until 1983 that the first comprehensive theoretical model of the cell was proposed (Ji 1985a, b, 2002b). In that year, a theoretical model of the living cell called the *Bhopalato*r (Fig. 2.11) appeared in which both the *energetic* and *informational* aspects of life were integrated on an equal footing, based on the

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_10,

supposition that life is driven by *gnergy*, the complementary union of *information* and *energy* (Sect. 2.3.2). The name Bhopalator reflects the fact that the cell model was born as a result of the two lectures that I presented at the international conference entitled *The Seminar on the Living State*, held in Bhopal, India in 1983. The suffix, "-ator" indicates that the model is based on the postulate that the cell is a *self-organizing chemical reaction-diffusion systems* (i.e., a dissipative structure or a dissipaton) (Sects. 3.1 and 9.1).

The Bhopalator model of the cell consists of a set of *arrows* (i.e., *directed edges*) and *nodes* enclosed within a three-dimensional volume delimited by the cell membrane (Fig. 2.11). The system is thermodynamically open so that it can exchange matter and energy with its environment (see Arrows 19 and 20) (Sect. 2.1.1). The arrows indicate the directional *flows of information* driven by free energy dissipation. The solid arrows indicate the flow of information from DNA to the final form of gene expression postulated to be the *dissipative structures* theoretically investigated by Prigogine and his schools (Babloyantz 1986; Kondepudi and Prigogine 1998; Kondepudi 2008). These dissipative structures are in turn assumed to exert feedback controls over all the solid arrows, as indicated by the dotted arrows (Fig. 2.11).

One of the most distinct features of the Bhopalator is the role assigned to *dissipative structures* of Prigogine. Thus, IDSs (intracellular dissipative structures) (Sect. 3.1.2) are assumed to be both the *final form* of gene expression and the *immediate or proximal causes* for cell functions. Another novel feature of the Bhopalator model of the cell is the assertion that all nonrandom (or goal-directed) motions of biopolymers and associated small molecules in the cell are driven by *conformons*, the packets of mechanical energy and control information embedded in biopolymers (Chap. 8). Although there was no direct empirical evidence for IDSs or conformons when the Bhopalator was first proposed in 1983, the experimental data supporting these molecular entities emerged in the mid-1980s and throughout the 1990s, as reviewed in Sects. 8.3 and 9.1.

An updated version of the Bhopalator is presented in Fig. 10.1 using the formalism of a bionetwork (Sect. 2.4). All of the 12 edges or steps shown in this figure are present in the original version of the Bhopalator (Fig. 2.11), except Steps 8, 9, 10, and 11. The unidirectional arrows indicate the direction of information flow driven by appropriate conformons (i.e., packets of gnergy), which are not shown explicitly. The symbol, A → B, can be interpreted to mean that A *affects*, *influences*, *causes,* or *gives rise to* B. IDSs are any structures inside the cell that require the dissipation of free energy into heat to be maintained and hence disappear upon the cessation of free energy supply to the cell (e.g., membrane potential, RNA levels, ATP levels).

In Fig. 10.1, Steps 1, 2, and 3 represent the familiar processes – *transcription*, *translation,* and *catalysis*, respectively. Steps 4, 5, and 6 indicate the feedback controls exerted by IDSs on DNA, RNA, and proteins. Step 12 implies that the cell affects its environment through IDSs; that is, IDSs are the immediate causes of cell functions (Sect. 10.2), although cell functions do implicate, in addition, DNA, RNA, proteins, as symbolized by the large square bracket. Steps 7, 8, 9, 10, and 11,

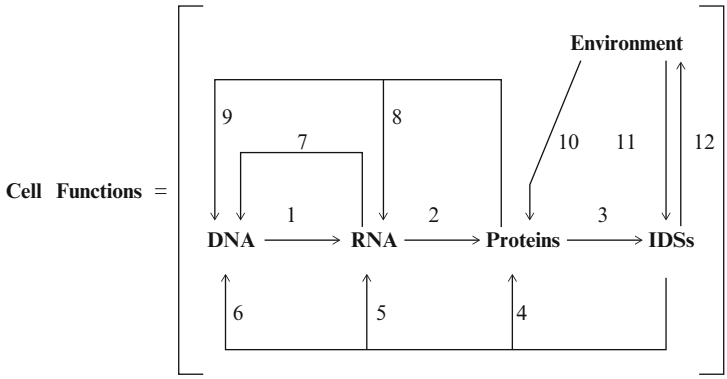


Fig. 10.1 The Bhopalator 2011: a bionetwork version of the Bhopalator model of the living cell (Sect. 2.11). Not shown in the figure are the *biochemicals* that serve as the free energy source for generating the mechanical energy packets called *conformons* (Sect. 8.4), which drive all goal-directed motions of biopolymers, the most fundamental characteristics of life at the cellular level

not included in the original version of the Bhopalator, represent the following unidirectional interactions:

7 = RNA control over DNA (e.g., siRNA, microRNA),
8 = protein control over DNA (e.g., transcription factors),
9 = protein control over RNA (e.g., RNA-binding proteins),
10 = receptor-mediated input of environmental information (e.g., hormones, cytokines, morphogens), and
11 = nonreceptor-mediated interactions with environment (e.g., mechanical pressure, osmotic pressure, radiative damages)

Figure 10.1 provides a convenient *visual* summary of the complex molecular interactions and their properties that underlie life on the cellular level. The *text* version of these interactions and properties is given below:

1. The ultimate form of expression of genes is not proteins (i.e., *equilibrons*) as is widely assumed but IDSs (*dissipatons*) (Sect. 3.1). To emphasize this point, IDSs are *prescinded* (Sect. 6.2.12) to formulate what I call the *IDS-cell function identity hypothesis* in Sect. 10.2.
2. IDSs exert feedback controls over DNA (Step 6), RNA (Step 5), and proteins (Step 4).
3. IDSs are postulated to be the sole agent through which the cell affects its environment as indicated by the unidirectional arrow 12 in Fig. 10.1. This postulate is an alternative expression of the *IDS-cell function identity hypothesis*.
4. Environment can affect DNA in two ways – through (1) receptor-mediated mechanisms (see Steps 10 and 9), and (2) nonreceptor-mediated mechanism (see Steps 11 and 6).

5. Through the two mechanisms described in (**4**), the environment of the cell can cause the two types of changes in DNA – (1) changes in nucleotide sequences (*genetics*), and (2) changes in the three-dimensional structure of DNA including covalent modification of bases and DNA-binding proteins without changing its nucleotide sequence (*epigenetics*; Riddihough and Zahn 2010; Bonasio et al. 2010).
6. There are two types of environment-induced genetic and epigenetic changes described in (5) – (1) *heritable* from one cell generation to the next, and (2) *nonheritable*. Heritable genetic changes are well known in biomedical sciences (Mundios and Olsen 1997; Chu and Tsuda 2004). Environment-induced heritable epigenetic changes (EIHEC), well established experimentally, is known as Lamarckism or lamarckian (Ji 1991, p. 178, Jablonka 2006, 2009) and may play a fundamental role in both *phenotypic plasticity* and *evolution* itself (West-Eberhard 2003).
7. There are two types of environment-induced heritable epigenetic changes (EIHEC) – (1) *rapid* with the time constant τ, comparable to or less than the life span of organisms, and (2) *slow* with the time constant τ', comparable to the lifespan of species (say, $10^2 \times \tau$ or greater) and to geological times. The study of rapid EIHEC constitutes a major part of developmental biology and phenotypic plasticity, whereas the study of slow EIHEC is a newly emerging aspect of biological evolution (West-Eberhard 2003).
8. The causes of cell functions, that is, the factors that affect cell functions directly or indirectly, can be identified with the directed arrows in Fig. 10.1, either singly or as groups of two or more arrows.
9. The causes of cell functions divide into two types – (1) *external causes* or environment (e.g., temperature, humidity, salinity, pressure, radiation, environmental chemicals including nutrients), and (2) *internal causes*, namely, DNA, RNA, proteins, and/or IDSs.
10. The internal causes of cell functions may be divided into at least three groups – (1) the proximal (IDSs in Fig. 10.1), (2) the intermediate (proteins and RNA), and (3) the distal causes (DNA). The external causes of cell functions may be similarly divided. Thus, the living cell, as modeled in the Bhopalator 2011, embodies a complex web of both internal and external causes that interact with one another. Such complex systems of interactions may be difficult to analyze and discuss without the aid of the visual diagram provided by the Bhopalator 2011, that is, Fig. 10.1.
11. The system of the unidirectional arrows constituting the Bhopalator model of the living cell symbolizes orderly, nonrandom motions/movements of biopolymers and their associated small molecules inside the living cell (e.g., active transport of ions across cell membrane mediated by membrane ion pumps, RNA polymerse movement along DNA, myosin movement along actin filament, kinesin and dynein movement along microtubules, and chromosome remodeling). According to the Second Law of Thermodynamics (Sect. 2.1.4), no orderly motions such as these are possible without dissipating requisite free energy, and this free energy dissipation is postulated to be

mediated by conformons, which provide the molecular mechanism for the chemical-to-mechanical energy conversion based on the generalized Franck–Condon principle (Chap. 8).

12. Cell functions entail transmitting *genetic information* in space (e.g., from the nucleus to the cytosol; from the cytosol to the extracellular space) and time (e.g., from an embryo to its adult form; from one cell generation to the next) through what has been referred to as the Prigoginian and the Watson-Crick forms of genetic information, respectively (Ji 1988). The Bhopaltor model of the living cell identifies the Prigoginian form of genetic information with IDSs and the Watson-Crick form with DNA.

To recapitulate, the updated version of the Bhopalator shown in Fig. 10.1 embodies the following key principles, theories, and concepts discussed in this book:

1. The *principle of self-organization* and dissipative structures (Sect. 3.1).
2. The *gnergy principle* that all self-organizing physicochemical processes in the Universe are driven by gnergy (Fig. 4.8), the complementary union of information (gn-) and energy (-ergy), the discrete units of which being referred to as gnergons which include *conformons* and *IDSs* (Sect. 2.3.2).
3. The living cell is a *renomalizable bionetwork* of *SOWAWN machines* (Sect. 2.4.2).
4. The cell function is an *irreducible triad* of *equilibrons*, *dissipatons*, and *mechanisms* (Sect. 6.2.11).
5. *The IDS-cell function identity hypothesis* (see Sect. 10.2) results from *prescinding* (Sect. 6.2.12) IDS from other more distal causal factors of cell functions.
6. The Bhopalator can provide a common theoretical framework for effectuating both *development* (Sect. 15.8) and *evolution* (Sect. 14.7) through genetic and epigenetic mechanisms obeying the Principle of Slow and Fast Processes, also known as the *generalized Franck–Condon principle* (Sect. 2.2.3).
7. Because of (6), the Bhopalator provides a sound theoretical basis for unifying *genetics* and *epigenetics* on the one hand and *evolutionary developmental biology* (EvoDevo) (Carroll 2006) and *developmental evolutionary biology* (West-Eberhard 2003) on the other.

10.2 The IDS-Cell Function Identity Hypothesis

As already pointed out in Sect. 10.1, IDSs in Fig. 10.1 are the only node among the four nodes that is connected to cell's environment via a unidirectional arrow, implying that IDSs are the *most proximate causes* of cell functions (also called cell behaviors, phenotypes, or phenons). Thus, IDSs are unique among the possible causes of cell functions that are at different distances from the effects or cell functions, DNA being most distant. The idea that IDSs are the immediate causes

of cell functions will be referred to as the *IDS-cell function identity hypothesis* (ICFIH). It is clear that asserting ICFIH does not entail denying the causal roles for other cell constituents, namely, proteins, RNA, and DNA but emphasizes the immediacy of IDSs among the four possible causes of cell functions (see Sect. 12.5 for further details).

10.3 The Triadic Structure of the Living Cell

Dissipative structures are distinct from *covalent* and *conformational* (also called *noncovalent*) structures in that they are "far-reaching" or "global" in contrast to covalent and noncovalent structures whose effects are localized within one (in the case of covalent structures) or a set of contiguous molecules in physical contact (in the case of noncovalent structures). The "far-reaching" (or "global") effects of dissipative structures inside the cell can be mediated by electric field (in the case of action potentials) or mechanical tensions (in the case of the cytoskeletons, the dynamics of interconnected microfilaments, intermediate filaments, and microtubules, supported by ATP or GTP hydrolysis). Ingber (1998) and his colleagues have obtained direct experimental evidence showing that local perturbations of a living cell under mechanical tensions can propagate throughout the cell, which phenomenon these authors referred to as "tensegrity," or *tensional integrity*. Thus, Ingber's *tensegrity* belongs to the class of intracellular dissipative structures (IDSs).

It is suggested here that dissipative structures are essential (along with covalent and noncovalent ones) for cell *reasoning* and *computing* because their "far-reaching" effects provide mechanisms to coordinate many physicochemical processes occurring at different loci inside the cell, just as the "far-reaching" axons allow the physicochemical processes occurring within individual neurons to get coordinated and organized in the brain to effectuate human reasoning (Table 10.1).

If these assignments are correct, the following conclusions may be drawn:

1. In agreement with Hartwell et al. (1999) and Norris et al. (1999, 2007a, b), it is suggested here that a new category of structures (i.e., dissipative structures or dissipatons) must be invoked before biologists can understand the workings of the *living cell* (e.g., metabolic regulations, signal transduction, mitosis, morphogenesis, etc.), just as physicists had to invoke the notion of *strong force* (in addition to *electromagnetic force*) before they could explain the stability of atomic nuclei or quantum dots (see Sect. 4.15) to explain size-dependent optical properties of nanoparticles (http://en.wikipedia.org/wiki/Quantum.dot).
2. Reasoning process is not unique to the human brain but can be manifested by cellular and abiotic systems meeting certain structural requirements in agreement with the ideas of Wolfram (2002) and Lloyd (2006) in the field of computer science. This conclusion seems in line with Wolfram's *Principle of Computational Equivalence,* according to which all natural and artifactual processes

Table 10.1 Three categories of structures in the cell and the brain. The third structure, which is built on the first two structures, is thought to be essential for reasoning/computing, or the ability of a physical system to respond to input stimuli according to a set of rules or programs

	Peircean categories[a]		
Level	Firstness	Secondness	Thirdness
Cell	*Chemical reactions* (covalent interactions)	Biopolymer–biopolymer interactions (noncovalent interactions)	*Dissipative structures* (space- and time-dependent gradients)
Brain	*Gradient structures* (e.g., membrane potentials)	*Information transmission* (from one neuron to another)	*Neural networks* (connected via action potentials and neuro-transmitters; space- and time-dependent)

[a]See Sect. 6.2.2

obeying a set of rules are equivalent to computation (Wolfram 2002, pp. 715–846). Also the postulated ability of the cell to reason seems consistent with the isomorphism thesis between cell and human languages (Ji 1997a, b, 1999b, 2002b), since, without being 'rational', neither humans nor cells would be able to use a language for the purpose of communication.

3. Humans can reason (i.e., the *Thirdness* phenomenon exists in the human brain), only because cells and abiotic systems in nature in general behave rationally (and not randomly); i.e., the *Thirdness* phenomenon exists in Nature, independent of human mind. The universality of *Thirdness* asserted here may be closely related to what Rosen called *Natural Law* that guarantees the ability of the human mind to model nature (Rosen 1991).

10.4 A Topological Model of the Living Cell

There is now an abundance of experimental evidence suggesting that cells, both normal and diseased, are affected by *five distinct classes* of factors or determinants as indicated in Table 10.2.

It is clear that the Bhopalator 2011 shown in Fig. 10.1 is consistent with the content of Table 10.2, although biochemicals are not explicitly indicated in the cell model. To graphically represent the equal importance (to be referred to as the "equipotency hypotheses") of all of these five factors in determining the properties and behaviors of the cell, the *body-centered tetrahedron* may be utilized as shown in Fig. 10.2.

One difference between the cell models depicted in Figs. 10.1 and 10.2 is that, in Fig. 10.1, the five possible causes for cell functions are organized in the order of their distance from their ultimate effects, namely, cell functions, whereas Fig. 10.2 does not contain such hierarchical information.

Table 10.2 The five classes of factors affecting the behavior of living cells

Determinants	Examples	Explanations
1. DNA	Mutations in certain genes (e.g., p53 gene [Levine et al. 2004]) lead to cancer and other pathological consequences	Mutated genes lead to alterations in protein amino acid sequences which often lead to altered protein conformations and functions
2. RNA	Colon cancer cells show statistically significantly different patterns of changes in mRNA levels compared to those of normal cells (Stengel 2005)	RNA molecules not only mediate (through mRNA) but also regulate (through snRNA, and microRNA, etc.) the coupling between genotypes (DNA) and phenotypes (proteins)
3. Proteins	A diarylquinoline drug, known as R207910, binds to the membrane component of the ATP synthase in *Mycobacterium tuberculosis*, thereby killing the organism (Andries et al. 2005)	Proteins are the only macromolecules in the cell (except ribozymes) that can harvest free energy from chemical reactions by catalyzing them. This means that, without proteins, no energy-requiring processes (without which no life can exist) can be carried out by the cell. Proteins are molecular engines/motors/rotors/machines out of which the cell is constructed (Alberts 1998) (Chap. 10)
4. Biochemicals	Depriving oxygen kills all aerobic cells	Without biochemicals, no chemical reactions can occur inside the cell, depriving the cell of all free energy sources and hence of life
5. Environment	Most cells can survive only within narrow ranges of environmental conditions to which they have adapted through long evolutionary history, including temperature, pressure, humidity, neighboring cells, radiation, and nutrient chemicals, etc.	Most cells have evolved to survive and perform their specialized functions only under stringently defined environmental conditions. For example, although all the cells in the human body have about 25,000 genes, different subsets of them are expressed in different parts of our body, depending on their *micro-environmental conditions*, leading to the liver, the kidneys, the heart, or the brain, etc.

Several testable predictions in the field of DNA microarray technology (Alon et al. 1999) may be formulated based on the model of the cell shown in Fig. 10.2:

1. When the level of a mRNA molecule changes in a cell due to some perturbations, it is impossible to attribute such changes solely to DNA changes (e.g., changes in transcription rates), because proteins (e.g., transcription factors, RNA polymerase, histones, DNA topoisomerases, etc.), biochemicals (e.g., ions, pH, ATP, etc.), and environmental conditions (e.g., tissue specificity, microcirculatory situations, neighboring cells, etc.) may be responsible for a part or all of the changes in mRNA levels being measured (cf. the "equipotency hypothesis" above).

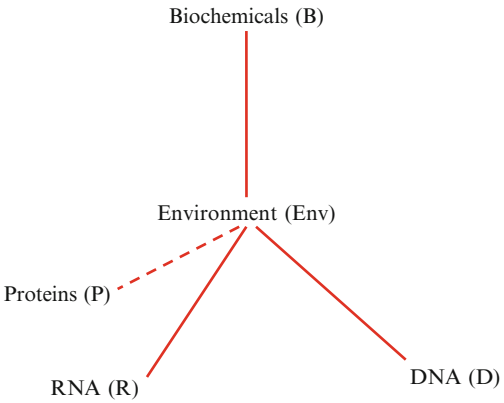


Fig. 10.2 A simple topological model of the living cell viewed as a *body-centered tetrahedron (BCT)*. The tetrahedron is the simplex of the three-dimensional space, an *n-dimensional simplex* being defined as the simplest polyhedron in an n dimensional space (Aleksandrov et al. 1984). The six edges connecting the four vertices (B, D, R, and P) are not shown for brevity. One unique feature of BCT is that all the nodes (including the center) are in simultaneous contact with one another, a topological property suggestive of the physical situation where changing one node affects all the others

2. We may distinguish two kinds of causalities – the *direct* and the *indirect* causalities. For example, if a perturbation causes mRNA levels to change, it may be due to *direct* effects on any one or more of the apexes (i.e., biochemicals, DNA, RNA and proteins), or indirect effects mediated by environment which are affected by the perturbation, or due to indirect effects on DNA, proteins, or biochemicals which affect mRNA levels through their actions on the environment.
3. Mutations in DNA may affect mRNA levels measured with DNA microarrays in some but not all mutated cells, depending on the environmental conditions (e.g., tissue specificity, or microcirculatory variations within a given tissue).

The model of the cell depicted in Figure 10.2 reveals the material components of the cell that determine the structure and function of the cell under a given environmental condition. A similar *topological structure* of the cell can be constructed (see Figure 10.2a) wherein the nodes are occupied by *theoretical* (rather than *physical*) components that have been proposed to account for the structure and function of the living cell over a period of two and a half decades (1972-1997). It is interesting to point out that the experimental evidence for the cell force concept was not recognized until toward end of writing this book as discussed in Section 12.13. The theoretical components of the Bhopalator are collected in Table 10.2A in the order of their publication and with the experimental evidence supporting them.

The four theoretical components of the Bhopalator are all essential to account for the phenomenon of life on the cellular level in molecular terms and inseparably linked to one another mechanistically. The intimate relations among these components can be diagrammatically represented as a *body-centered tetrahedron* (BCT) (Figure 10.2a) wherein every node is in direct contact with all the other

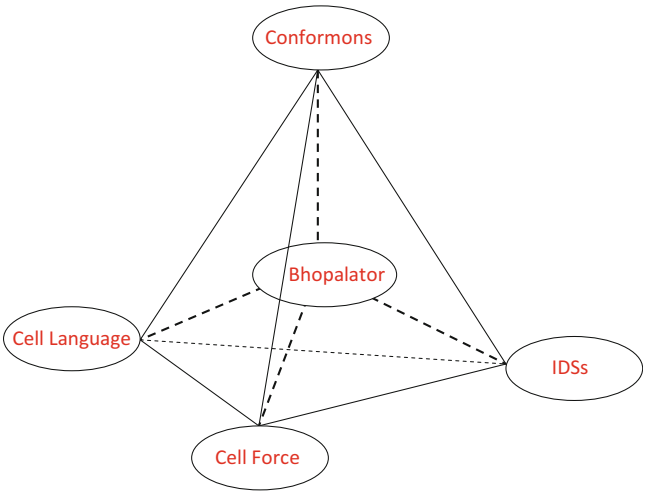


Figure 10.2a The body-centered tetrahedron representation (BCT) of the Bhopalator model of the living cell. The four major theoretical elements of the Bhopalator have been proposed between 1972 and 1997 (see Table 10.2A). The inseparable connections among the four theoretical components are symbolized by the BCT whose vertices/nodes are in direct contact with one another without any mediation

Table 10.2A The theoretical components of the Bhopalator (Ji 1985a,b). IDSs = intracellular dissipative structures. BRE = blackbody radiation-like equation

Theoretical Components		Reference	Experimental Evidence	Discussed in
1	Conformons	Green and Ji 1972a,b; Ji 2000	Single-molecule mechanics of the myosin head	Chapter 8 and Section 11.4.1
2	IDSs	Ji 1985a,b	Intracellular Ca^{++} gradients	Chapter 3
3	Cell force	Ji 1991	Whole-cell RNA metabolic data fitting BRE	Sections 12.12 and 12.13 & Appendix L
4	Cell language	Ji 1997a,b	Quasi-determinism in genotype-phenotype coupling	Sections 6.1.2 and 12.10

nodes without any mediation. The Bhopalator model of the living cell has both a *physical structure* (see Figures 2.11 and 10.2) and a *theoretical structure*. The theoretical structure of the Bhopalator is the *inseparable connectedness among the four theoretical elements* listed in Table 10.2A that can be geometrically represented by BCT. What the BCT representation of the Bhopalator implies is that

> "*It is impossible to account for the workings of the living cell without simultaneously taking into account all of the four theoretical elements, i.e., the conformon, IDS, the cell force, and the cell language, and that no single theory is therefore sufficient to provide a complete understanding of the living cell.*" (10.1a)

We may refer to Statement (10.1a) as the *four-fold theoretical requirement* of the living cell.

The BCT is a 3-dimensional network with 5 nodes and 10 edges. The meanings of the nodes are evident in their names, but those of the 10 edges are not so obvious and require explanations. For example, the edge connecting nodes 3 (cell force) and 4 (cell language) embodies the following explanations:

a) Cell language is a form of organization.
b) Organization is a form of work.
c) Work is the product of a *force* and a *displacement*.
d) Therefore, cell language requires the existence of a *force* acting inside the cell (whichwas named the *cell force* in 1991).

Similar sets of explanations may be constructed for most, if not all, of the remaining edges.The *cell force* was postulated in 1991 to be a new force in nature (after gravitational, electromagnetic, weak, and strong forces) that is responsible for the *functional stability* of the biochemical processes going on inside the living cell, just as the strong force is responsible for the *structural stability* of atomic nuclei despite electrostatic repulsion. The cell force concept was formulated in analogy to the strong force and is supported by a qualitative application of the Yang-Mills gauge field theory to cell biology (Section 12.13; see also Appendix L). In Section 12.13, the first experimental evidence is discussed that is provided by the whole-cell RNA metabolic kinetic data measured with DNA microarrays and interpreted using the concepts derived from the *renormalization group theory* (Huang 2007).

10.5 The Atom-Cell Isomorphism Postulate

There may exist a set of principles and properties commonly manifest in both the atom and the living cell. For convenience, we will refer to this notion as the *atom-cell isomorphism postulate* (ACIP), and the set of the principles and the features common to the atom and the cell as the ACIP set. If ACIP is true, we can anticipate that our current knowledge on the atom will provide us with a useful theoretical guide for modeling the living cell. Whether ACIP is true or not will depend solely on whether or not the cell model constructed on the basis of it leads to results useful in (1) explaining and organizing existing experimental data on the cell, (2) generating testable hypotheses in basic as well as applied researches in cell biology (e.g., drug design, predictive toxicology, stem cell research, etc.), and (3) resolving cell-related controversies such as the definition of genes (Sapp 1987), the evolution-creation debate (Ruse 2005), stem cell wars (Herold 2007), and science-religion discourses (Ji 1993; Barbour 1997; Polkinghorne 2002, 2010; Kurtz 2003).

One of the elements of the ACIP set is the notion that the atom and the cell can be viewed as networks constructed out of two types of nodes emanating from a common root, as shown in Fig. 10.3 and explained in Table 10.3. Just as the atom is composed of hadrons (i.e., heavy particles, including protons and neutrons) and leptons (i.e., light particles, including electrons and muons) interacting through

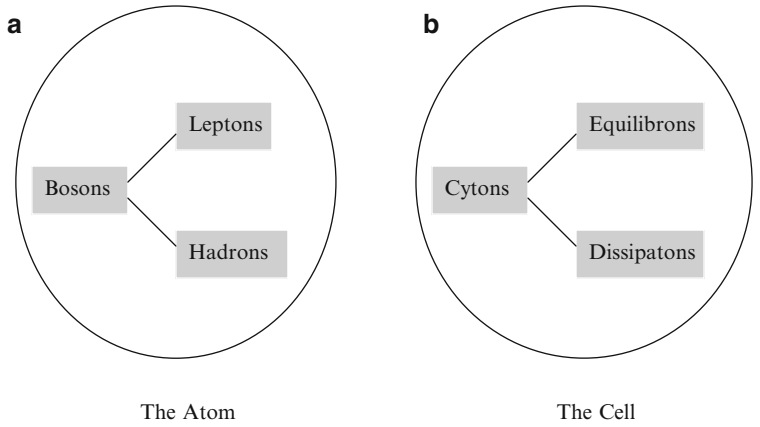


Fig. 10.3 Two types of particles constituting the atom and the cell. Hadrons are heavy particles such as protons and neutrons, and leptons are light particles including electrons and muons (Han 1999). *Cytons*, first invoked in (Ji 1991) are the hypothetical physical entity operating inside the cell and analogous to bosons in physics that mediate the interactions between equilibrons and dissipatons

Table 10.3 The atom and the living cell as two different types of networks consisting of two different types of nodes and edges

	Atom	Cell
1. Node type 1	Hadrons	Equilibrons
2. Edge type 1	Strong force (mediated by gluons)	Covalent bonds (mediated by electrons)
3. Node type 2	Leptons	Dissipatons
4. Edge type 2	Electromagnetic force (mediated by photons)	Noncovalent bonds
5. Interaction mechanisms	Exchange of bosons (e.g., photons, gluons)	Exchange of *cytons* (e.g., conformons, IDSs)
6. Common principle	Franck–Condon principle	Generalized Franck–Condon principle
7. Diameter, m	10^{-10}	10^{-5}
8. Relative volume	1	10^{15}
9. Relative complexity[a]	1	10^{15}
10. Thermodynamic systems	Closed	Open
11. Networks	Passive	Active (and renormalizable) (Sect. 2.4)

[a] It is assumed that the complexity of a physical system as measured by its algorithmic information content (Sect. 4.3) is approximately proportional to its volume

bosons (e.g., photons; see Glossary for definitions of these terms), so the cell can be thought of as composed of two types of particles, equilibrium and dissipative structures that interact through the mediation of *cytons*, the cellular analog of bosons (Ji 1991, pp. 94–96) (see Rows 1, 3 and 5 in Table 10.3).

As indicated earlier, the terms e*quilibrons* and *dissipatons* have been coined to represent the concepts of the *equilibrium* and *dissipative structures,* respectively, that were formulated by I. Prigogine in the 1970s (Babloyantz 1986; Prigogine 1977, 1980; Kondepudi and Prigogine 1998; Kondepudi 2008). *Equilibrons* include DNA nucleotide sequences, and three-dimensional protein structures that can exist without any dissipation of free energy, while *dissipatons* include dynamic structures such as action potentials, intracellular gradients of all kinds, including Ca^{++} (Sawyer et al. 1985) and RNA gradients in space (Lécuyer et al. 2007) and time (Garcia-Martinez et al. 2004), whose maintenance requires continuous dissipation of free energy (Sect. 3.1). In addition, each network contains two types of edges as indicated in Rows 2 and 4 in Table 10.3. The internal structure of the atom is held together by the forces acting on subatomic particles through the mechanisms of exchanging gluons and photons, two of the members of the family of bosons in quantum field theory (Han 1999; Oerter 2006). The cellular analogs of these interactions in the atom are not yet known but two possibilities have been suggested – *conformons*, mechanical strains of biopolymers driving goal-directed molecular motions (Sect. 8) (Ji 1985a, 2000), and *IDSs*, cytoplasmic chemical concentration and mechanical stress gradients that integrate molecular processes inside the cell (Sect. 9) (Ji 1991, 2002b). Conformons and *IDSs* may be considered to be reifications of the *cyton* (also called the *cell force*) (Ji 1991, pp. 95–118), just as photons and gluons can be viewed as reifications of bosons (more on this in Fig. 10.4). The electronic transitions in atoms obey the Franck–Condon principle (see Fig. 2.4). In (Ji 1974b, 1991), this principle was generalized and applied to enzymic catalysis (see Row 6 in Table 10.3) (Sects. 2.2.3, 7.1.3, and 8.2).

The last three rows in Table 10.3 exemplify those features and principles that are distinct between the atom and the cell and hence do not belong to the ACIP set. For example, under physiological conditions of temperature and pressure, the atom acts as a closed thermodynamic system (being able to exchange energy but not matter with its environment, except under very harsh conditions such as in a nuclear reactor), while the cell acts as an open system (able to exchange not only energy but also matter with its environment) (Sect. 2.1). In part because of this thermodynamic difference, the edges in the atomic network are fixed and unable to change, while those of the cell are dynamic and able to form or dissolve wherever (space) and whenever (time) needed by the cell, driven by the free energy of chemical reactions catalyzed by intracellular enzymes. For this reason, we can refer to the atomic network as *passive* and the network constituting the cell as *active* (see Row 9 in Table 10.3). The time- and space-dependent intracellular network conceptualized here can also be viewed as a *renormalizable* network in the sense that the cell is capable of reorganizing or regrouping its nodes to realize different functions in response to environmental inputs (Sect. 2.4) and cells themselves can become nodes of multicellular systems such as the brain.

It is truly amazing to find that there apparently exists a set of common principles and features that are operative in two material systems whose linear dimensions

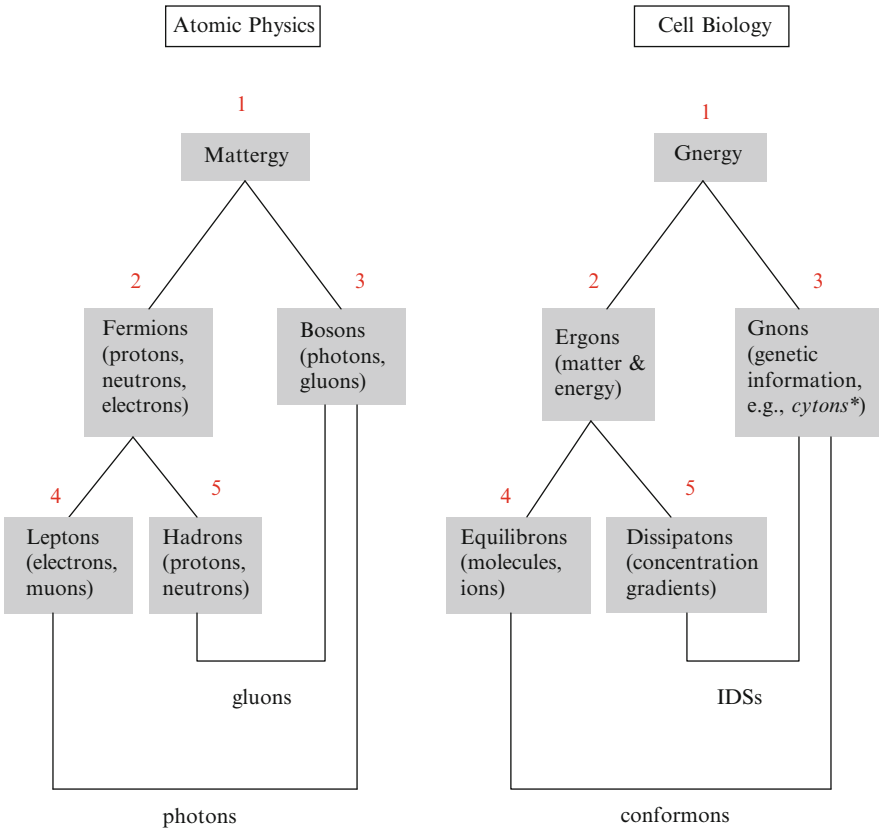


Fig. 10.4 A more detailed network representation of the atom-cell isomorphism postulate (ACIP). The claim of ACIP that the structures and functions of the atom and the cell share a common set of principles and features thought to be reflected in the symmetry between the topologies of the two networks: Although the labels of the nodes and edges are different, the two networks are topologically identical. It is interesting to note that, since mattergy and ergons are synonymous, the mattergy tree (i.e., atomic physics) is enfolded in the gnergy tree (i.e., cell biology), which makes the topology self-similar or recursive (Sect. 5.2.4). For the unusual terms indicated by italics, see the text. *The term *cyton* was coined in (Ji 1991, pp. 110–114) to indicate the physical mediator of the cell force. The cell force is postulated to be the fifth force of Nature (after the strong, weak, electromagnetic and gravitational forces) that is responsible for the life-preserving dissipative structures of the living cell, in analogy to the gluon that mediates the equilibrium structure-preserving strong force acting inside the nucleus of the atom despite the electrostatic repulsion between protons (Han 1999). The non-Abelian gauge theory of Yang and Mills (Huang 2007) provides a qualitative support for the concept of the cell force as detailed in my January 19, 1990 letter to Prof. C. N. Yang (see Appendix K), and it is hoped that this letter will be of some interest to those mathematical physicists who may be interested in *mathematicizing* the cell force concept only qualitatively connected to the Yang-Mills gauge theory in Table 10.1 in the latter

differ by a factor of 10^5 and volumes by a factor of 10^{15}. The natural question that arises is whether this is just a coincidence or a reflection of some deeper connection that exists between the atom and the cell. The latter possibility appears to gain some credibility when we expand the comparison between the atom and the cell even further as detailed in Fig. 10.4.

Equilibrons are stable under normal conditions, while *dissipatons* are unstable, requiring continuous dissipation of free energy to be maintained.

The three types of particles shown in Fig. 10.3 that constitute the atom are actually embedded in a more complex network rooted in matter/energy (or mattergy) as shown on the left-hand side of Fig. 10.4. The *atomic network* shown here consists of five nodes (labeled 1 through 5) and six edges, two of which are identified as gluons (see Edge 3–5) and photons (Edge 3–4). If ACIP is valid, it should be possible to construct a similar network for the cell, and this anticipation appears largely realized by the cell network topology shown on the right-hand side of Fig. 10.4. To populate the nodes and edges of the cell network in accordance with ACIP, it was necessary to introduce five new terms (in addition to *equilibrons*, *dissipatons*, and *cytons*), namely, *gnergy*, *ergons, gnons, conformons,* and *IDSs* that had all been previously invoked in connection with the model of the universe (known as the Shillongator) based on the gnergy principle that originated in cell biology (Sect. 2.3.2) (Ji 1991, pp. 156–163, 230–237). It should be pointed out (1) that all the terms appearing in the cell network are written in italics to indicate the fact they are new to science, and (2) that the names of these terms are arbitrary and can be replaced by other terms as long as they serve equivalent roles in the cell network consistent with ACIP. It is clear that the topology of the atomic network (i.e., the left-hand side of Fig. 10.4) provides a useful theoretical framework to organize the set of the eight new concepts and terms, that is, *gnergy, ergons, gnons, cytons, equilibrons, dissipatons, conformons,* and *IDSs,* that I have introduced into cell and molecular biology during the past four decades (Green and Ji 1972a, b; Ji 1974a, b, 1991, 2000, 2002b, 2004a, b), which may be interpreted as indirectly supporting the ACIP.

A quantitative support for the ACIP was provided by the surprising findings that the mathematical equations similar in form to the blackbody radiation equation discovered by M. Planck in 1900 accounted for single-molecule enzyme kinetics of cholesterol oxidase (Ji 2008b) and the genome-wide RNA metabolism of budding yeast undergoing glucose-galactose shift (Ji and So 2009d) (see Sects. 11.3.3 and 12.12). The first systematic characterization of the ACIP was presented in Table 1.15 in (Ji 1991) where the term 'the cyton' appears for the first time and the force mediated by the cyton was given the name 'cell force', in analogy to the 'strong force' mediated by gluons. Therefore, if the ACIP is true, there must exist a new force, the cell force, which may be viewed as constituting the fifth force of nature after the strong, weak, electromagnetic, and gravitational forces (Han 1999, Huang 2007). Thus the ACIP may be alternatively referred to as the *cell force hypothesis* (CFH), and it may be asserted that the CFH formulated in 1991 was in part quantitatively validated in 2008–2009 (Ji 2008b, Ji and So 2009d).

10.6 A Historical Analogy Between Atomic Physics and Cell Biology

When I first saw a picture similar to the one shown in Fig. 10.5a in an international conference on DNA microarray data analysis held at Rutgers around 2003, I was struck by the superficial similarity between this picture and the atomic absorption spectra such as shown in Fig. 10.5b. The former displays the concentration of RNA molecules in cells encoded by various genes displayed on the left-hand side of the

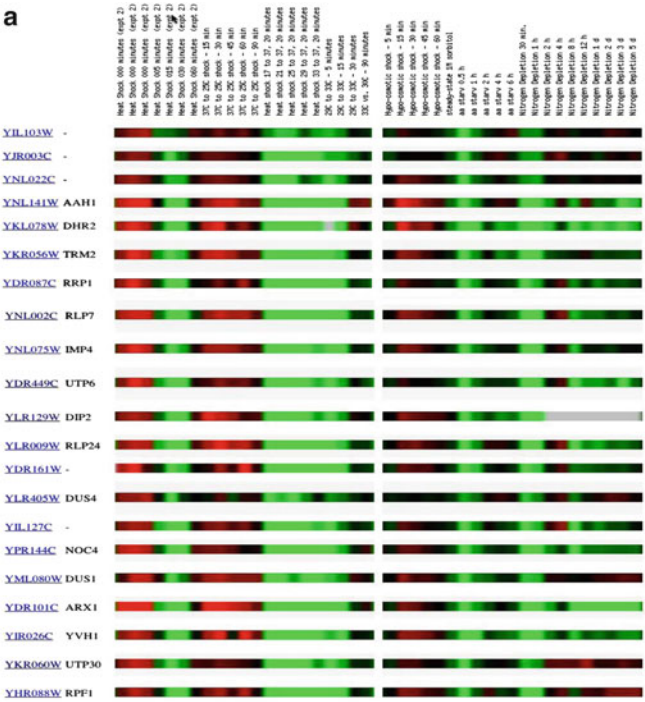


Fig. 10.5 (**a**) *The microarray expression profiles*: The changes in the RNA levels of a group of yeast genes induced by environmental manipulations; *red* = increase; *black* = no change; *green* = decrease; *gray* = data missing or not measured. (**b**) The atomic spectra of the hydrogen atom: (*1*) The hydrogen atom absorption lines detected in the light from *Zeta Tauri*. (*2*) The same absorption lines observed in the light from another star, 11 *Camelopaadlis* (Moore 1963, p. 472)

figure that are induced to increase (red/yellow) or decrease (blue) under different experimental conditions (listed in the top row), whereas the latter shows the wave numbers (i.e., the number of waves per cm) of light *absorbed* when the electron in the hydrogen atom undergoes transitions from one energy level to another upon illumination (Moore 1963; Corney 1977). Figure 10.5a is about the cell and Fig. 10.5b is about the atom, but they both reflect the probabilities of some events occurring along appropriate structural coordinates in each system. The two columns of colored horizontal bars in (**A**) represent the RNA level profiles of two different mice subject to different experimental perturbations, and the tw rows in (**B**) represent the absorption or emission bands of hydrogen atoms in two different stars.

If this qualitative similarity between *the cell* and *the atom* is not limited to the surface appearance but reflects a deeper connection as suggested in Table 10.4, cell biologists might derive some useful lessons from the history of atomic physics. For example, around 1890, Johannes Lydberg found that the absorption or the emission lines of the hydrogen atom obeyed a simple formula,

$$\acute{\upsilon} = \mathrm{R}\,(1/\mathrm{m}^2 - 1/\mathrm{n}^2) \tag{10.1}$$

where $\acute{\upsilon}$ is the wave number (or the number of waves per cm) of the light absorbed, m and n are positive integers where $\mathrm{n} = \mathrm{m} + 1, \mathrm{m} + 2, \ldots$, for different series of absorption lines such as the Balmer series, Lyman series, Paschen series, etc., and R is the Rydberg constant (109,677 cm^{-1}) (Atkins 1998). N. Bohr later showed that m and n are associated with the ground and excited states, respectively, of the electron in the hydrogen atom (Moore 1963; Corney 1977) (see Fig. 10.6). This formula remained a mystery until 1913, when Bohr proposed a theoretical model of the hydrogen atom based on the combination of the experimental data on atoms obtained by Rutherford and the theoretical concept of the *quantum of action* discovered by M. Planck in 1900 from his analysis of blackbody radiation data. The Bohr's atomic model led to the correct interpretations of the meanings of m and n as indicated above and to the calculation of the Rydberg constant from the fundamental constants of physics.

The superficial similarities between the microarray data shown in Fig. 10.5a and the line spectra shown in Fig. 10.5b led me to entertain the following analogy:

> The cDNA array technology may be to cell biology of the twenty-first century what the line spectroscopy was to the atomic physics of the twentieth century. (10.2)

This and other related analogies and comparisons are summarized in Table 10.4. This table is not meant to be exhaustively complete but lists only those items related to the theoretical cell biological research that I have been engaged in during the past four decades and, thus, may omit many related contributions made by other researchers, for example, the work of Craig Benham on SIDSs (stress-induced duplex destabilizations) which is directly related to the concept of conformons (Benham 1996a, b).

The term "ribonoscopy" appearing in Row 2 is defined as the experimental technique for studying genome-wide (i.e., over the whole set of genes in a cell) changes in the levels of the RNA (ribonucleic acid) molecules inside the cell

Table 10.4 An analogy between atomic physics and cell biology based on the similarity between *line spectra* and *microarray gene expression profiles* shown in Fig. 10.5

Parameter	Atomic physics	Cell biology
1. Time	Nineteenth to twentieth century	Twentieth to twenty-first century
2. Experimental technique	Atomic absorption/ emission Spectroscopy (nineteenth century)	cDNA array technology (1995) (*ribonoscopy*; Sect. 12.8.2)
3. Changes measured	Electronic energy levels	RNA concentration levels (ascending, descending, or staying steady) associated with specific metabolic functions
4. Perturbed by	Photons	Environmental chemicals/factors including hormones, cytokines, and neurotransmitters
5. Experimental data	Atomic line spectra	Patterns of RNA level changes in the cell (*ribons*, RNA trajectories or RNA waves)
6. Data determined by	Atomic structure	Cell structure
7. Regularities	Lyman series Balmer series Pfund series, etc.	Patterns of RNA level changes (or ribonic spectra) obeying the blackbody radiation-like equation (BRE) (Sect. 12.12)
8. Theoretical model	Bohr's atom (1913)	The Bhopalator (Ji 1985a, b, 2002b)
9. Basic concepts	Quantum of action (1900)	The conformon as the *quantum of biological communication* (Green and Ji 1972a, b; Ji 1991, 2000) IDSs (Ji 1985a, b) Modular biology (Hartwell et al. 1999) Hyperstructures (Norris et al. 1999, 2007a, b) SOWAWN machines (Ji 2006b)
10. Theory and principles	Quantum theory (1925) Franck–Condon principle (Reynolds and Lumry 1966)	The conformon theory of molecular machines (Ji 1974a, b, 2000) Cell language theory (Ji 1997a, b) Molecular information theory (Ji 2004a) Generalized Franck–Codnon principle (Ji 1974a, 1991)
11. Philosophy	Complementarity (1915)	Complementarism (Ji 1995) (Sect. 2.3.4)
12. A unified theory of physics, biology, and Philosophy	*The Tarragonator* (Appendix A; Ji 2004b)	

measured by cDNA arrays (Sect. 12.1) and other methods as functions of environmental perturbations. So defined, ribonoscopy is an experimental technique for ribonomics, a term recently coined by Keene (2006) to denote the genome-wide study of RNA changes in cells. In other words, it may be suggested that

Ribonoscopy is to ribonomics what spectroscopy is to atomic physics. (10.3)

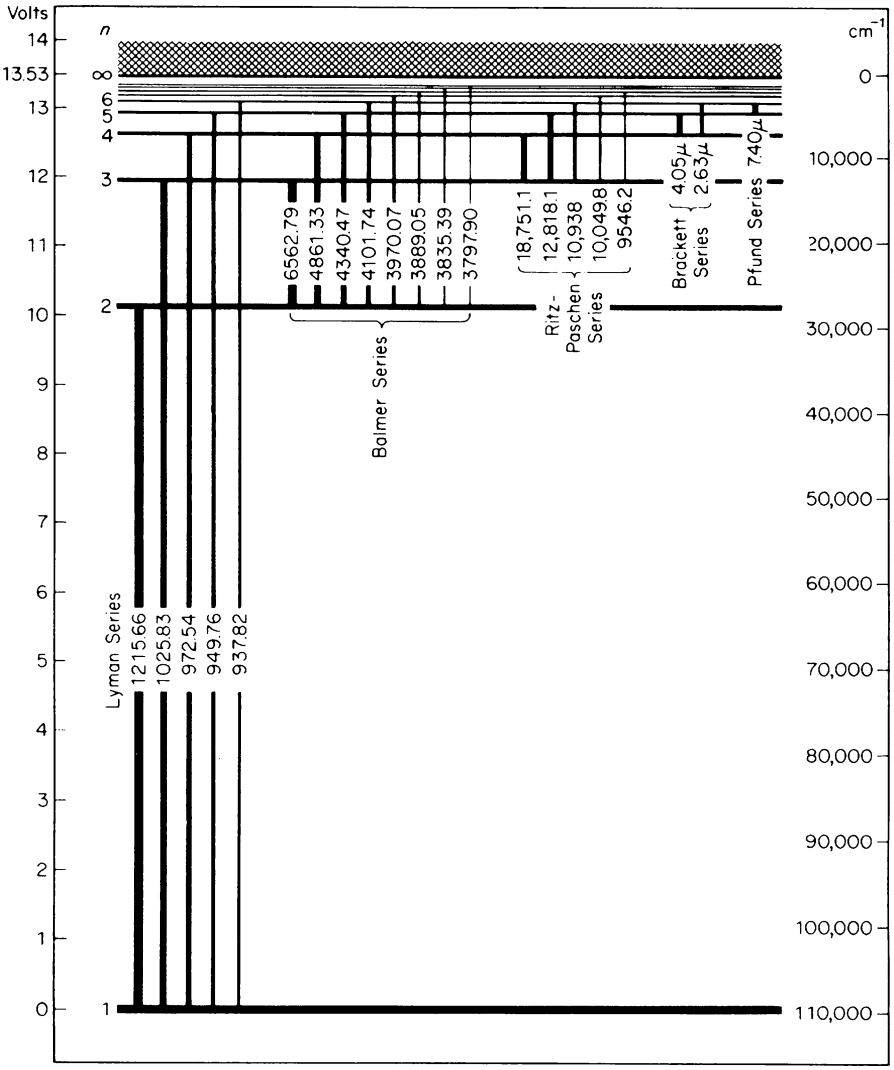


Fig. 10.6 Energy levels of the hydrogen atom (Moore 1963, p. 475)

The term "ribon" is derived from "rib-" meaning *ribonucleic acid* and "-on" meaning discrete entity or trajectory and defined as the *patterns* of time-dependent variations of RNA levels measured with DNA arrays *inside the cell* (such as exemplified by the RNA trajectories shown in Fig. 9.1 in Sect. 9.2). Ribonics is then the study of *ribons*. When convenient, *ribons* can also be referred to as *RNA dissipatons, r-dissipatons, RNA trajectories, or RNA waves*, since all these terms refer to different aspects of the same reality. Since the mRNA levels are determined by both transcription rates and degradation rates (Ji et al. 2009a), *ribons* are

evidently species of IDSs (intracellular dissipative structures; see Sect. 3.1.2). The advantage and the utility of the term "ribons" derive from the fact that it is directly connected to the rich results of the theories of *dissipative structures* formulated by Prigogine and others in the 1980s (Babloyantz 1986; Kondepudi and Prigogine 1998; Kondepudi 2008).

Just as the atomic spectroscopic technique measures the electronic energy levels in the atom, so *ribonoscopy* measures the RNA concentration levels (ascending, descending, or staying steady) in the cell that appear to be quantized (see Sect. 12.13) and are associated with target metabolic functions (Row 3). The former is affected by the absorption of photons by the atom and the latter by the binding of environmental signaling molecules by the cell (Row 4). The results of measurements are *atomic line spectra* for the atom and the *time-dependent patterns* of the changes in RNA concentrations in the cell, namely, *ribons* or *r-dissipatons, RNA trajectories, or RNA waves* (Row 5). An important lesson to be learned from the atom-cell analogy is that, just as the atomic spectra are determined by (or reflect) the internal structure of the whole atom including electrons, protons, and neutrons, so the patterns of the RNA concentration profiles measured with DNA arrays are determined by (or reflect) the functional state of the whole cell, including the sate of enzymes, the cytoskeletons, and biochemical concentrations (Rows 6 and 7). Another lesson to be learned from the atom-cell analogy may be this: Just as the atomic line spectra of the hydrogen atom were impossible to interpret quantitatively before Bohr's model of the atom was formulated in 1913, so it may be that the patterns of RNA levels measured with DNA arrays may be impossible to interpret without a theoretical model of the living cell such as the Bhopalator proposed in 1985 (Row 8). The basic theoretical concept embodied in the model of the atom proposed was that of the quantum of action discovered by Planck in 1900. The basic concepts underlying the Bhopalator model of the cell include the conformon viewed as the quantum of biological communication (Ji 1991, p. 122), IDSs, and SOWAWN machines (also called modules and hyperstructures) (Row 9). Quantum mechanical principles such as the Franck–Condon principle are necessary and sufficient to account for all atomic phenomena. Similarly, it is suggested here that the conformon theory of molecular machines (which includes or enfolds the generalized Franck–Condon principle), the cell language theory, and the molecular information theory are necessary and sufficient to account for the observable properties of the living cell (Row 10). It is of particular interest to note that the same principle known as the *Principle of Slow and Fast Processes* (Ji 1991, pp. 52–56) is postulated to operate at both the atomic and cellular levels in the form of the Franck–Condon principle and the generalized Franck–Condon principle, respectively (Row 10). Bohr developed the philosophy of complementarity beginning in 1915 based on the principles of quantum mechanics (Murdoch 1987; Pais 1991; Plotnitsky 2006; Herbert 1987). The realization in the 1970s and 1980s that Bohr's complementarity concept can be extended into enzymology in the form of the information-energy complementarity, which in turn could be extended back to physics in the form of the principle of *gnergy*, the ultimate driving force for all self-organizing processes in the Universe (see Fig. 4.8), led to the formulation of a

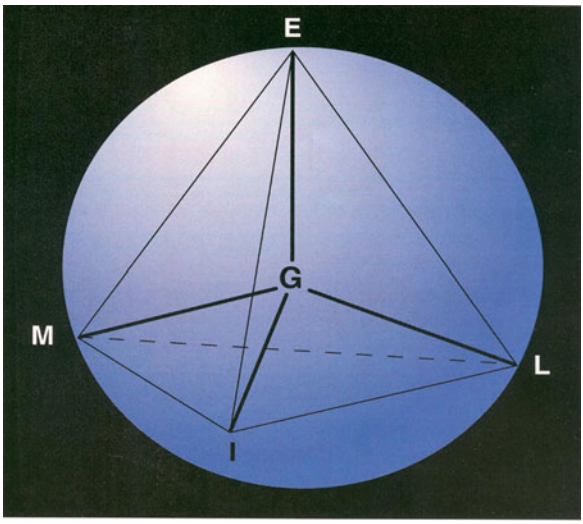


Fig. 10.7 The gnergy principle of the Universe depicted as a body-centered tetrahedron. There are five nodes: (1) Gnergy (**G**), (2) Energy (**E**), (3) Matter (**M**), (4) Information (**I**), and (5) Life (**L**). There are two supplementary pairs in this Figure: (1) the (E + M) pair constituting *mattergy*, and (2) the (I + L) pair constituting *liformation*. *Mattergy* and *liformation* are complementary aspects of *gnergy* (see Table 2.6). The model of the Universe based on the gnergy principle is known as the Shillongator (Ji 1991) (Reproduced from Ji 2004b)

Table 10.5 The body-centered tetrahedron as an iconic sign (Sect. 6.2.1) of the Universe and its constituents. The five nodes are numbered as in Fig. 10.7 (Reproduced from Ji 2004b)

	The five nodes of the body-centered tetrahedron				
Systems	1	2	3	4	5
1. Universe (Ji 1991)	Gnergy (G)	Energy (E)	Matter (M)	Information (I)	Life (L)
2. Cell (Fig. 10.2)	Environment	Biochemicals	Proteins	RNA	DNA
3. Body (Ji 1991)	Motion system	Nervous system	Circulatory system	Endocrine system	Immune system
4. Mind (Ji 2004b)	Biochemicals	DNA	Cells	Brain	Mind
5. Signs (Ji 2004b)	Gnergy	Sign processor	Representamen (*Firstness*)	Object (Secondness)	Interpretant (*Thirdness*)

new philosophical framework called complementarism (Ji 1991, 1993, 1995) (Row 11), according to which the ultimate reality is the complementary union of irreconcilable opposites.

Finally, as evident in Table 2.6, complementarity enfolds supplementarity in that the two nodes of gnergy are occupied with two supplementary pairs called *mattergy* or matter and energy on the one hand and *liformation* or life and information

on the other. Hence, Gnergy can be geometrically represented as the center of a body-centered tetrahedron with four vertices occupied by energy (E), matter (M), information (I), and life (L) as shown in Fig. 10.7. The model of *computation*, *mind,* and *signs* constructed on the basis of BCT (body-centered tetrahedron) has been referred to as the *Tarragonator* (Row 12) (Ji 2003a, b; Appendix A).

The *body-centered tetrahedron* (BCT) was found to provide a useful topological template to organize the various sets of related ideas in many fields of inquiries, as summarized in Table 10.5, which has led me to suggest that BCT may represent a universal code (Ji 2004b).

10.7 Evolving Models of the Living Cell

It appears that one of the first theoretical models of the living cell was proposed by J. Watson when he described a model of protein synthesis in cells diagrammatically (see Fig. 10.8a) in a letter to Crick in 1954, 1 year after the publication of their historic paper announcing the double-helical structure of DNA (Judson 1979, pp. 262–270). Watson's model of protein synthesis consists of three nodes (DNA, RNA, and proteins) and four edges. The main point of the model was the idea that protein synthesis occurs not on the DNA double-helix as suggested earlier by Gamow (Judson 1979) but on RNA molecules (see the vertical line in Fig. 10.8a), which idea was later superseded by the Crick's notion of the adaptor molecule subsequently identified as transfer RNA. The Watson mechanism of protein synthesis contained a deficiency – namely, the idea of chemically transforming one of the two strands of DNA double helix into an RNA molecule in the nucleus, which was then exported to the cytosol for protein synthesis (see the horizontal edge connecting DNA and RNA in Fig. 10.8a). Despite this shortcoming in mechanistic details, the Watson model of protein synthesis may be accorded a great historical significance because it is one of the first theoretical models of the cell ever proposed on the molecular level based on then available experimental data.

In contrast to the Watson model of 1954, which contained three types of objects (i.e., DNA, RNA, and proteins), the Bhopalator model of the cell proposed in 1982 at a conference held in Bhopal, India (and published 3 years later in [Ji 1985a, b]) contains two additional types of biological objects, i.e., *dissipative structures* of Prigogine, also called Intracellular Dissipative Structures (IDSs) in Ji (1985a, b) or *dissipatons* in Sect. 3.1) and *conformons*, conformational strains of biopolymers carrying mechanical energy to drive goal-directed molecular motions (Chap. 8). IDSs (a species or token of *dissipations*) are dynamic structures (also called "attractors" in nonlinear dynamics [Scott 2005]) consisting of chemical concentration and mechanical stress gradients within the cell, whereas conformons are dynamic mechanical deformations that are postulated to be localized to sequence-specific sites within biopolymers (Ji 1974b, 2000).

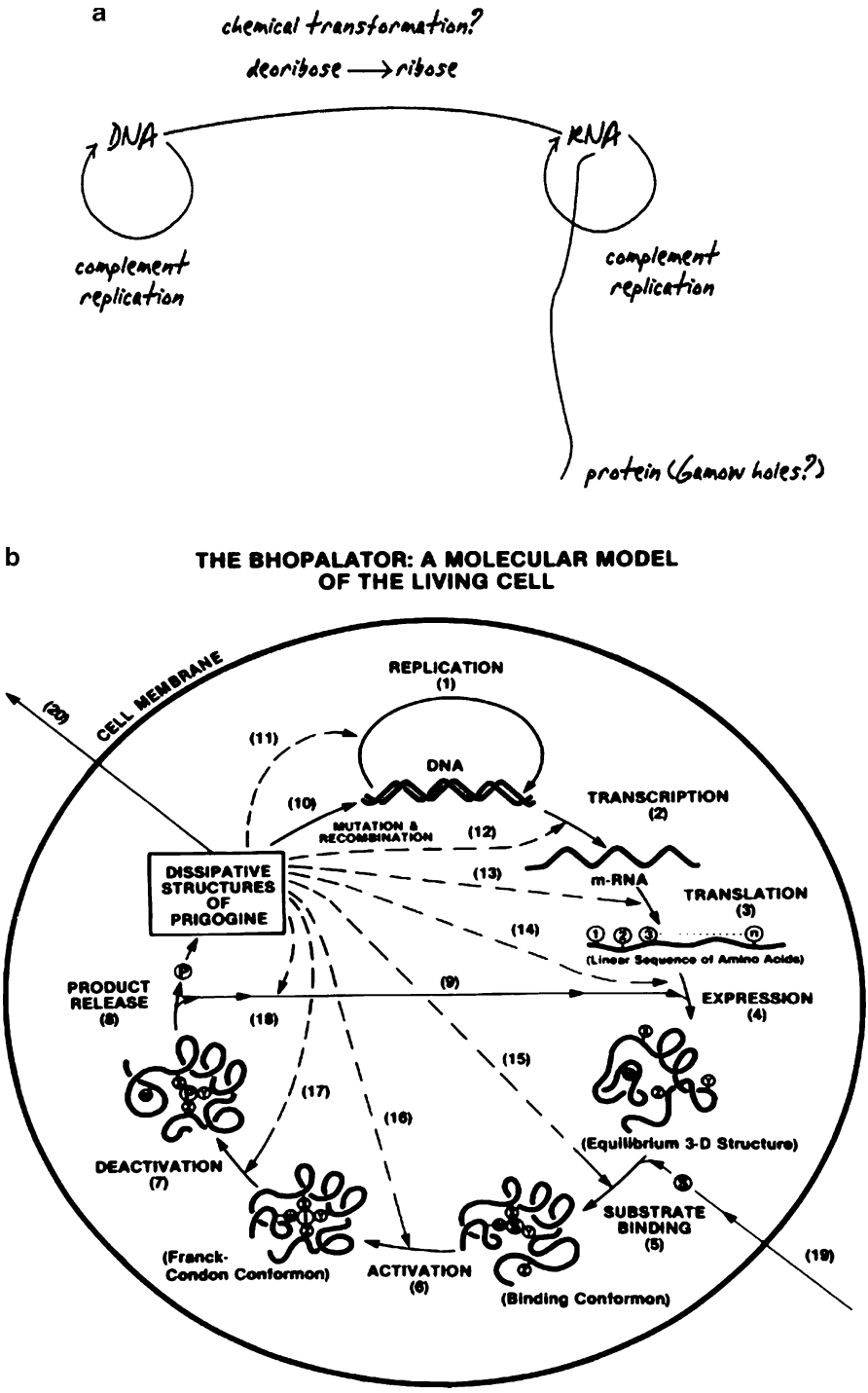


Fig. 10.8 Evolving cell models. (**a**) The protein synthesis model of J.D. Watson (1954). (**b**) The Bhopalator model of the living cell (Ji 1985a, b). (**c**) A network model of the living cell (see Sect. 10.4)

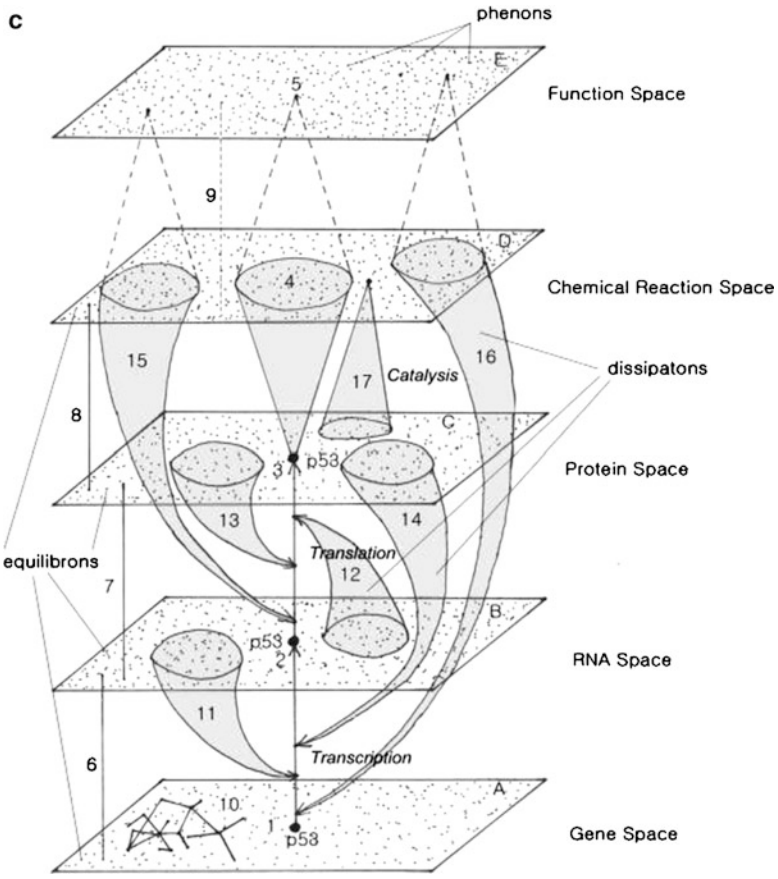


Fig. 10.8 (continued)

The eight-dimensional *supernetwork* of Fig. 9.2 reproduced as Fig. 10.8c, is a *network* version of the Bhopalator model of the cell which is a *molecular* version. The most important new addition to the supernetwork model is the concept of "renormalization" (Sect. 2.4), namely, the cooperation among many entities of the cell to act as a transient unit of biological action. These so-called renormalization cones (also referred to as *dissipatons,* SOWAWN machines, or hyperstructures (Norris et al. 1999)) are symbolically represented as circular cones in Fig. 10.8c. The characteristic features of these three models of the cell are summarized in Table 10.6. The key theoretical concepts embodied in the models are listed in the second row of the table. The experimental findings that played key roles in the genesis of the models are given in the third row. The most pronounced differences among the models are their increasing complexities as evident in the increasing number of nodes and edges summarized in Rows 4 and 5. One surprising finding about Table 10.6 is the fact that, despite the enormous increase in the complexity of the models over the

Table 10.6 The evolution of the theoretical model of the living cell, 1954–2011

	Cell models		
	Watson (1954)	Ji (1985a, b)	Ji (2012)
1. Components	(1) DNA, (2) RNA, and (3) proteins	(1), (2), (3), (4) ion gradients, and (5) mechanical stress gradients	(1), (2), (3), (4), (5) and (6) Pathway-specific concentration waves as sounds of cell language (Sect. 12.8)
2. New theoretical concepts	*DNA double-helix* (1)	*Conformons* (2) and *dissipative structures* (3)	*Renormalizable networks* (4)
3. Experimental data	(1) Chargaff's rules of base pairing, (2) role of RNA in protein synthesis, and (3) X-ray structure of DNA	(1) Mechanically flexible proteins, (2) DNA supercoils, and (3) intracellular Ca^{++} ion gradients	(1) Signal transduction pathways, (2) DNA microarray data, and (3) developmental biology
4. Nodes	3	8	?
5. Edges	4	20	?

period of a half century, the number of new concepts underlying the models did not increase proportionately. It only increased from 1 to 3 to 4 (see Row 2). This may indicate that the eight-dimensional *supernetwork* model of the cell shown in Fig. 10.8c contains most, if not all, of the fundamental concepts needed to model the living cell.

Part III
Applications: From Molecules to Mind and Evolution

Chapter 11
Subcellular Systems

11.1 Protein Folding and "Info-statistical Mechanics"

The field of protein folding appears to have gone through a paradigm shift around 1995, largely due to the work of Wolynes and his group (Wolynes et al. 1995; Dill and Chan 1997; Harrison and Durbin 1985). The paradigm shift involves replacing the idea of *folding pathways* with the so-called folding funnel. In other words, the earlier notion of a denatured protein folding to its final native conformation through a series of distinct intermediate conformational states has been replaced by a new view, according to which an ensemble of conformational isomers (often called "conformers," not to be confused with "conformons"; a conformer can carry many conformons in it; see Sect. 11.3.2) of a denatured protein undergoes a transition to a final native conformation through a series of "ensembles" of conformational intermediates, each intermediate following a unique folding path to the final common native structure. In short, the paradigm shift is from *individual intermediate conformational isomers* of a protein to an *ensemble of the conformational isomers*, on the one hand, and from a *single folding pathway* to an *ensemble of folding pathways* (down the folding funnel), on the other.

Leopold et al. (1992) characterize the "protein folding funnel" as follows:

> . . . a kinetic mechanism for understanding the self-organizing principle of the sequence-structure relationship. This concept follows from a few general considerations. (i) Proteins fold from a random state by collapsing and reconfiguring [i.e., mainly conformationally rearranging polypeptides without breaking or forming covalent bonds: *my addition*], (ii) reconfiguration occurs diffusively [i.e., as a consequence of Brownian motions of proteins: *my addition*] and follows a general drift from higher energy to lower energy conformations, and (iii) reconfiguration occurs between conformations that are geometrically similar – i.e., global interconversions are energetically prohibitive after collapse – so local interconversions alone are considered. We define the folding funnel as a collection of geometrically similar collapsed structures, one of which is thermodynamically stable with respect to the rest, though not necessarily with respect to the whole conformation space . . ..

Just as water flows down a funnel, higher energy conformers (i.e., conformational isomers) of a denatured protein are thought to "flow" down the folding funnel

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_11,

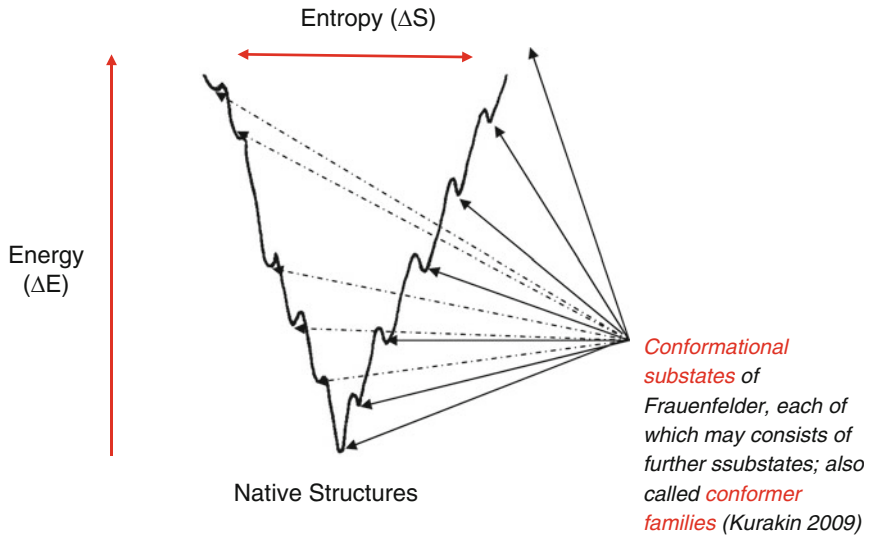


Fig. 11.1 The free energy landscape for protein folding (adopted from Brooks et al. 2009). The *vertical axis* encodes the energy changes, ΔE, accompanying a protein folding process, and the *horizontal axis* encodes the associated entropy changes, ΔS. The unfolded proteins have high potential energy and high entropy content, whereas the folded proteins have low energy and low entropy. Therefore the unfolded-to-folded transition leads to the so-called enthalpy-entropy compensation (i.e., the mutual cancellation between ΔE and TΔS) (Lumry 1974; Lumry and Gregory 1986) due to the mathematics of the Gibbs free energy change i.e., $\Delta G = \Delta E - T\Delta S$, when volume changes, ΔV, are negligible (see Eq. 2.1)

toward lower free energy conformers through several conformational states ("molten globular states," "transition state," "glass transition," "discrete folding intermediates," etc.) to the final native structure. The movement of protein conformers down the folding funnel is accompanied by two kinds of thermodynamic changes: (a) *energy* (i.e., Gibbs free energy under most conditions) decrease due to downward movement and (b) *entropy* decrease due to the narrowing of the funnel width, leading to increased conformational constraints (i.e., as conformations of a protein become more compact to minimize energy, the conformational motions of proteins become confined to an increasingly smaller volume, leading to a decrease in entropy).

Since protein folding is ultimately driven by Gibbs free energy changes under constant T and P conditions, $\Delta G = \Delta E + P\Delta V - T\Delta S$ (see Eq. 2.1 in Sect. 2.1.1), which becomes $\Delta G = \Delta E - T\Delta S$, if the pressure-volume work is negligible in protein folding, it would follow that, at some point along the vertical axis of the folding funnel, the free energy decrease ($-\Delta G$), due to energy decrease, $-\Delta E$, should exactly cancel out the free energy gain ($+\Delta G$) due to entropy decrease, $-\Delta S$, resulting in $\Delta G = 0$. At this point, spontaneous protein folding process would cease (except thermal fluctuations) and an equilibrium state established (see Fig. 11.1).

In April 2004, I had the privilege of attending a lecture on protein folding given by P. Wolynes at Rutgers. After his lecture, it occurred to me that the folding funnel theory as now formulated might lack a "biological dimension," because the theory seems to be based on the fundamental assumption that protein folding is driven by the tendency of proteins to minimize Gibbs free energy (cf., the "principle of minimal frustrations" [Bryngelson and Wolynes 1987]) in contrast to the alternative possibility that proteins in living cells have been selected by evolution not based on *free energy minimization* but rather based on their *biological functions*, regardless of their free energy levels. Their biological functions in turn would depend on their three-dimensional molecular shapes (Ji and Ciobanu 2003). When I asked Dr. Wolynes whether it would be possible to expand his two-dimensional folding funnel diagram (similar to the one shown in Fig. 11.1, wherein the *y*-axis encodes energy, E, and the *x*-axis encodes entropy, S) by erecting a *z*-axis perpendicular to the *xy*-plane to encode genetic information, I, the effects of biological evolution on protein folds, he did neither object nor explicitly endorse the idea. However, he did acknowledge the importance of taking into account biological evolution in theorizing about protein folding. Such an extension of the protein folding funnel model would bring protein folding processes within the purview of what was referred to as the *info-statistical mechanics* defined in Sect. 4.9.

The "folding funnel" model is also called "energy landscape" model. One way to incorporate biological evolution (and hence the genetic information) into the energy landscape theory of protein folding may be to identify the topology (i.e., surface shape) of the energy landscape as the extra dimension for encoding the effects of biological evolution. Although no proof is yet available, it seems that there may be a good correlation between the degree of the bumpiness or *frustrations* (Bryngelson and Wolynes 1987) of the energy landscape and the genetic information encoded in amino acid sequence of proteins, if the bumpiness somehow contributed to the fitness of the cell under given environmental condition and thus affected the I value (see below). The bumpier the surface of the energy landscape of a protein, the higher would be its information content of the Shannon type (Klir 1993). Thus, the notion of "bumpy folding funnel" may embody the following three elements

1. E, energy encoded in the depth of the funnel
2. S, entropy encoded in its width
3. I, genetic information encoded in the "bumpiness" or "ruggedness" of the funnel surface

The protein folding theory incorporating these three elements, E, S, and I, as described here may be referred to as the "information-energy landscape" theory of protein folding ("entropy" being included as a part of "energy," an abbreviation for "free energy") to contrast with the now widely accepted "energy landscape" theory of protein folding. It is my opinion that the "energy landscape theory" of protein folding is a physical theory and not a biological one, since there is no role (or room) for genetic information and, hence, biological evolution in it. To transform the energy landscape theory into a biological theory, it may be necessary to combine it

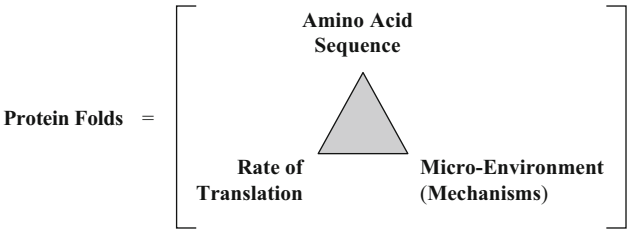


Fig. 11.2 A triadic model of protein folding inside the cell. According to this model, protein folds are dissipative structures (Sect. 3.1)

with a theory of biological evolution (in the form of say a cell model). One such biological theory is the "information-energy" landscape theory outlined here, which can be viewed as another manifestation of the *information-energy complementarity principle* presented in Sect. 2.3.2.

There are two contrasting views on the genotype-phenotype relation in protein folding: (a) the so-called Anfinsen's dogma that a protein's 3-D structure is completely determined by its amino acid sequence (but see Sect. 6.1.1) and (b) the opposite view that genotype has no *predictable* influence on three-dimensional protein folds. Belonging to the latter group is the *translation-dependent folding* (TDF) hypothesis recently proposed by Newman and Bhat (2007), according to which the differences in the rates of the translation of the mRNAs on the ribosomes can lead to different protein folds. In contrast to the TDF hypothesis of Newman and Bhat, Anfinsen's dogma may be referred to as the *sequence-dependent folding* (SDF) hypothesis. Although I support TDF hypothesis, it is deemed unnecessary to view the SDF hypothesis as completely irrelevant. Rather it appears to me that both SDF and TDF hypotheses are needed to formulate a coherent molecular theory of protein folding. One such effort is shown below which utilizes the definition of the function given in Sect. 6.2.11, the justification of which being that protein functions are determined by their folds, i.e., molecular shapes (Ji and Ciobanu 2003).

Workers in the field of protein folding have tended to think in term of thermodynamic principles only as exemplified by the *energy landscape model* of protein folding (see above) but Newman and Bhat (2007) suggest an alternative approach and emphasize the role of kinetics as being dominant in protein folding. As indicated in Fig. 11.2, I advocate a third view, the view that protein folding is an example of dissipative structure encompassing the following three irreducible elements:

1. Amino acid sequence (or the nucleotide sequence of mRNA)
2. Thermodynamic and kinetic factors determining the rates of translation of mRNA on the ribosome
3. Microenvironmental factors inside the cell that select a subset of translation rates compatible with the needs of the cell

It may be that these three aspects are inseparably "fused" together in the phenomenon of protein folding. We can only prescind (Sect. 6.2.12) one of them

at a time for the convenience of thought, but in reality they may all represent different aspects of the one and the same phenomenon we refer to as protein folding.

It is interesting to note that the *triadic model* of protein folding depicted in Fig. 11.2 is consistent with the protein folding mechanism deduced from an entirely different direction, namely, based on the *principle of constrained freedom*, the molecular version of the linguistic principle known as the *rule-governed creativity* (see Sect. 6.1.4).

11.2 What Is a Gene?

11.2.1 Historical Background

Prior to 2007, when the results of an international research effort known as the ENCODE (Encyclopedia of DNA Elements) Project was announced, the definition of gene was simple: *DNA segments encoding RNAs leading to protein synthesis* (Gerstein et al. 2007). But the ENCODE project has revealed numerous findings that cannot be readily accommodated by such a simple conception of a gene, and a new definition of a gene is called for. The failure of the pre-ENCODE conception of a gene may be traced ultimately to the following fact: *Biologists have been measuring the functions of genes (which belong to the class P of processes) and reduced the results to nucleotide sequences of DNA (which belongs to the class S of static structures) without specifying requisite mechanisms (which belongs to the class M of mechanisms)*. To stimulate discussions, such approaches in biological research where P is erroneously inferred from S alone may be referred to as the *P-to-S reduction error*. One way to resolve the problems revealed by the ENCODE project is to postulate that there are two equally important classes of genes – the S-genes and P-genes. The former is identified with the pre-ENCODE conception of genes (also called the Watson-Crick genes [Ji 1988]) and the latter is a new class of genes called the Prigoginian genes (Ji 1988). S-genes are analogous to *sheet music* (or written language) and P-genes are analogous to *audio music* (or spoken language) (see Fig. 11.3). Just as the sheet music is converted into audio music by a pianist, so are the Watson-Crick genes postulated to be transduced into Prigoginian genes by molecular motions driven by conformons, the sequence-specific conformational strains of enzymes (Chap. 8). Thus, conformons in biology may be analogous to the de Broglie equation in quantum physics, since mechanisms based on conformons can convert structure (S-genes) to processes (P-genes) in cells, just as the de Broglie equation can convert the particle-like properties of moving objects to their wave-like properties (Herbert 1987; Morrison 1990). If this analogy is true, it may be predicted that *conformons will resolve the structure-process paradox in molecular cell biology in the twenty-first century just as the de Broglie equation resolved the wave-particle paradox in particle physics in the twentieth century*.

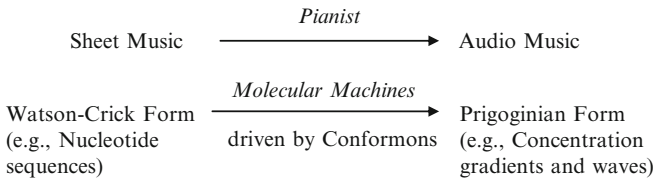


Fig. 11.3 The hypothesis that there are two forms of genes in the cell in analogy to music – (1) the Watson-Crick form analogous to *sheet music* and (2) the Prigoginian form analogous to *audio music*. The examples of the former include static nucleotide sequences of DNA and RNA, while the examples of the latter include the concentration gradients or waves of diffusible molecules such as RNA and mechanical deformations of biopolymers such as SIDDs in supercoiled DNA duplexes (see Sect. 8.3)

The history of the concept of the gene is at least one and a half centuries old (see Table 11.1) and yet its definition is still in flux. The concept of a gene as a heritable trait was established through the experiments with pea plants performed by the Austrian monk G. Mendel in the mid-nineteenth century. The term "gene" itself was coined by W. Johannsen in 1909 in analogy to the term "pangene" used by Darwin in formulating his ill-fated pangenesis hypothesis which Johannsen opposed (see Table 11.1). The modern idea of a gene as a sequence of nucleotides in DNA was firmly established by three main discoveries: (a) Avery, MacLeod, and McCarthy found that DNA is the carrier of genetic information, (b) Watson and Crick discovered that DNA is a double helix formed from two complementary strands of deoxyribonucleic acid intertwining with each other, and (c) the discovery by Crick, Brenner, Watts-Tobin, Nirenberg, Matthaei, and Khorana that triplets of nucleotides code for an amino acid. These and other historical facts about the evolution of the gene concept have been reviewed by Gerstein et al. (2007).

Unlike Gerstein et al. (2007), the history of the gene concept reviewed in Table 11.1 includes several additional facts that have to do with the energetic (E) aspect of the gene in addition to its information (I) aspect, as indicated by the last two columns labeled I and E. The decision to list both these aspects of the gene is based on the fundamental postulate that *a complete understanding of the nature of the gene on the molecular and cellular levels is impossible without taking into account both the informational and energetic aspects of the genetic processes* in line with the gnergy theory of self-organization (Sects. 2.3.2 and 4.13).

The idea that there must exist some material entity that is responsible for transmitting physical characteristics from one generation to the next (the process known as *inheritance*) must have occurred to the human mind from prehistoric times. This inference is based on the well-known facts that (1) children resemble their parents in appearance and (2) father's sperm must enter mother's womb for conception to occur. It would not have taken ancient humans too long to realize the next logical conclusion that the material entity mediating the transfer of traits from parents to offspring must be contributed not only by father's sperm but also by some material entity from mother later identified as eggs. Thus the concept of *heritable traits* must have been established in the human mind long before the Austrian

Table 11.1 A brief history of the gene concept. The following abbreviations are used: *I* informational aspect; *E* energetic aspect; *WC* Watson-Crick; *IDSs* intracellular dissipative structures (e.g., the Ca^{++} ion gradient in the cytosol); "=>" signifies "leads to," "indicates," or "causes"; + explained; − unexplained

Year	Author(s)	Key events and ideas	I	E
1. 1865	G. Mendel (1822–1884)	A *factor* that conveys traits from parent to offspring was hypothesized to exist in pea plant seeds	+	−
2. 1868	C. Darwin (1809–1882)	The *pangenesis* hypothesis was proposed as a possible mechanism for inheritance. Body cells were postulated to shed *gemmule* which collected in the reproductive organs before fertilization. Through gemmule, every cell's influence was thought to be transmitted from the parent to the offspring	+	−
3. 1886	H. de Vries (1848–1935)	The smallest particle representing one hereditary characteristic was named *pangene*	+	−
4. 1903	W. Johannsen	The terms *genotype* and *phenotype* were introduced	+	−
1909	(1857–1927)	The term *gene* was coined in opposition to *pangene* derived from Darwin's pangenesis hypothesis		
5. 1910	T. H. Morgan (1866–1945)	Genes occupy specific locations on chromosomes. The *beads on a string* model of genes	+	−
6. 1941	G. W. Beadle E. L Tatum	Mutations in genes were found to cause errors in specific steps in metabolic pathways, which led to the *one-gene-one-enzyme hypothesis*	+	−
7. 1943	E. Schrödinger (1887–1961)	The gene is a molecule capable of encoding genetic information and of executing it to form an organism	+	+
8. 1944	O. Avery C. M. MacLeod M. McCarthy	*DNA* carries genetic information	+	−
9. 1953	J. D. Watson F. Crick	The *DNA* double helix was discovered, which suggested possible molecular mechanisms underlying inheritance	+	−
10. 1958	F. Crick	The central dogma was proposed: DNA=> RNA => proteins => function	+	−
11. 1961	F. Crick S. Brenner Others	The *triplet genetic code* was discovered	+	−

(continued)

Table 11.1 (continued)

Year	Author(s)	Key events and ideas	I	E
12. 1969–1975	R. Lumry C. McClare W. Jencks	Enzymes can store mechanical energy as conformational trains to be utilized to drive molecular work processes (Ji 2000; Astumian 2001; Lumry 2009)	–	+
13. 1972	D. E. Green S. Ji	*Conformons*, defined as the mechanical energy stored in conformational strains of enzymes, were postulated to mediate energy transfer from respiration to ATP synthesis in mitochondria	–	+
14. 1972	W. Fries et al.	The first *nucleotide sequence* of a gene, *COAT_BPMS2*, was determined	+	–
15. 1976	M. Gilbert K. Mizuuchi M. H. O'Dea H. A. Nash	*DNA gyrase* was discovered that introduces *negative supercoils* into circular double-stranded DNA. DNA supercoils were later found to be essential for DNA functions, including transcription, replication, and recombination (Cozzarelli 1980; Reece and Maxwell 1991)	-	+
16. 1977	R. J. Roberts P. Sharp	*Exons* and *introns* were discovered. Genes could be split into segments, and one gene could make several proteins through alternative splicing	+	–
17. 1985 1988	S. Ji	*Conformons* were redefined as packets *of mechanical energy* and *genetic information* localized in sequence-specific sites within biopolymers and postulated to drive all goal-directed molecular movements inside the cell Two forms of genetic information are postulated to exist; *sequence information* (called Watson-Crick genes) and *time-varying patterns of chemical concentrations* (called *Prigoginian genes*) *Watson-Crick genes* = Equilibrium structures Sheet music Information transmission in time *Prigoginian genes* = Dissipative structures Audio music Information transmission in space	+	+

18. 1992	C. J. Benham	Superhelical coil–induced strand separations (called Stress-Induced DNA duplex Destabilizations, or *SIDDs*) occur in DNA duplexes predominantly at 5′ and 3′ *regulatory sites*	+	+
19. 1994	Stanford University scientists	The first genome-wide analysis of RNA functions was made possible through the invention of cDNA microarrays	+	+
20. 2007	ENCODE Project Consortium	Regions of the DNA coding for distinct proteins may overlap = > *genes are one long continuum* (ENCODE Project Consortium 2007; Gerstein et al. 2007)	+	−
21. 2009	S. Ji	(1) Genes = Dissipatons = Functions (2) Dissipatons = Equilibrons + Processes + Mechanisms (3) Prigoginian genes = WC genes + Free Energy (4) *Conformons* are *Prigoginian genes* residing in *biopolymers* (sequence information being WC genes) (Chap. 8) (5) IDSs are *Prigoginian genes* residing in the *cytosol* (molecular structures of solutes being WC genes) (Chap. 9)	+	+

monk, G. Mendel (1822–1884), established it as a scientific fact based on his experimental studies on heritable traits in pea plants in the mid-nineteenth century (See Row 1, Table 11.1). Mendel referred to the material entity or agent responsible for transmitting heritable traits as a "factor," which was later renamed as the "gene" in 1909 (Row 4, Table 11.1). The term "gene" was coined in opposition to "pangene," the smallest particle representing one hereditary characteristic within the framework of Darwin's ill-fated *pangenesis hypothesis* of inheritance (Row 3, Table 11.1), as already mentioned above. Darwin himself referred to the inherited material entity as *gemmule*, the material factor thought to be shed by every cell in the body that collects in the reproductive organs before fertilization (Row 2, Table 11.1).

Before proceeding further, it is important to stop and recall that, according to Prigogine's theory of irreversible thermodynamics (Babloyantz 1986; Kondepudi and Prigogine 1998; Kondepudi 2008), there are two and only two classes of structures in the Universe – *equilibrium* and *dissipative structures* (Sects. 3.1 and 3.1.5). The main difference between these two classes of structures is that *equilibrium structures* (or *equilibrons*) are stable within the time window of observations, requiring no expenditure of free energy, while *dissipative structures* (or *dissipatons*) are unstable and dynamic, absolutely dependent on a continuous utilization of free energy to be maintained. It is often the case that one equilibrium structure (e.g., candle) is transformed into another (e.g., CO_2 and water vapor) spontaneously, generating unstable intermediates in the process (e.g., reactive carbon-centered radicals) that self-organize into concentration patterns recognized by human eyes as dissipative structures. Thus it can be stated that dissipative structures presuppose equilibrium structures, that dissipative structures enclose equilibrium structures, or that equilibrium structures can exist without dissipative structures but dissipative structures cannot exist without equilibrium structures. These relations are embodied in the *triadic diagram* shown in Fig. 3.3.

The concept of the gene as the *material agent responsible for transmitting heritable traits from parents to offspring* as established by Mendel by the mid-nineteenth century is here claimed to belong to the class of *dissipative structures* because transmitting anything is a form of work requiring dissipation of free energy (Row 21, Table 11.1) and not to that of *equilibrium structures* as has been widely assumed by molecular biologists in recent decades. It is further suggested that the turning point when the original concept of the gene of Mendel was reduced to static sequences of nucleotides occurred around the mid-twentieth century when in agreement with Schrödinger's prediction, DNA was found to be the molecule encoding heritable traits (see Rows 7–11, Table 11.1).

The transmission of heritable traits from one generation to the next requires not only *information* (to be transmitted) but also *energy* dissipation to drive the information transmission as mandated by the principle of the *minimum energy requirement for information transfer* (see Shannon's channel capacity equation in Sect. 4.8). Of the 21 items listed in Table 11.1, 15 are concerned mainly with the informational aspect of the gene, 3 items (i.e., Rows 11, 12, and 15) are related to the energetic aspect, and only 3 items (Rows 17, 18, and 21) address both the energy

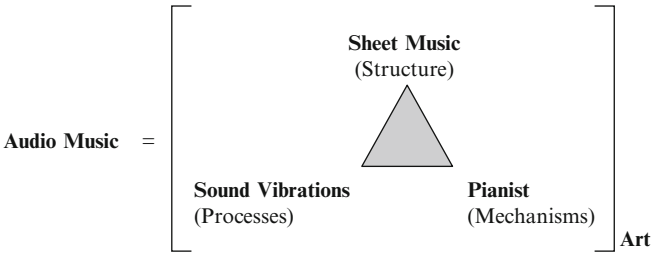


Fig. 11.4 Music as a Peircean sign. The piano music heard in a concert hall is an irreducible triad of sheet music, audio music, and pianist's performance

and information aspects simultaneously, consonant with the principle of information-energy complementarity discussed in Sects. 2.3.2 and 4.9.

One of the most significant conclusions given in Table 11.1 is that a gene is a dissipative structure selected by evolution for its functional value (see Row 21). This conclusion appears reasonable in view of the fact that functions in general are dissipative structures (Fig. 6.9) and *genes can be viewed as heritable functions*. The new conception of a gene and its relation to the traditional conception of genes as nucleotide sequences (or Watson-Crick form of genes) is discussed in Sect. 11.2.2 using Fig. 11.3. If correct, this will have many important consequences in our understanding of how the living cell works (see Items 2–5 in Row 21, Table 11.1).

*11.2.2 The Watson-Crick (*Sheet Music*) and Prigoginian Forms (*Audio Music*) of Genetic Information*

In Ji (1988), the concepts of *equilibrium* and *dissipative* structures were utilized to distinguish between two forms of genetic information: (a) the Watson-Crick form whose function was postulated to be to transmit information in *time* and (b) the Prigoginian form whose function was postulated to be to transmit information in *space*. It was then suggested that the former is akin to *musical scores* (i.e., sheet music) and the latter to *musical sounds* (i.e., audio music). Just as converting a *sheet music* to *audio music* requires a *pianist*, converting the genetic information encoded in *nucleotide sequences* to the *concentration gradients*, *waves*, or *trajectories* of chemicals inside the cell (e.g., RNA concentration trajectories shown in Fig. 11.6) requires *enzymes* acting as decoders and molecular motors such as RNA polymerase and topoisomerases:

Music can be viewed as a sign to human mind standing for human mood and emotion in the context of art. As such music can be represented using the same triadic template employed to represent the Peircean sign (Fig. 6.2) as shown in Fig. 11.4.

In analogy to music, a gene in the context of the cellular boundary conditions may be viewed as an irreducible triad of the Watson-Crick and the Prigoginian

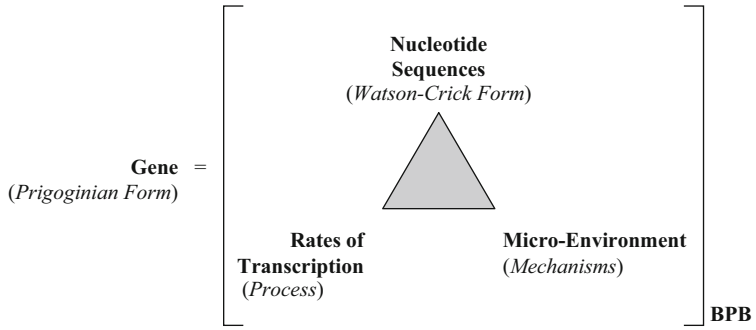


Fig. 11.5 The triadic definition of the gene based on the triadic model of function viewed as an irreducible triad of *structure*, *process*, and *mechanism* (Sect. 6.2.11). The subscript attached to the *lower right-hand side* of the bracket, BPB, stands for the "Bernstein-Polanyi boundaries" which control the mechanisms of selecting the functional processes out of all the processes allowed for by the laws of physics and chemistry

forms of genetic information and the complex mechanisms of transcription, translation, and associated processes in microregions within the cell (Fig. 11.5).

The Watson-Crick and Prigoginian forms of genes can be illustrated using Fig. 11.6 (see also Sect. 12.2) which depicts the kinetics of RNA levels (i.e., also called *ribbons*, RNA waves, or RNA trajectories) measured using DNA arrays (Sect. 12.2) in budding yeast undergoing the glucose-galactose shift (Garcia-Martinez et al. 2004; Ji et al. 2009a). The kinetic traces shown here contain two types of information: (a) the *sequence information* of individual RNA molecules, i.e., their open reading frames (ORFs), listed in the box on the right-hand side, and (b) the time-dependent *concentration levels* of the RNA molecules (i.e., ribbons, *RNA trajectories,* or *RNA waves*). The former can be identified with the *Watson-Crick form* (i.e., sheet music, equilibrium structures, or *equilibrons*) and the latter with the *Prigoginian form* (i.e., audio music, dissipative structures, or *dissipatons*) of genetic information, since the former is unaffected while that latter disappears when free energy supply to yeast cells is interrupted.

Since *dissipatons* encompass or embed *equilibrons* (see Fig. 3.4), it would follow that the Prigoginian form of genetic information embeds (or encompasses) the Watson-Crick form. This "encompassing" or "embedding" relation between the Watson-Crick form of genes and the Prigoginian form are represented using the *triadic diagram* derived from Peircean semiotics (Sect. 6.2), as shown in Fig. 11.5.

It may be significant that the definition of the gene given in Fig. 11.5 utilizes the same *triadic topological template* as used in defining Peircean signs (Fig. 6.2), *dissipative structures* (Fig. 3.4), functions (Fig. 6.10), and the model of protein folding (Fig. 11.2), indicating that *genes*, *dissipative structures*, *functions*, and *protein folding* all belong to the same class or category of entities, namely, the Peircean sign, which agrees with *Sebeok's doctrine of signs* described in Sect. 6.2. If the definition of the gene given in Fig. 11.5 is valid, genes can be described as follows:

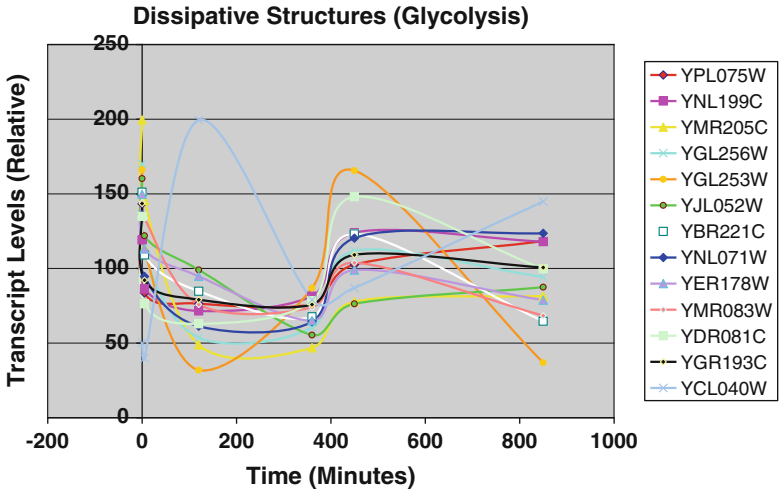


Fig. 11.6 The time-dependent RNA levels (i.e., RNA trajectories, *ribbons* or RNA waves) of the glycolytic genes of budding yeast measured with DNA arrays after switching glucose to galactose at t = 0 (Garcia-Martinez et al. 2004). RNA levels were measured in triplicates at six time points; t = 0, 5, 120, 360, 450, and 850 min, and the data points are the averages over the triplicates with coefficients of variations less than 50%. Of the 13 *ribbons* shown in this figure, the ribbon labeled YCL040W (*light blue*) exhibits an unusual behavior of increasing (rather than decreasing) its concentration between 5 and 120 min. This is most likely because the transcription of YCL040W gene is suppressed by glucose under normal physiological condition and the removal of glucose at t = 0 leads to glucose derepression of the gene (DeRisi et al. 1997; Johnston 1999; Ashe et al. 2000; Jona et al 2000; Kuhn et al. 2001)

> *Genes* are *functions* encoded in static *structures* (e.g., nucleotide sequences) which are activated into *processes* (e.g., transcription) by molecular *machines* that have been selected by evolution for their ability to fulfill the needs of the cell under a given environmental condition. (11.1)

For convenience, Statement 11.1 will be referred to as the *triadic model of the gene* (TMG) which can be logically derived from combining the concepts and theories embodied in Figs. 3.4, 6.10, and 11.3.

The concepts of *genotype* and *phenotype* were introduced by Johannsen in 1903 (see Row 4, Table 11.1). Johannsen was motivated to coin these terms to account for his finding that genetically identical common beans revealed normally distributed seed sizes (http://en.wikipedia.org/wiki/Wilhelm_Johannsen). Genotypes are heritable information stored in genes, while phenotypes are the observable manifestations of genes, on either macroscopic (e.g., morphology, behavior, biochemical properties of blood) or microscopic (e.g., amino acid sequences of proteins, RNA trajectories in cells) scale. Referring to Fig. 11.5, we can identify genotypes with the Watson-Crick form of genetic information and phenotypes with the Prigoginian form.

Phenotypes are commonly associated with stable structures such as the shape of seeds, height of plants, etc., while dissipatons (of which the Prigoginian form of genetic information is an example) are associated with unstable, dynamic structures

such as the flame of a candle and ion gradients across cell membranes. However, upon a closer examination, it is clear that neither of these initial impressions can be valid, since phenotypes can be unstable structures with short lifetimes such as RNA levels inside the cell (Fig. 11.6) and dissipatons can have stable structures with long lifetimes such as us human beings. So it appears necessary to specify lifetimes whenever we discuss dissipatons (or the Prigoginian form of genetic information). If we denote the lifetime of a dissipaton t_D, depending on the level of observations, t_D may range from nanoseconds (10^{-9} s) to years and centuries. Examples of the former include substrate levels/concentrations of enzymic catalysis (e.g., RNA levels) and neuronal firing patterns in the brain, and the examples of the latter include centuries (10^9 s)-old trees. Therefore, t_D can span 18 orders of magnitudes in time. Similarly the physical size of a dissipaton can range from about a micron (10^{-6} m) to tens of meters (10 m), thus spanning 7 orders of magnitude in linear dimension or 21 orders of magnitude in volume and mass. In other words, *dissipatons* can vary over about 20 orders of magnitude in both time and mass, the same order of magnitude spanned by the number of molecules in a macroscopic volume, i.e., the Avogadro's number, 6×10^{23}. Thus dissipatons and the Prigoginian form of genetic information can cover the whole range of space, time, and mass from the microscopic to the macroscopic, whereas the Watson-Crick form of genetic information always remains at the microscopic level (within the volume of about 10^{-20} m^3), most likely because self-replication of material systems is possible only at the molecular level where thermal fluctuations and the associated fluctuation-dissipation theorem (Ji 1991, pp. 50–51) become effective and operative (see Sect. 8.2 and Fig. 8.1 for the essential role played by thermal fluctuations in generating virtual conformons which are subsequently converted into real conforms by chemical reactions). In Sect. 5.2.3, snowflakes were compared with RNA trajectories in yeast cells which are microscopic dissipatons. This analogy can now be extended to the process of growth – just as snowflakes represent the process of the growth (i.e., crystallization) of an *equilibron* (i.e., a water molecule) from the microscopic to the macroscopic dimensions (see the left-hand side of Fig. 5.3), the human body may represent (or be the sign of) the process of the growth of a *dissipaton* from the microscopic level (i.e., cells) to the macroscopic level. In other words, *equilibrons* can grow from the microscopic level to the macroscopic one as exemplified by snowflake formation, so can *dissipatons* as exemplified by the development (or morphogenesis) of a mature human body from a fertilized egg.

11.2.3 The Iconic, Indexical, and Symbolic Aspects of the Gene

Although the birth of molecular biology was four decades away when Peirce (1839–1914) (Sect. 6.2.1) passed away, it is here assumed that the basic theory of signs he developed applies to molecular biology as well. According to Peirce

A sign (1) stands for something (2) to someone (3) in some context (4). (11.2)

We can conveniently represent Statement 11.2 diagrammatically as shown in Fig. 11.7. As pointed out in Sect. 6.2.1, the term "sign" has a dual meaning: (a) the

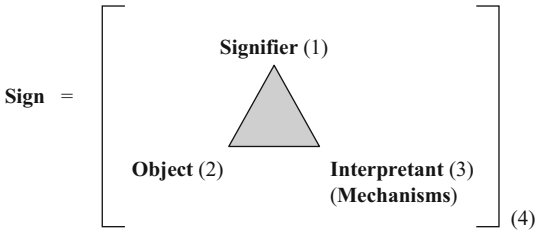


Fig. 11.7 A diagrammatic representation of the sign as a signifier, distinct from the sign as a function (see *left*). Unless otherwise noted, the term "sign" will be used in this book in the sense of signifier, following the common practice in the semiotics literature

Table 11.2 Three kinds of signs and their examples

Sign	Sign is related to object through	Examples
1. Iconic	Similarity (including structural complementarity)	Statues Portraits
2. Indexical	Causality (deterministic, one-to-one)	Smoke Weather vane
3. Symbolic	Conventions or codes (nondeterministic, one-to-many, arbitrary, creative, environment-sensitive)	Words Sentences Texts

sign as a representamen or sign vehicle (also called signifier) and (b) the sign as a function (i.e., semiosis) which is triadic as discussed in Sect. 6.2.11 (see Fig. 6.9). In Statement 11.2, as is the common practice in the semiotics literature, the term "sign" is used in the first sense.

Statement 11.2 is essentially the same statement as Statement 6.19 of Peirce (Buchler 1955, p. 99) and Statement 6.20 of Houser et al. (1998). Figure 11.7 is also essentially the same as Fig. 6.2.

Peirce distinguishes three kinds of signs as pointed out in Sect. 6.2.5 and summarized in Table 11.2.

It is assumed that Peirce's triadic division of signs is applicable to microscopic signs as well, lending support to the notion that semiotics of Peirce can be divided into two branches – *macrosemiotics* dealing with signs on the macroscopic level (e.g., words, texts) and *microsemiotics* concerned with signs on the microscopic level (e.g., molecules, DNA) (Ji 2001, 2002a). Some examples of signs, objects and sign processing mechanisms (or interpretants) at these three levels of material organization are listed in Table 11.3.

Row (1) is concerned with macrosemiotics which is a further elaboration of Table 11.2. Row (2) is about microsemiotics which is here identified with cell language (Sect. 6.1.2). Cell language (conveniently called *cellese*) is a hierarchically organized system of four sublanguages – DNA language (*DNese*), RNA language (*RNese*), protein language (*proteinese*), and biochemical language (*biochemicalese*). The question as to why the *cellese* consists of these multiple

Table 11.3 Sign processes (semiosis) at the macroscopic and microscopic levels. (1) = Sign, signifier, representamen, or sign vehicle; (2) = Object, signified, or referent; (3) = Sign processing mechanisms or interpretants; (4) = Environment or context

Levels		Sign (1)	Object (2)	Interpretant (3)	Context (4)
1. *Human language* (macrosemiotics)	Iconic	Statute	Person	Visual processing	Human brain
	Indexical	Smoke	Fire	Visual processing and reasoning	Human brain
	Symbolic	Words	Object signified	Language processing	Brain and society
2. *Cell language* (*cellese*[a]) (microsemitoics)					
(a) *DNA language* (*DNese*[a])	Iconic	DNA shape	RNA shape	Cell	Cell state[b]
	Indexical	DNA supercoil	Conformons[c]	Cell	Cell state
	Symbolic	Regulatory genes	Structural genes	Cell	Cell state
(b) *RNA language* (*RNese*[a])	Iconic	mRNA shape	tRNA	Cell	Cell state
	Indexical	RNA hairpins (?)	Conformons[c]	Cell	Cell state
	Symbolic	tRNA anti-codons	Amino acids	Cell	Cell state
(c) *Protein language* (*proteinese*[a])	Iconic	Active site shape	Ligand shape	Cell	Cell state
	Indexical	Virtual conformons[d]	Conformons[c]	Cell	Cell state
	Symbolic	Amino acid sequence	3-D protein folds	Cell	Cell state
(d) *Biochemical language* (*biochemicalese*[a])	Iconic	First messengers	Receptors	Cell	Cell state
	Indexical	Binding affinity	Virtual conformons of receptors	Cell	Cell state
	Symbolic	Acetyl-choline	Contraction	Smooth muscle cell	Cell state
			Relaxation	Cardiac muscle cell	Cell state
		Histamine	Contraction	Bronchial muscle cell	Cell state
			Relaxation	Vascular smooth muscle cell	Cell state

[a] The terms, *DNese*, *RNese* and *proteinese* were coined by a young American biochemist whom I met at the International Workshop on the Linguistics of Biology and the Biology of Language held in Cuernavaca, Mexico, in 1998, where I had presented the cell language ("cellese") theory, prior to the young biochemist's lecture in which he announced these neologisms. I am responsible for the coinage of *cellese* and *biochemicalese*

[b] The study of which is called "cytosociology" in Smith and Welch (1991)

[c] Conformational or mechanical energy stored in sequence-specific sites in DNA, RNA, or proteins (Chap. 8)

[d] *Virtual conformons* are the transient local conformational strains induced at a binding packet by thermal fluctuations of a protein which can be converted into real conformons upon exergonic binding of a ligand (Ji 2000) (Sect. 8.2)

sublanguages is not entirely clear to me but may be for the same reason that the computer language is hierarchically organized into multiple layers starting from the machine language level to (a) the micro architecture level, to (b) the instruction set architecture (ISA) level, to (c) the operating system machine level, to (d) the assembly language level, and finally to (5) the problem-oriented language level (Tanenbaum 2003). Just as all these computer languages are necessary in the computer architecture to facilitate the communication between humans and the computer, it is here postulated that the multiple sublanguages in the cell are necessary to couple the molecular (i.e., microscopic) processes (studied in molecular biology and enzymology) to the mesoscopic or macroscopic processes (studied in cell biology and animal physiology, respectively) that span spatial and temporal dimensions differing in scale by 5–15 orders of magnitude (see Statement 11.3). According to the *spatiotemporal scaling hypothesis* (Ji 1991, p. 56) quoted below, the generalized Franck-Condon principle may be ultimately responsible for the number of levels into which cell metabolism is organized:

> . . . Cellular metabolism implicates spatial structures ranging in size from 10^{-10} cm (diameter of the proton) to 10^{-5} cm (diameter of a cell), spanning 5 orders of magnitude, and in time from 10^{-9} s (electron transfer reactions) to 10^{6} s (cellular differentiation), spanning 15 orders of magnitude. To organize the intracellular processes that span such wide ranges of space and time, these processes may have to be "chunked" into manageable functional units, to each of which the generalized Franck-Condon Principle may apply. Various intracellular structures from DNA to enzymes to subcellular organelles may be viewed as a part of the cell's tactics for subdividing the spatial and temporal scales into optimal sizes for efficient control and regulation. (11.3)

We will refer to Statement 11.3 as the "Spatiotemporal Scaling Hypothesis of Biology."

Within each sublanguage, we can recognize *iconic*, *indexical*, and *symbolic* signs as indicated in Rows (2a)–(2d). When DNA is viewed as a molecular sign, its immediate object can be identified with either RNA for transcription or DNA itself for self-replication. The relation between DNA and its objects is *iconic* due to the structural similarity resulting from the Watson-Crick base paring, *indexical* due to the causal role postulated to be played by the mechanical energy stored in DNA supercoils in effectuating transcription factor binding (see the *TF-conformon collision hypothesis* discussed in Sect. 8.3), and *symbolic* due to the arbitrariness of the relation between the structural genes and the DNA segments regulating their expression (Ji et al. 2009b).

Similarly, within the RNese, mRNA is *iconically* related to tRNA through Watson-Crick base paring, *indexically* through the postulated causal role of conformons during the translation step catalyzed by ribosomes. The symbolicity in the interaction between mRNA and tRNA is probably not present but the relation between the anticodons located in the middle of a tRNA molecule and the corresponding amino acyl group located at the amino acid attachment site at the 3′ end of tRNA is clearly arbitrary and thus *symbolic*.

When proteins act as molecular signs, their objects can be identified with their cognate ligands which can be small molecular-weight organic or inorganic species or biopolymers such as DNA, RNA, carbohydrates, glycoproteins, or other proteins.

Proteins are related to their objects *iconically* due to their complementary molecular shapes and *indexically* due to the postulated requirement for converting virtual conformons to real conformons during binding processes, as required by the pre-fit hypothesis (Sect. 7.1.3). The symbolicity of *proteinese* may be best illustrated by the arbitrary relation between the primary and tertiary structure of a protein as summarized in the *postulate of the unpredictability of the 3-D protein fold* discussed in Sect. 6.1.1. Another example of the symbolicity of the proteinese is provided by the arbitrariness of the rate constants of the chemical reaction catalyzed by an enzyme, as exemplified by the single-molecule enzyme kinetics of cholesterol oxidase discussed in Sect. 11.3 (see Fig. 11.18).

In the *biochemicalese*, biochemicals are viewed as molecular signs (also called first messengers) and their objects can be receptors, second messengers, or gene-directed molecular processes that they trigger. The iconicity and the indexicality of the relations between first messengers and their cognate receptors are clear from the previous examples given in connection with the proteinese. The symbolicity of the relation between first messengers and the gene-directed intracellular processes is exemplified by the two opposite processes triggered by the same ligands, depending on cell types, as shown in the bottom four rows in Table 11.3.

When, say, a smooth muscle cell chooses to contract rather than relax when acetylcholine binds to its cell membrane receptors, what dictate the choice is not any thermodynamic changes resulting from ligand-receptor interactions but rather the cell states; smooth muscle cells contract while cardiac muscle cells relax, which reflects the history of biological evolution. Thus physical systems follow the laws of physics and chemistry (including thermodynamics) but living systems follow in addition the rules of biological evolution, most likely to increase the probability of reproduction. This is consistent with what H. Pattee (2001, 2008) refers to as the principle of matter-symbol complementarity.

Table 11.3 exemplifies the utility of Peircean semiotics in differentiating between physical systems and biological ones:

1. Molecules in physical systems act as iconic and/or indexical signs, whereas those in living systems act as symbolic signs in addition to iconic and indexical signs.
2. Iconic and indexical signs obey the laws of physics and chemistry.
3. Symbolic signs obey the rules (or codes) forged by evolution, which allows arbitrariness or *freedom within* (not beyond) the constraints of the laws of physics and chemistry (e.g., see "phenotypic freedom with genotypic constraints" discussed in Sect. 12.10).

11.2.4 Three Kinds of Genes: drp-, dr-, and d-Genes

The new concept of genes (as dissipatons and functions as defined in Fig. 11.5 and Statement 11.1) views the traditional conception of genes (as protein-coding DNA segments) as projections of the functional genes onto the three-dimensional Euclidean space. Since DNA can serve as the template for self-replication, the DNA

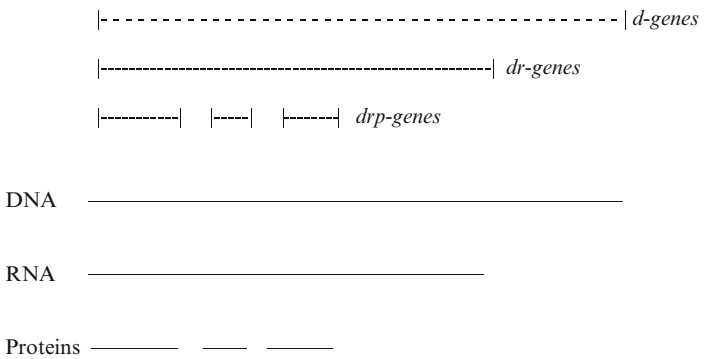


Fig. 11.8 The "overlapping triadic gene" (OTG) model of DNA

Table 11.4 The postulated hierarchical genetic architecture of DNA

New names	Traditional names
1. d-genes	Junk DNA, noncoding DNA, regulatory regions, silencers, enhancers
2. dr-genes	Introns, RNA-coding regions
3. drp-genes	Structural genes, exons

molecules as a whole can be defined as a gene, to be denoted as the *d-gene*. It is now known that about 30% of the human DNA molecule serves as the template for RNA, leading to the concept of dr-gene, namely, the DNA segments encoding not only DNA but also pre-mRNA. As is also well known, only less than 3% of the total DNA mass of the human genome codes for proteins and such DNA segments can be referred to as the drp-genes, since they code for not only proteins (p) but also DNA (d) and RNA (r). So the genetic architecture of DNA can be schematically depicted as shown in Fig. 11.8.

According to Fig. 11.8, exons are drp-genes and introns are dr- or d-genes. The parts of the DNA molecule not included in the dr-gene category are denoted as d-genes, which can be identified with the so-called noncoding DNA, including promoters, silencers, and enhancers. It was suggested elsewhere that noncoding DNA, i.e., d-genes, play a role in chromatin remodeling and hence in timing of gene expressions, driven by conformons stored in DNA double helix (Ji 1991, 1999b, 2002b). So I am suggesting here a completely new way of classifying genes in DNA structure as summarized in Table 11.4.

The DNA of the cell is often referred to as the *book of life*. This metaphor was analyzed in detail elsewhere (Table 8 in Ji 2002a), which is reproduced as Table 11.5, with the last row (starting with drp-genes) added anew.

A book contains more than just a set of words. In addition, it contains the *information* about the *order* in which the words are arranged in a linear series from the opening to the last page. The literary information and skills that were needed to select and order the words in a given pattern (i.e., a network topology [Barabasi 2002]) in a book came from the brain of the author who is physically

Table 11.5 An analysis of the DNA-book-of-life metaphor. The symbols p-, r-, and d- in the last row stand for protein, RNA, and DNA, respectively

	Words	Ordering information	Information processor
Book	Dictionary	Author's brain	Author/reader
DNA	Coding regions: "Lexical Genes" (Ji 1999b, 2002a) *drp-genes* (this book)	Noncoding regions: Semantic genes (Ji 1999b, 2002a) *dr-* and *d-genes* (this book)	The cell

absent in the book he produced. In other words, what are necessary to produce a book are *words* and the author's *literary skills*, since words alone cannot self-arrange into a book. The interesting question that arises is: What in DNA corresponds to the author's literary skills? Based on then-available data it was conjectured in Ji (1991, 1997a, b, 1999b, 2002b) that the information required to order gene expression in *time* and *space* is encoded in the so-called noncoding (or silent) regions of DNA that do not code for proteins. It should be pointed out that space and time are postulated to be inseparably linked on the molecular level in cells due to Brownian motions and the operation of the generalized Franck-Condon principle discussed in Sect. 2.2.3 and in Ji (1991, pp. 52–56). These and related ideas are summarized in Table 11.5.

The so-called regulatory RNA molecules recently reviewed by Mattick (2003, 2004) can be viewed as indirectly supporting the concept of *spatiotemporal genes* that was postulated in 1991 to be located in non-protein-coding DNA (Ji 1991), although I was not aware then that at least a part of such non-protein-coding DNA could code for regulatory RNAs (cf. dr-genes). The *spatiotemporal gene hypothesis* formulated in Ji (1991) can now be updated as follows:

> DNA molecules contain drp-, dr-, and d-genes that are located, respectively, in:
>
> (1) Protein coding regions (1–3% of the total DNA mass in humans [Mattick 2004])
> (2) RNA coding regions (~30% of the total human DNA mass)
> (3) DNA-coding regions (the total human DNA mass)
>
> The term "DNA-coding genes," or d-genes, is self-referential, since DNA itself, without being first transduced to RNA, is postulated to transmit genetic information as during the replication step of the cell cycle. The d-genes include cis-regulatory regions, enhancers, and silencers as already indicated above (Tjian 1995). It is further postulated that drp- and dr-genes primarily encode *equilibrium* structures and d-genes primarily encode dissipative structures consisting of conformationally deformed DNA. (11.4)

Statement 11.4 will be referred to as the postulate of the "triadic overlapping genomic architecture TOGA)," the triadicity stemming from the trichotomy of the drp-, dr-, and d-genes and "overlapping" referring to the fact that drp genes code for DNA, RNA, and proteins and dr genes code for DNA and RNA. Statement 11.4 clearly is a "spatiotemporal gene" hypothesis, because the drp- and dr-genes carry spatial (or geometric) information specifying protein and RNA structures,

whereas d-genes are thought to carry *timing* information about *when* and *for how long* target genes are to be expressed in the nucleus, which will lead to the production of various dissipative structures inside the cell. The letter "d" in d-genes can be viewed as "dual" in the sense that it can be interpreted either as "dissipative structure-forming" or "DNA," which may be viewed as being consistent with the *information-energy complementarity principle* (Sect. 2.3.2).

An interesting difference between the *spatiotemporal gene hypothesis* (Ji 1991) updated in Statement 11.4 and the *regulatory RNA hypothesis* of Mattick (2003, 2004) is that the former endows the non-RNA-coding regions of DNA with a full gene status (i.e., as d-genes) storing the conformons with timing information about gene expression, whereas the Mattick hypothesis endows the timing information only to RNA-coding DNA segments and does not explicitly specify any biological role for non-RNA-coding DNA regions which accounts for more than a half of the total DNA mass in the human genome.

It is also possible that d-regions of DNA carry information required to control or effectuate *long-range correlations* within DNA (and hence indirectly within RNA and proteins as well), leading to the couplings between *the very small* (e.g., ions, atoms) and *the very large* (e.g., cell behaviors including shape changes, and cell migration), and *the very fast* (e.g., time constant in the range of 10^{-12} s characteristic of covalent bond rearrangement events occurring locally on DNA) and *the very slow* (e.g., time constants in the rage of years or decades, $10^8 \sim 10^9$ s, associated with DNA sequence evolution by genetic drift) (Ji 1991, pp. 52–56). Thus, it is predicted that the d-genes will be found to play a critical role in effectuating *long-range spatiotemporal correlations* both within DNA molecules and within cells generally in order to transduce genetic information to various intracellular dissipative structures (IDSs), the final form of gene expression according to the Bhopalator model of the cell (Fig. 2.11).

Fink et al. (2007) recently analyzed the variations of the coding (C) and noncoding (N) DNAs for 800 prokaryotic and eukaryotic species (see Fig. 11.9). The double-logarithmic plot of N against C of these species produced a straight line passing through mostly prokaryotic species (67) with a slope of 1.07 and a set of lines that can be drawn through eukaryotic species (733) with an average slope of 4.33 (individual slopes ranging from 2 to about 10). Fink et al. (2007) proposed that eukaryotes require a certain minimum amount of noncoding DNA which increases with the amount of coding DNA. This allowed them to account for the slope of about 2 in Fig. 11.9 (see the slightly curved solid line) but left unexplained the wide upward divergences of data points from this lower bound.

Based on the spatiotemporal gene hypothesis, Statement 11.4, we can provide alternative explanations for the distribution patterns of the data points shown in Fig. 11.9:

There exists a general power law relation between N and C:

$$\mathrm{N} = \alpha \mathrm{C}^{w} \tag{11.5}$$

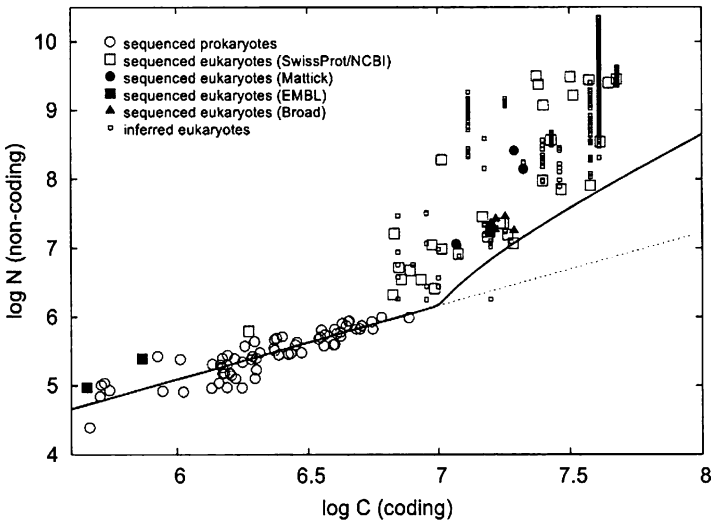


Fig. 11.9 The relation between the amounts of coding (C) versus noncoding (N) DNA of 67 prokaryotic and 733 eukaryotic species in units of base pairs (Reproduced from Fink et al. 2007)

where α is proportionality constant and w is a "critical exponent" postulated to be unique to organisms, reflecting the functional characteristics of their genomes.

For the prokaryotic genomes which consist of mostly drp genes and are devoid of any dr- and d-genes:

$$w = 1 \tag{11.6}$$

For eukaryotic species with only drp- and dr-genes:

$$w = 2 \tag{11.7}$$

For eukaryotic species with drp-, dr-, and d-genes:

$$2 < w < 10 \tag{11.8}$$

It is interesting to note that drp- and dr-genes each contribute one unit to the numerical value of w, leaving d-genes to contribute one to about eight units to the numerical value of w. It is suggested here that the numerical values of w greater than 2 be referred to as "excess critical exponent (ECE)." Although the physical meaning of ECE defined here is not yet clear, ECE may be related to the *number of subunits in multisubunit complexes of enzymes* such as those participating in signal transduction networks, translation, protein degradation, transcription (cf. transcriptosomes), transcript degradation (cf. degradosomes), and nuclear pore complexes. The number of the subunits constituting an enzyme complex ranges from 30 to 100. If this interpretation of ECE is correct, there may be a profound difference between

a *simple enzyme* and an *enzyme complex* besides their physical sizes, indirectly supporting the conclusion drawn in Table 4.7, where the difference between enzymes and enzyme complexes was compared to the difference between atoms and quantum dots.

In addition, the explanations suggested here are consistent with the general hypothesis proposed in (Ji and Zinovyev 2007b; Ji 2007a) that *life is a critical phenomenon*, wherein long-range interactions among microscopic entities or particles lead to macroscopic behaviors of organisms (see also Sect. 16.7). If this hypothesis is correct, the numerical values of w ranging from 1 to 10 revealed in Fig. 11.9 may be analogous to the variable numerical values for the critical exponents measured in condensed matter physics which vary from 0.1 to about 5 (Domb 1996; Landau and Lifshitz 1990).

The DNA-book analogy described in Table 11.5 can be expanded by replacing "book" with "survival manual." That is, DNA can be more accurately viewed as the *molecular record* of all the instructions found useful for cell survival throughout the evolutionary history of a lineage. In other words, DNA can be viewed as *survival programs* or *algorithms* written in atoms and hence may be referred to as the "atomic survival programs (ASP)" or "atomic survival algorithms (ASA)." The maximum number of ASPs stored in the human genome may be estimated as shown in Eqs. 11.9 and 11.10, if we can assume that (a) protein-coding genes (whose number will be denoted as a, which is about 30,000, in the human genome) are equivalent to words in human language; (b) the average number of words, b, in a cell-linguistic sentence is about 10; and (c) the average number, c, of cell linguistic sentences in an ASP is 5.

$$\begin{aligned}\text{Log (Maximum Number of ASPs)} &= \text{c log } a^{b} \\ &= 5 \log (3 \times 10^{4})^{10} \\ &= 5 \times 40 \log 3 \\ &= 95.42 \end{aligned} \tag{11.9}$$

$$\text{Maximum Number of ASPs} = 10^{95.42} \tag{11.10}$$

The information, I, required to retrieve one of these ASPs from the nucleus may be estimated as in Eq. 11.11:

$$\begin{aligned} \mathrm{I} &= \log_2\left(10^{95.42}\right) \\ &= \left(\log_{10} 10^{95.42}\right)/(\log_{10} 2) \\ &= (95.42)/0.303 \\ &= 315 \text{ bits} \end{aligned} \tag{11.11}$$

Equation 11.11 indicates that the cell will need 315 bits of information to be able to select one ASP out of all possible ASPs stored in DNA. With this information the cell will be able to make 315 binary choices or decisions. In order for

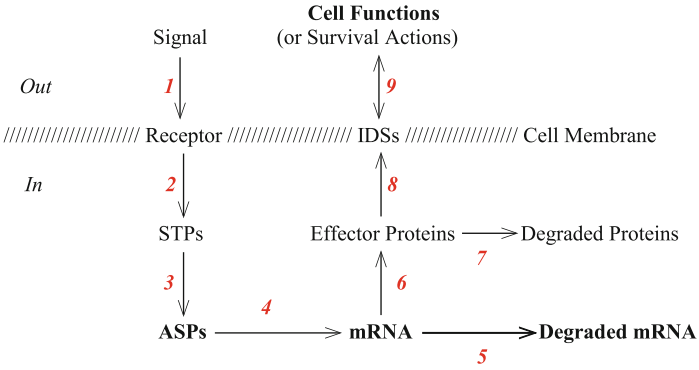


Fig. 11.10 The cell viewed as a system (or network) of *molecular machines* that has evolved to carry out two main functions: (1) *signal transduction* (see Steps 1, 2, and 3) to retrieve select "atomic survival programs" (ASPs) stored in DNA,and (2) *gene expression* (see Steps 4, 6, and 8) to transduce ASPs into survival actions or mechanisms, otherwise known as cell functions. See Figs. 12.34 and 12.35 for more detailed signal transduction pathways

the cell to be able to make such complex decisions, it would need similarly complex internal states, according to the Law of Requisite Variety (see Sect. 5.3.2), and we can identify the signal transduction pathways as the cellular machinery carrying out the required selective actions. So the well-recognized complexities of signal transduction pathways can now be understood as resulting from the cell's need to retrieve select ASPs from the nucleus and to execute them into actions in order to survive under very complex environmental conditions that are constantly changing. We may represent this idea schematically as shown in Fig. 11.10:

Step 1 is where the external signal is recognized through the receptors embedded in the cell membrane or nuclear receptors present in the cytosol and the nucleus (not shown), and in Step 2 the original signal is transformed to retrieve appropriate information from DNA in the nucleus in Step 3. In Step 4, selected ASPs are retrieved from chromosomes and transcribed into mRNA expressed at right times and for right durations. It is important to note here that mRNA levels are functions of not only the rates of transcription (Step 4) but also of the rates of transcript degradation (Step 5). Ignoring this simple fact has led to many false positive and false negative conclusions in the field of microarray technology as pointed out in Ji et al. (2009a). Similarly, effector protein levels are functions of both translation (Step 6) and protein degradation (Step 7). Step 8 represents catalysis, the all-important step where chemical reactions are catalyzed to generate free energy that drives all intracellular molecular processes. Abbreviations are as follows: STP = signal transducing proteins; IDSs = intracellular dissipative structures such as intracellular ion gradients (Chap. 9) and mechanical stress gradients of cytoskeletons (Ingber 1998). Effector proteins include transcription initiation/elongation complexes (acting on Step 4 thus constituting a feedback loop), molecular motors and pumps, kinases, phosphatases, synthetic enzymes, cytoskeletons, etc.

The double-headed arrow in Step 9 indicates that IDSs and survival actions are synonymous or identical. This idea has been referred to as the *IDS-cell function identity hypothesis* (Sect. 10.2).

11.2.5 Two-Dimensional Genes: The Quality-Quantity Complementarity of Genes

The currently most widely accepted definition of a gene is "a segment of DNA that encodes an RNA or a protein molecule." This definition was probably established around 1961 when the *triplet genetic code* was discovered (see Table 11.1 and Crick et al. 1961). Such a definition of a gene is no longer adequate to completely account for what we can now measure about a gene. For example, the DNA microarray technique invented in the mid-1990s (see Sect. 12.1) measures two aspects of a gene simultaneously: (a) the nucleotide sequence and (b) the copy number (also called abundance, levels, or concentrations) (see Fig. 11.6). The former reflects the qualitative aspect of a gene and the latter reflects the quantitative aspect, and *quality* and *quantity* are complementary to each other in the Bohrian sense (see Sect. 2.3.1). Thus a gene may be viewed as the complementary union of the two irreconcilably opposite properties, sequence, and copy number, just as light can be regarded as the complementary union of irreconcilably opposite waves and particles (see Sect. 2.3.5). We may represent this idea algebraically as shown in Eq. 11.12:

$$\textbf{Gene} = [\textbf{S},\ \textbf{CN}] \tag{11.12}$$

where S is the nucleotide *sequence* and CN is copy number. In Fig. 11.6, Ss are given in the column on the right-hand side of the figure, and CNs (in relative units) are indicated on the *y*-axis. Eq. 11.12 also indicates that a gene is two-dimensional, since a gene is a function of two independent variables, S and CN. Eq. 11.12 also applies to gene products, RNAs, and proteins.

$$\textbf{RNA} = [\textbf{S},\ \textbf{CN}] \tag{11.12a}$$

$$\textbf{Protein} = [\textbf{S},\ \textbf{CN}] \tag{11.12b}$$

The microarray data measured in budding yeast undergoing glucose-galactose shift (described in Sect. 12.3) demonstrate that there is a good correlation between metabolic functions of the cell and the kinetic behavior (or trajectory) of an mRNA molecule (Sect. 10.2), leading to the following triple correlation:

$$\textbf{Gene X} \sim \textbf{mRNA X} \sim \textbf{CellFunction X} \tag{11.12c}$$

where X is the name of S such as "ORF (open reading frame)" or "ATPase," etc., and the symbol "A ~ B" reads "A is associated with B" or more specifically "A is the necessary condition for B." To emphasize the latter sense which is "hierarchical" or "ordinal" (i.e., without Gene X, no mRNA X; without mRNA X, no Cell Function X), Eq. 11.12c can be rewritten as:

$$\textbf{Gene X} < \textbf{mRNA X} < \textbf{CellFunction X} \tag{11.12d}$$

where the symbol "<" indicates the hierarchical or ordinal relation. Because of the importance of Inequality (11.12d) in interpreting microarray data, it may be justified to refer to Inequality (11.12d) as the *Principle of the Ordinal Relation among Genes, RNAs, and Cell Functions* or *PORAGRF*. One practical consequence of PORAGRF is this: Although genes, RNAs, and cell functions are often given the same name (e.g., "glycolysis gene," "glycolysis mRNA," "glyclysis proteins"), they cannot be *equated* or *interchanged*, ultimately because a gene and its products are not one dimensional entities but two-dimensional so that, although they have the same S, they can have different CNs (see Eqs. 11.12, 11.12a, 11.12b).

Most of the papers on microarray data experiments that have been published since the beginning of the microarray era in the mid-1990s have made false positive and false negative conclusions (Ji et al. 2009a). The reason for such errors may be traced ultimately to the following two erroneous assumptions which are interconnected:

1. "Gene X" can be replaced by "mRNA X" (violating PORAGRF, Inequality (11.12d)).
2. Microarrays measure the expression of "gene X" because "gene X" is synonymous with "mRNA X."

11.2.6 DNA and RNA as Secondary and Primary Memories of the Cell

To understand the role of RNAs in cell functions, it may be instructive to use the digital computer as a model, in agreement with the so-called Simpson thesis discussed in the Preface that biology is the study of phenomena to which all principles apply, including most likely the architectural principles of modern-day digital computers. It is interesting in this connection to point out that Wang and Gribskov's (2005) made a theoretical comparison between the digital computer and the living cell in a complementary way to the comparison made in Ji (1999a). According to Wang and Gribskov, DNA is analogous to the *secondary* memory and RNA to the *primary* memory of computers (Fig. 11.11).

One of the crucial differences between the primary and secondary memories of the computer is that the former is dynamic and disappears when the computer is turned off, whereas the secondary memory (e.g., stored in hard drives, CDs, etc.)

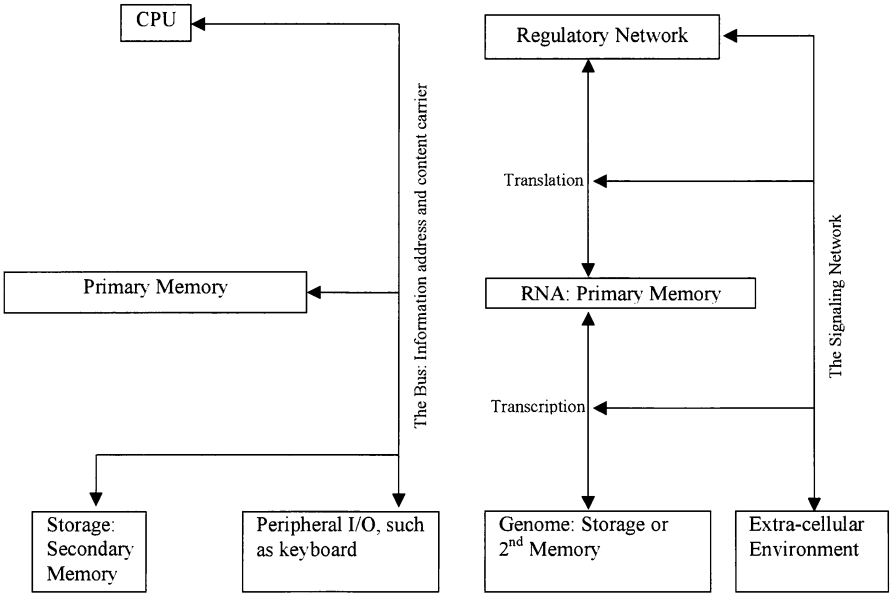


Fig. 11.11 A comparison between the architecture of the computer and the living cell (Reproduced from Wang and Gribskov 2005). *CPU* central processing unit, *I/O* input/output device

is stable even when the computer is turned off. This is reminiscent of the metabolic difference between RNA and DNA in cell biology; the former levels are changing with cell functions, disappearing when the free energy sources are turned off (Garcia-Martinez et al. 2004; Ji et al. 2009a), while the latter is relatively stable in cells, maintaining its sequence information even when cells are deprived of free energy. The dynamic nature of RNA levels in cells is the consequence of the fact that RNA is both produced via the transcription process and degraded via the transcript degradation process simultaneously and with comparable kinetic constants (see Figs. 11.6, 12.1, 12.2). Another interesting similarity between the computer and the cell is that, just as the CPU of the computer cannot utilize the information stored in the secondary memory without first converting it to the primary one, the cell cannot utilize the genetic information encoded in DNA without first converting it to RNA and then to proteins, since the utilization of DNA information requires *free energy dissipation* which in turn requires proteins acting as catalysts for free-energy supplying chemical reactions (Fig. 11.12).

Another way to describe the fundamental difference between DNA and RNA is in terms of the concepts of *equilibrium* and *dissipative* structures (Babloyantz 1986; Kondepudi and Prigogine 1998; Prigogine 1977, 1980; Kondepudi 2008). DNA is an equilibrium structure and RNA levels are dissipative structures, for the obvious reason that the former remains and the latter disappears when free energy input into the cell is blocked as mentioned above (Sect. 3.1). The concentration of DNA in cells remain more or less constant except during the S phase in the cell cycle,

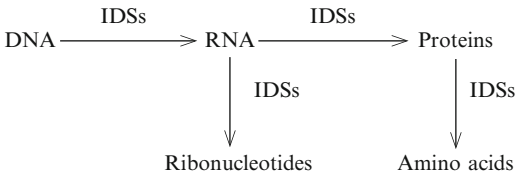


Fig. 11.12 A simplified representation of the Bhopalator model of the living cell, highlighting the relationship among the key structural components – DNA, RNA, proteins, and IDSs, and the last including biochemical concentration gradients

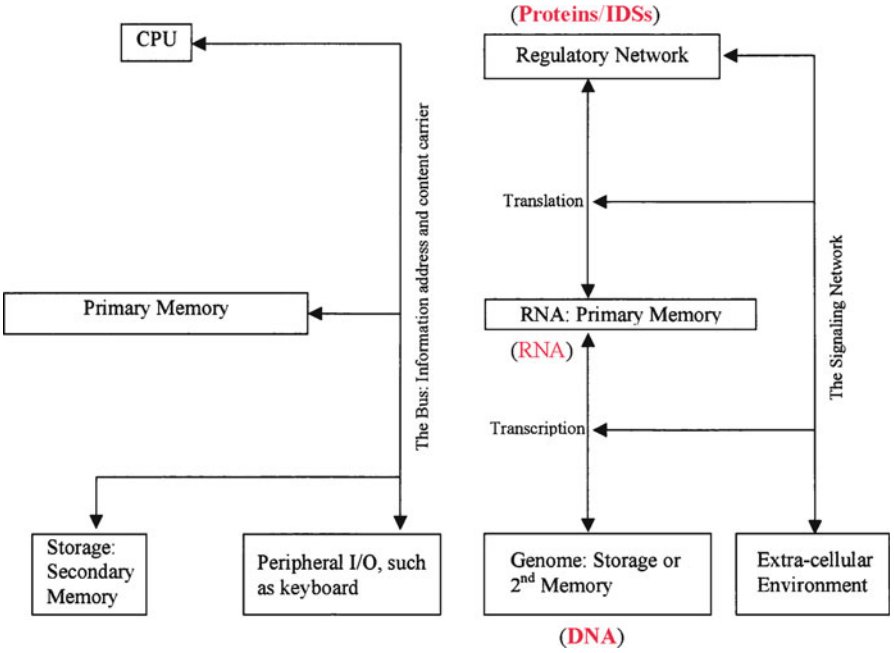


Fig. 11.13 A comparison between the Wang-Gribskov model (*left*) of the cell and the Bhopalator (*right*). The main difference is the concept of IDSs which is absent in the former model of the cell. See text for more details

whereas the concentrations of RNA molecules, both large such as mRNA and small such as siRNA (small interfering RNA), can change dramatically while cells carry out their functions in interaction with their environment throughout the cell cycle.

There is one important difference between the Wang-Gribskov model of the cell shown on the right-hand side of Fig. 11.11 and the Bhopalator model of the cell shown in Figs. 2.11 and 11.13. In the former, what corresponds to CPU of the computer is "regulatory network" and proteins (Wang and Gribskov 2005), whereas what corresponds to CPU in the Bhopalator model is the combination of proteins and IDSs, the final form of gene expression. One of the most interesting points of

the Wang-Gribskov model of the cell is the importance placed on RNA as the primary memory relative to DNA viewed as the secondary memory, which may seem to go against the DNA-centered paradigm in cell biology that has been dominating the field of molecular biology since the discovery of the DNA double helix in 1953. But this shift in emphasis from DNA to RNA embodied in the Wang-Gribskov model of the cell is consistent with the emerging prominence of RNA not only as the reliable indicator of biological complexity (Mattick 2004) but also as the regulators of cell metabolism and functions (Mattick 2003, 2004; Storz 2002; Zamore 2002). One of the reasons for the prominence of RNA over DNA in cell biology may derive from the fact that RNA can serve as an enzyme but DNA cannot. Thus RNA may have played an essential role in the origin of life because of its ability to manipulate both *energy* and *information* and thus control organization (see Fig. 4.8).

11.2.7 Cell Architectonics

The study of the principles and theories of the architecture of the living cell may be referred to as the *cell architectonics*. Just as a human architect designs a building to achieve a set of functions desired by the occupant, the biological evolution has designed the living cell to accomplish a set of functions that are essential for self-reproduction or self-replication. It is important to recognize the fundamental difference between *artificial buildings* and *natural cells*, however. The former is *other-designed* and the latter is *self-designed* and *self-organizing* (Sect. 3.1).

If we designate the *d*iameter of a *c*ell as DC and the average *d*iameter of the *p*articles inside the cell as DP, the *n*umber of *p*articles inside the *c*ell, NPC, can be approximated as $\mathrm{NPC} = (\mathrm{DC}/\mathrm{DP})^3$. Typically, a eukaryotic cell has a diameter of 10^{-5} m, and the average diameter of cell components (e.g., protons, oxygen, water, metal ions, metabolites, proteins, RNAs, and DNA) can be estimated to be 10^{-9} m, leading to 10^{12} as the approximate total number of particles inside the cell. These particles are not randomly distributed inside the cell but organized in space and time to accomplish a set of functions that are beyond individual component particles. In other words, to produce the properties essential for cell survival that are beyond the capabilities of the components of the cell, these components must be organized into higher-order structures according to the principle referred to as the Principle of Emergent Properties (PEP) (Ji 1991). PEP states that:

> Whenever a complex system S is constructed out of n sub-systems, s_1, s_2, s_3, …, s_n, according to a set R of m rules, r_1, r_2, r_3, …, r_m, then a set P of k properties, p_1, p_2, p_3, …, p_k can emerge that is not found in less complex systems composed of any subset of S. (11.13)

To organize the large number (~10^{12}) of particles inside the cell, the following two requirements must be met.

Thermodynamic Requirement: Most, if not all, molecular motions of the intracellular particles must be driven away from random directions and random durations, utilizing the free energy supplied by exergonic chemical reactions (e.g., ATP hydrolysis), since random motions are incompatible with life. (11.14)

Control Information Requirement: The non-random molecular motions of the intracellular particles must be constrained in space and time by the *boundary conditions* that embody both the genetic information (or "internal constraints") and environmental information (or "external constraints"). (11.15)

Requirement 11.14 is met by the *conformon theory of molecular machines* (Ji 1974a, b, 2000, 2004a), according to which all molecular machines (e.g., molecular motors, ion pumps, and enzymes) inside the cell are driven by sequence-specific conformational strains called *conformons* that are generated from exergonic chemical reactions or ligand-binding processes based on the generalized Franck-Condon mechanisms (Chaps. 7, 8).

The control information essential for cell functions may be transferred in two distinct ways – through (a) covalent interactions (e.g., via forming equilibrium structures such as phosphorylated proteins, RNAs, etc.), and (b) noncovalent interactions (e.g., via forming dissipative structures such as transient protein complexes, cytosolic ion gradients, etc.). The former may act as *internal* constraints that transmit control information through time, i.e., from one moment to the next during the lifetime of a cell or from one cell generation to the next, while the latter may act as external constraints on molecular machines (e.g., membrane potentials, cytosolic ion gradients, ATP levels in the cytosol, etc.) transmitting control information through space, e.g., between the nucleus and the cytosol and between the cytosol and the extracellular space (Ji 1988). Through these two mechanisms, the cell can control its molecular processes or events in space and time.

More specifically, the cell must control its molecular processes (conformational motions, ATP hydrolysis, etc.) that can occur on the subpicosecond (10^{-12} s) timescales and the subnanometer (10^{-9} m) length scales (referred to as the *microscopic* level) to drive the molecular processes that occur on the time- and length scales of 10^{-3} s and 10^{-5} m, respectively (referred to as the *mesoscopic* level). Thus, the micro- and mesoscopic levels are separated from each other by approximately 10 orders of magnitude in time- and mass scales. The coupling of events separated by such divergent temporal and spatial scales will be referred to as the *micro-meso coupling*. The fundamental significance of the *micro-meso coupling* in biology stems from the fact that the free energy needed to drive all living processes inside the cell ultimately derives from exergonic chemical reactions (e.g., oxidation of glucose, ATP hydrolysis) that occur only on the microscopic level. The question as to how the cell accomplishes the micro-meso couplings across the spatiotemporal gaps separated by 10 orders of magnitude is one of the most challenging problems facing the contemporary biology, since they underlie most of the unsolved problems in molecular and cell biology, including the mechanisms of force generation in muscle, gene expression in the nucleus, and morphogenesis of living tissues (Sect. 15.1).

The possible mechanism employed by the cell to accomplish the *micro-meso coupling* on the mass scale is suggested by the molecular tactics used by the cell to control its DNA molecule during cell division, namely, the *chunk-and-control* mechanism discussed in Sect. 2.4.2. The figure showing the chunking of DNA double helix into a chromosome is reproduced from Fig. 2.9 on the right-hand side of Fig. 11.14. As indicated in Sect. 2.4.2, the chunking operation not only compactifies DNA by a factor of 10^9 but also *constrains* the motional degrees of freedom of DNA components such as atoms, nucleotides, and DNA segments. In addition, since the frequency of an oscillator is inversely proportional to the square root of its reduced mass (http://en.wikipedia.org/wiki/Molecular_vibration), it is here postulated that the chunking operation (which increases mass) applied to biopolymers can lead to *slowing down* of their global oscillatory motions. For convenience, this idea will be referred to as the principle of "slowing down oscillation by increasing mass" (SDOBIM). Hence, the principle of SDOBIM defined here can provide the theoretical foundation for the principle of "chunk-and-control" (C&C) (Sect. 2.4.2), and these two principles may be viewed as the two sides of the same coin. As will be discussed in Sect. 11.3, the principle of SDOBIM appears to apply to single-molecule enzyme mechanics, i.e., to the low-frequency oscillations of cholesterol oxidase measured with a single-molecule manipulation technique (Lu et al. 1998).

It is interesting to note that the chunk-and-control operation depicted in Fig. 11.14 involves a single molecule consisting of a set of monomeric units *covalently* linked in a linear chain. It is postulated here that the chunk-and-control operation can be applied to a set of molecules that are not covalently linked to one another but nevertheless interact through *noncovalent bonds* such as electrostatic bond, hydrophobic bond, and the van der Waals force. Thus it may be necessary to distinguish between two kinds of chunk-and-control operations: (a) the *covalent-chunk-and-control* (CC&C) operation and (b) the *non-covalent-chunk-and-control* (NC&C) operation. The DNA packaging shown in Fig. 11.14 embodies both CC&C (e.g., covalent linking of thousands of structural genes and regulatory regions into a chromatin) and NC&C (e.g., beads-on-a-string to form a chromatin).

11.3 Single-Molecule Enzymology

Single-molecule measurements can provide mechanistic information on enzymic catalysis that is not available through conventional ensemble-averaged enzyme kinetic studies (Xie 2001; Ishii and Yanagida 2007; Deniz et al. 2008). A good example of single-molecule enzyme experiments is provided by Lu et al. (1998) who monitored the fluorescence emission from a single molecule of the flavin adenine dinucleotide (FAD) bound to the active site of cholesterol oxidase (COx) as it went through catalytic cycles (Figs. 11.15, 11.17). The principle underlying the phenomenon of fluorescence emission is explained in Fig. 11.16.

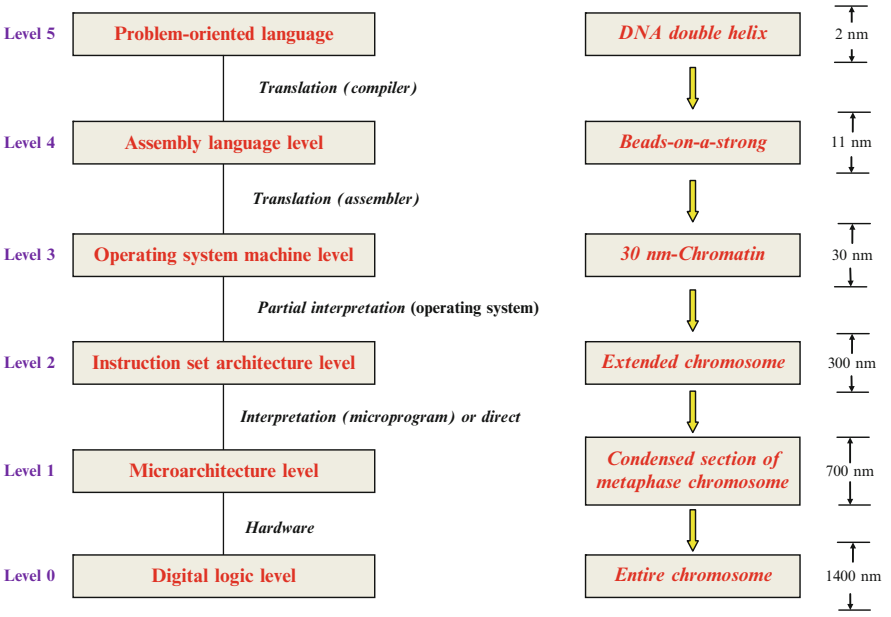


Fig. 11.14 (*Left*) The multilevel structural organization of the computer (Adapted from Tanenbaum 2003). Digital logic => Microarchitecture => Instruction set architecture => Operating system machine => Assembly language => Problem-oriented language. (*Right*) Multistep chunking of DNA into chromosome. DNA double helix => beads-on-a-string form of chromatin => 30-nm chromatin fiber => 300-nm section chromosome => 700-nm section chromosome => 1,400-nm section metaphase chromosome

Many mathematical models have been proposed to account for the results of the single-molecule enzymological measurements on COx (Lu et al. 1998; Kurzynski 2006; Qian and Xie 2006; Prakash and Marcus 2007), but they are all rooted in the conventional Michaelis-Menten mechanisms as applied to individual molecules of enzyme and couched in the language of physics- and chemistry-based continuous mathematical functions such as Eq. 11.25 shown in Sect. 11.3.3. The main objective of this section is to propose an alternative theory of single-molecule enzymology that is based on the concept of *conformons* (i.e., the packets of conformational *energy* and genetic *information* stored at sequence-specific sites within biopolymers that are postulated to drive all goal-directed molecular processes in the cell including catalysis; see Chap. 8). The concept of conformons was originally developed to account for the energy-coupled processes of the living cell such as oxidative phosphorylation, muscle contraction, and active transport (Green and Ji 1972a, b; Ji 1974b, 1985a, b, 2000) but has also been found to provide a reasonable explanation for the mechanistic isomorphism (or similarity) between *blackbody radiation* and *enzymic catalysis* (see Fig. 11.24) as found in Ji (2008b). If the conformon-based explanation for single-molecule enzymological data on COx proves to be correct, it would be possible to conclude that the single-molecule enzymological

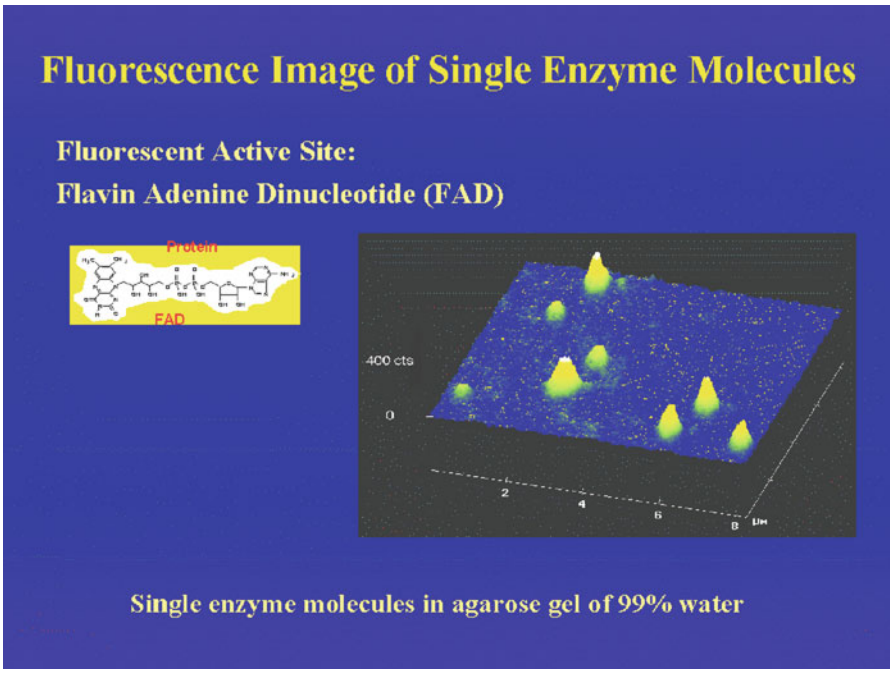
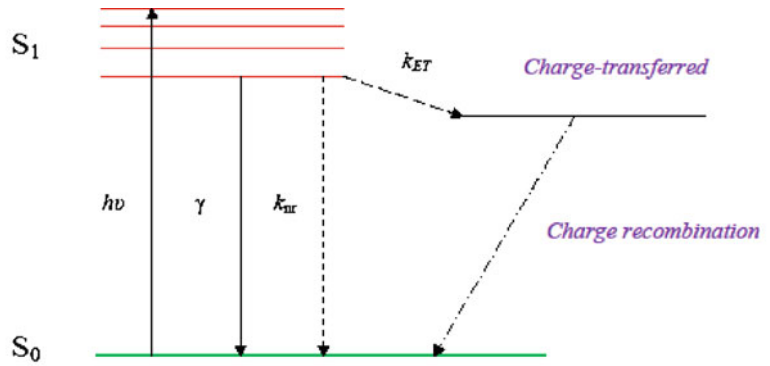


Fig. 11.15 The fluorescence image of single molecules of cholesterol oxidase (COx) immobilized in agarose gel. When FAD is illuminated at 442 nm (see the *upward arrow* in Fig. 11.16), the prosthetic group absorbs this photon and emits fluorescence at 530 nm (see the *solid downward arrow* in Fig. 11.16). This image was taken in 4 min with an inverted fluorescence microscope by raster-scanning the sample with a focused laser beam of 500 nW at the excitation wavelength. Each individual fluorescent spot indicates the presence of a single molecule of COx. The intensity variations are due to different longitudinal positions of COx molecules in the gel (Reproduced from http://www.nigms.nih.gov/News/Reports/single_molecules.htm)

data on COx cannot be fully explained unless the traditional physics- and chemistry-based mathematical formalisms are supplemented with the evolution-derived *catalytic information* of the kind discussed by the Ranganathan group (Poole and Ranganathan 2006; Socolich et al. 2005; Süel et al. 2003) and others. One possible way by which "catalytic information" may affect the probability of the occurrence of a given waiting time (or a rate constant) was constructed using as a metaphor the potential energy transfer between the *garage door* and its *spring* as explained in Table 11.12 in Sect. 11.3.3.

11.3.1 Waiting Time Distribution of Cholesterol Oxidase

Cholesterol oxidase is a 53,000 Da protein with 504 amino acid residues that catalyzes the oxidation of cholesterol by oxygen to form cholesterone. The active



S_0 = ground electronic state of the fluorophore, i.e., the dye molecule emitting fluorescence
S_1 = first electronic excited state of the fluorophore with 4 vibrational states
γ = the wavelength of fluorescence emitted
k_{nr} = rate of non-radiative (nr) decay
k_{ET} = rate of electron transfer from the fluorophore to a to a nearby electron acceptor.
$h\nu$ = the absorption of the excitation light which promotes the electron from the ground electronic energy level, S_0, to the first excited electronic energy level, S_1, with excess vibrational energies, which are quickly lost to fall to the ground vibrational level, from which fluorescence emission

Fig. 11.16 The diagram showing the submolecular processes underlying photon-molecule interactions

site of the enzyme contains one FAD molecule, which is fluorescent in its oxidized form. FAD is reduced by a cholesterol molecule to $FADH_2$, which is then oxidized back to FAD by molecular oxygen (Fig. 11.17). The fluorescence of FAD is turned on and off (giving rise to the so-called blinking phenomenon) as the redox state of the FAD undergoes transitions between the oxidized and reduced states, each on-off cycle corresponding to one turnover of the enzyme.

The electronically excited state S_1 in Fig. 11.16 can decay back to the ground state S_0 through three different mechanisms:

1. The radiative pathway (i.e., the γ step)
2. The nonradiative (nr) pathway (i.e., the k_{nr} step)
3. The electron transfer (ET) pathway (i.e., the k_{ET} step)

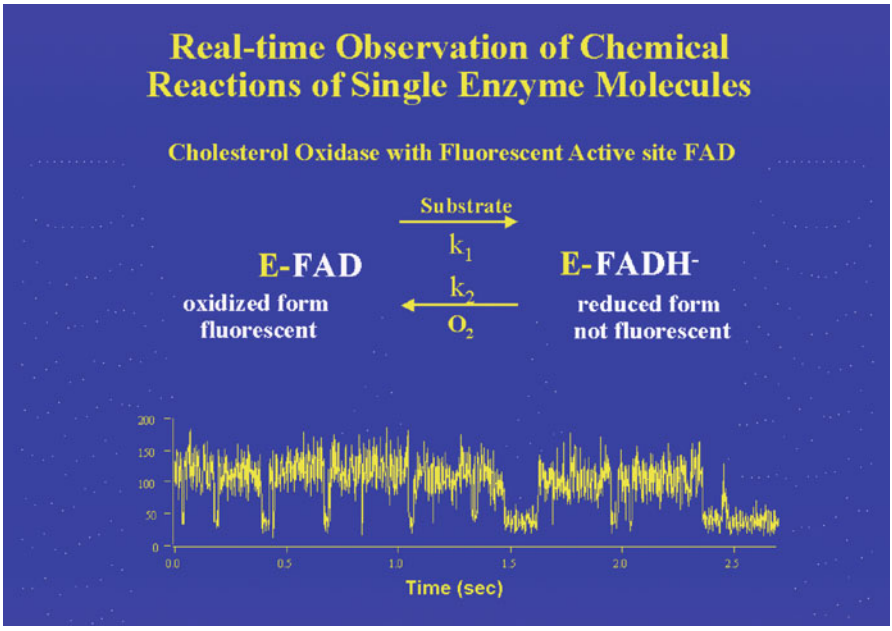


Fig. 11.17 The measurement of the turnover of a cholesterol oxidase (COx) molecule in the presence of cholesterol (0.20 mM) and oxygen (0.25 mM). The prosthetic group, FAD, is fluorescent when in its oxidized state with an average relative intensity of about 130 units (which is referred to as the "on" state) and nonfluorescent when in its reduced state with an average intensity of about 40 units (which is referred to as the "off" state) (Reproduced from http://www.nigms.nih.gov/News/Reports/single_molecules.htm)

The relative importance of these pathways during a given cycle of photon absorption and emission probably depends on the conformation of FAD molecule which is in turn most likely affected by the local conformational structure of the FAD binding pocket of COx. It is for this reason that, as the conformation of COx fluctuates, the fluorescence efficiency, defined as $k_\gamma/(k_\gamma + k_{nr} + k_{ET})$, also fluctuates, thus accounting for the fluorescence fluctuations observed during the on- or off-times as shown in Fig. 11.17, or between A and B and between C and D in Fig. 11.20.

Lu et al. (1998) used a single-molecule manipulation technique (Xie 2001; Ishii and Yanagida 2007) to measure the cycling of cholesterol oxidase between its oxidized ("on") and reduced ("off") states (Fig. 11.17). Two of the most significant findings Lu et al. (1998) made are (a) that the enzyme molecule spends variable times in on- or off-states and (b) that the on- and off-times are not distributed randomly (or normally) but have a long tail. As can be seen on the lower left corner of Fig. 11.18, the on-times varied from about 70 ms (milliseconds) to 1,300 ms with most probable on-times lying between 100 and 200 ms. Estimating from the area under the "on-time" distribution histogram in Fig. 11.18, it may be concluded that

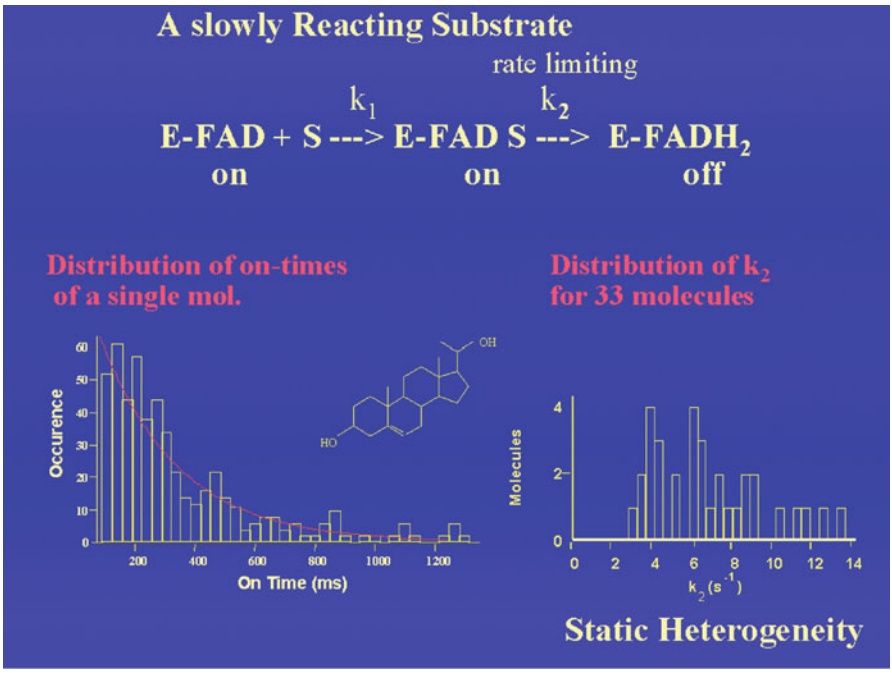


Fig. 11.18 The distribution of the kinetic parameters (on-times) measured from COx molecules. (*Left*) The distribution of the on-times (i.e., the duration of the times that the FAD molecule remains in its oxidized state and fluorescent). This phenomenon of varying on-times is known as "dynamic disorder" or "dynamic heterogeneity" (Zwanzig 1990). Cholesterol concentration = 0.2 mM. (*Right*) The distribution of the rate constants, k_2, for the reduction of FAD to $FADH_2$ measured from 33 COx molecules. At any given time, the k_2 values measured from different molecules of COx vary by a factor of up to 5 (Reproduced from http://www.nigms.nih.gov/News/Reports/single_molecules.htm)

the probability of the oxidized form of COx to be reduced by cholesterol (present at 0.2 mM) within less than 500 ms is about 80%. Since the off-times in Fig. 11.17 appear shorter than the on-times on average, the probability of reduced COx being reoxidized by molecular oxygen is faster than the rate of the reduction of COx by cholesterol. Also, since the concentration of cholesterol and oxygen molecules were approximately the same (0.20 vs. 0.25 mM), it may be concluded that the rate constant for the reduction of COx, i.e., k_1 in Fig. 11.17, is smaller than the rate constant, k_2, for the reoxidation of COx.

Lu et al. (1998) proposed a simple mechanism, Scheme (11.16), to account for the distribution of the off-times shown in Fig. 11.18:

$$\underset{a}{\text{E-FAD}} + \text{S} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \underset{b}{\text{E-FAD} \bullet \text{S}} \xrightarrow{k_2} \underset{c}{\text{E-FADH}_2} + \text{P} \tag{11.16}$$

where k's are rate constants. A similar mechanism, Scheme (11.17), was proposed for the on-time distribution.

$$\underset{d}{\text{E-FADH}_2} + \text{O}_2 \rightleftarrows \underset{e}{\text{E-FAD} \bullet \text{O}_2} \rightarrow \underset{f}{\text{E-FAD}} + \text{H}_2\text{O}_2 \tag{11.17}$$

Schemes (11.16) and (11.17) do not obey the *Principle of Microscopic Reversibility* (PMR) (discussed in Sect. 3.3). In other words, the transitions from *b* to *c* or from *e* to *f* are not symmetric as demanded by PMR. An alternative mechanism that obeys PMR is proposed in Fig. 11.19. Since this mechanism is based on the generalized Franck-Condon principle discussed in Sect. 2.2.3, we may refer to the mechanisms proposed in Fig. 11.19 as the *Franck-Condon mechanism* of the action of cholesterol oxidase. The Franck-Condon mechanism entails expanding the number of the states involved in one cycle of the enzymatic turnover from the original 6 to a total of 16, as explained in the legend to Fig. 11.19a, b. The unique features of the Franck-Condon mechanism are:

1. The enzyme can exist in two states – the ground state (see *a, h, i* and *p*) and the thermally *activated/excited* state (see *b, g, j* and *o*).
2. The enzyme binds its substrate or product only when in a thermally activated/excited state (see *c, f, k,* and *n*). *It should be noted that "energized state" is synonymous with "thermally activated/excited state stabilized by ligand binding." Without such ligand-induced stabilization, thermally activated/excited states are thought to relax rapidly back to ground states.*
3. In the Franck-Condon state, the distinction between *substrate* and *product* disappears due to the highly unusual microenvironment of the enzyme active site prevailing in this state. This is tantamount to asserting that $d = e$, and $l = m$ at the Franck-Condon state, within the Heisenberg uncertainty principle (Reynolds and Lumry 1966; Ji 1974a).

The Franck-Condon mechanism proposed in Fig. 11.19 provides a novel set of explanations for the single-molecule fluorescence data reported by Lu et al. (1998). Their data are reproduced in Fig. 11.20 with a particular attention given to the variations in the amplitudes of the fluorescence fluctuations recorded in Fig. 1b of their paper. The features of their data that are of special interest are summarized in Table 11.6 along with the corresponding explanations offered by the Franck-Condon mechanism shown in Fig. 11.19.

One of the most significant outcomes of analyzing the single-molecule fluorescence data measured by Lu et al. (1998) as shown in Table 11.6 is that there may exist two high-energy states – one relatively long-lasting after stabilization by ligand binding (denoted by the superscript *) and capable of performing external work and the other short-lived (denoted by the superscript ‡). Thus we will refer to the former as the *energized state* distinct from the Franck-Condon state. Since energized states are characterized by their *stored energy* in the sense of McClare (1971, 1974) (see also Sect. 2.1.4), the enzymes in energized states are capable of

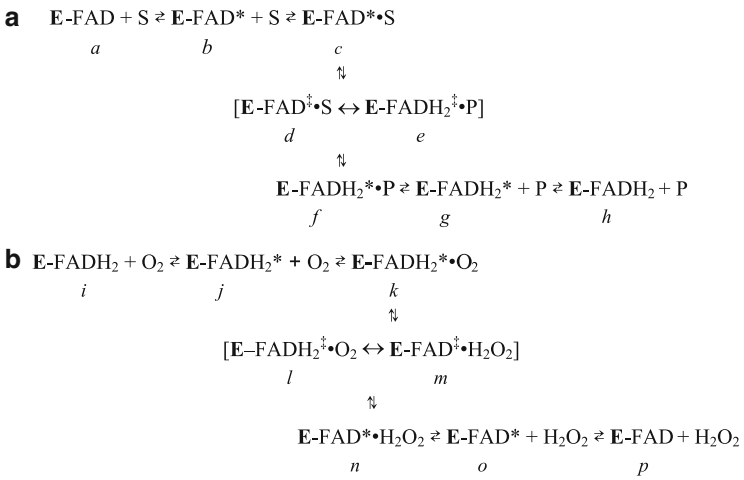


Fig. 11.19 A complete mechanism of the cholesterol redox cycle based on the *generalized Franck-Condon principle* (Sect. 2.2.3) and *the principle of microscopic reversibility* (Sect. 3.3). The *hyphen* and the *dot* symbolize noncovalent binding interactions. The superscript * indicates thermally activated/excited (*b, g, j,* and *o*) or energized (*c, f, k,* and *n*) states of the enzyme-ligand complex and the superscript ‡ denotes the transition state (also called the Franck-Condon state; Reynolds and Lumry 1966; Ji 1979). (**a**) **The reduction of the cholesterol oxidase molecule by cholesterol (S).** *a* = the oxidized enzyme before binding cholesterol; *b* = the oxidized enzyme in a *thermally activated/excited state* (or a *thermally activated conformer*; see Sect. 11.3.2); *c* = the energized state of the oxidized enzyme that has bound substrate S (thermal energy is thought to be transduced to mechanical energy upon binding S; see Sect. 11.3.2); *d* = the Franck-Condon state of the oxidized enzyme-substrate complex accessible from *c* through another round of thermal fluctuations; *e* = the Franck-Condon state of the reduced enzyme-product complex thermally accessible from *f*; *f* = the energized state of the reduced enzyme binding product P; *g* = the reduced enzyme in a thermally activated state; *h* = after the product dissociates from reduced COx. (**b**) **The oxidation of reduced cholesterol oxidase by molecular oxygen.** *i* = the COx in the reduced state before binding oxygen; *j* = the reduced COx in a thermally activated state; *k* = the energized COx in its reduced state binding oxygen; *l* = the Franck-Condon state of the reduced COx-oxygen complex; *m* = the Franck-Condon state of the oxidized COx-hydrogen peroxide complex; *n* = the energized COx in its oxidized state binding hydrogen peroxide; *o* = the oxidized COx in a thermally activated state; *p* = after hydrogen peroxide dissociates from the ground-state COx molecule

performing work either on their environment (as in ion pumping or movement of actin filament) or internally (e.g., modulation of the activation free energy barrier for catalysis, or k_2, in Scheme 11.17), the latter contributing to the dynamic disorder of the COx enzymic activity.

In constructing Table 11.7, the following assumptions have been made:

1. Both FAD and $FADH_2$ fluoresce, although the former is much more fluorescent than the latter probably by a factor of about 100.
2. Both FAD and $FADH_2$ molecules undergo many cycles of the photon absorption-radiative decay process during the lifetime of any of the four conformational states (or conformers) of COx labeled A, B, C, and D (see Fig. 11.20).

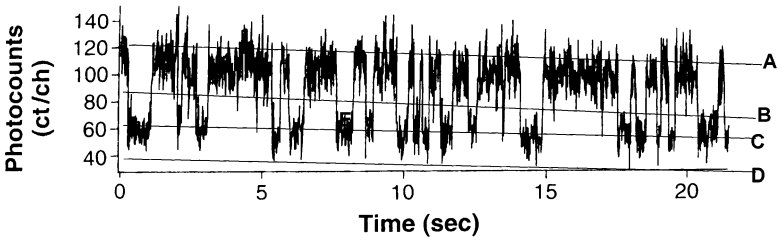


Fig. 11.20 The fluctuations of the fluorescence intensity of the cholesterol oxidase (COx) molecule in its oxidized and reduced states adopted from Fig. 1b in Lu et al. (1998). It is postulated here that the oxidized form of COx fluctuates between the fluorescence levels A and B, while the reduced form of the enzyme fluctuates between the florescence levels C and D. The four *lines* decline with time more or less in parallel, most likely due to light-induced structural damages suffered by the protein surrounding the fluorophore, which in turn alter the energy levels of the fluorophore, affecting the fluorescence efficiencies of both the oxidized and reduced form of COx. The average fluorescence intensity of the oxidized form of COx decreases from about 120 ct/ch (counts per channel) to 90 ct/ch in 22 s, while that of the reduced form decreases from about 60 to 40 ct/ch (in the same time period) which is near the background fluorescence. In addition to the fluorescence fluctuations occurring between A and B and between C and D, there are other fluorescence intensity transitions taking place from B to C and from C to B. See the region indicated by E (which is partially hidden) between B and C at around 8 s. Since there are four fluorescence states of COx, there are $4 \times 4 = 16$ possible transitions as shown in Table 11.7. Due to the diagonal symmetry of the table, there are only six distinct transitions whose probabilities of occurrences need not be equal. The relative transition probabilities predicted on the basis of the generalized Franck-Condon principle (Sect. 2.2.3) are given in the table

Table 11.6 The generalized Franck-Condon-principle-based explanations for the single-molecule measurements of the cholesterol oxidase enzymic activities reported by Lu et al. (1998). A, B, C, and D refer to the fluorescence levels defined in Fig. 11.20

Single-molecule measurements on cholesterol oxidase (see Figs. 11.17 and 11.18)	Explanations offered by the Franck-Condon-principle-based mechanism of action of COx (see Fig. 11.19)
1. There are two kinds of fluorescence fluctuations – one averaging around 100 ct/ch and the other around 50 ct/ch	The fluorescence intensity of both oxidized and reduced forms of COx fluctuates. The time-averaged fluorescence intensity of the oxidized form of the COx molecule is approximately 100 ct/ch, while the corresponding value for the reduced form is around 50 ct/ch
2. Each form of the COx molecule fluctuates between a high and low fluorescence level, giving rise to four fluorescence levels denoted as A, B, C, and D in Fig. 11.20	The molecular species responsible for the various fluorescence levels are postulated to be as follows: A = **E**-FAD B = **E**-FAD* and **E**-FAD*•S C = **E**-$FADH_2$*•P and **E**-$FADH_2$* D = **E**-$FADH_2$
3. There are two kinds of fluorescence transitions – (1) from level B to level C, and (2) from level C to level B, both taking place almost instantaneously compared to the on- and off-times (Fig. 11.17)	(1) The transition from B to C passes through and is rate-determined by the free energy level of the Franck-Condon state [**E** -$FAD^{\ddagger}$•S ↔ **E**-$FADH_2^{\ddagger}$•P] (2) The transition from C to B passes through and is rate-determined by the free energy level of the Franck-Condon state [**E**–$FADH_2^{\ddagger}$•O_2 ↔ **E**-$FAD^{\ddagger}$•H_2O_2]

Table 11.7 The relative transition probabilities among the four conformational states of COx-FAD complex predicted on the basis of the generalized Franck-Condon principle (Sect. 2.2.3). For the definition of the conformational states, A–D, see Figs. 11.17 and 11.20. The Arabic numerals in the table refer to the relative probabilities for the X to Y transition, where X and Y represent rows and columns, respectively, and the relative probabilities are in the order of $1 > 2 > 3 > 4 > 5$

	A	B	C	D
A	1	2	4	5
B	2	1	3	4
C	4	3	1	2
D	5	4	2	1

3. The generalized Franck-Condon principle is postulated to apply to the COx-FAD and COx-$FADH_2$ complexes in the sense that the probability of the fluorescence transitions of these complexes are inversely proportional to the Euclidean distances between the corresponding conformational states of COx indicated in Fig. 11.20.

Although the current state of development of single-molecule mechanics may not allow measurements to be made of these six transitions predicted in Table 11.7, it may be possible to detect them in the future when the single-molecule mechanics techniques improve.

11.3.2 Molecules, Conformers, and Conformons

In order to rigorously analyze single-molecule enzymological data such as shown in Figs. 11.18 and 11.24, it may be necessary to utilize some of the concepts, theories, and principles that have been developed in molecular enzymology and biology by various investigators since the mid-twentieth century, including Widom (1965), Volkenstein (1972, 1986), Green and Ji (1972a, b), Ji (1974a, b, 1990, 2000), Lumry (1974, 2009), Lumry and Gregory (1986), Lumry and Biltonen (1969), Northrup and Hynes (1980), Anderson (1983, 1987), Frauenfelder (1987), Frauenfelder et al. (2001), Welch and Kell (1986), Benham (1992, 1996a, b), Kurzynski (1993, 1997, 2006), and Eisenmesser et al. (2002).

In physical organic chemistry, the terms *configuration* and *conformation* are carefully differentiated (see Fig. 3.5) (Sect. 3.2) unlike in physics and molecular biology where they are often used interchangeably (Ji 1997a, see Table 4). Strictly speaking, not distinguishing *configurations* and *conformations* in chemistry is equivalent to conflating *electrons* and *protons* in physics, since *configurations* involve the movement of *electrons* while *conformations* entail *proton* displacement in molecules secondary to breaking and making H-bonds, the study of which being referred to

as the "electronic-conformational interactions" (Volkenstein 1986). A molecule has a unique *configuration* (as defined by the set of covalent bonds it possesses) and many *conformations* (as defined by the three-dimensional arrangements of the covalently bound atoms in a molecule which can be altered without breaking or forming any covalent bonds) (Sect. 3.2). Some of the simplest examples of molecules having different configurations are provided by isomers. Thus, cis- and trans-1-chloro-2-bromo-ehtylene have an identical set of atoms, i.e., C_2H_4BrCl, and yet have two different *configurations* (or arrangements of these atoms in the Euclidean space), namely, cis- and trans-isomers which cannot be interconverted without breaking at least one of the covalent bonds of C=C, C–H, C–Cl, and C–Br.

A given *configuration* of a set of atoms can assume numerous *conformations* (also called *conformers*). For example, 1-chloro-2-bromo-ethane, the product of reducing the C = C double bond in 1-chloro-2-bromo-ethylene, can exist in two conformations, one in which the chlorine and bromine atoms are located farthest apart and the other in which they are located nearest to each other, and these two conformations can be interconverted through rotations around covalent bonds. One crucial difference between *configurations* and *conformations* is that the activation free energy barrier separating one *configuration* from another is much higher (*50–100 kcal/mol*) than that separating one *conformation* from another within a given configuration (*1–3 kcal/mol*). Therefore, the thermal energy available under physiological conditions (about 0.6 kcal/mol) is usually not large enough to change configurations but sufficient to cause appreciable conformational changes, leading to the following general statement:

> *Configurations* of molecules are too robust to be altered but *conformations* of a molecule are labile enough to be interconverted, through thermal fluctuations. (11.18)

According to the cell language theory (Ji 1997a, 1999b), Statement 11.18 is ultimately responsible for the phenomenon known as "rule-governed creativity" (Sect. 6.1.4), namely, the ability of biopolymers (and cells) to generate indefinitely large numbers of states within the constraints of a finite number of components and syntactic rules. The relationship between *configurations* and *conformations* can be diagrammatically represented as shown in the first two columns in Fig. 11.21. Note that the energy separations between configurations are greater than those between conformations.

In discussing biochemistry, molecular biology and biophysics, it is useful to differentiate between *small molecules* (which may be referred to as "micromolecules" (e.g., glucose, ATP, NADH, and FAD) and *large molecules* (*or macromolecules*) including proteins, RNA, and DNA. What characterizes *biological macromolecules vis-à-vis micromolecules* of organic chemistry is that biological macromlecules (or *biomacromolecules*) are the product of a long biological evolution and hence carry biological (also called evolutionary or genetic) information, whereas micromolecules do not. In other words, biomacromolecules possess an extra degree of freedom not available to micromolecules, i.e., the dimension of *genetic* or *evolutionary information* (Fig. 4.2). This extra degree of

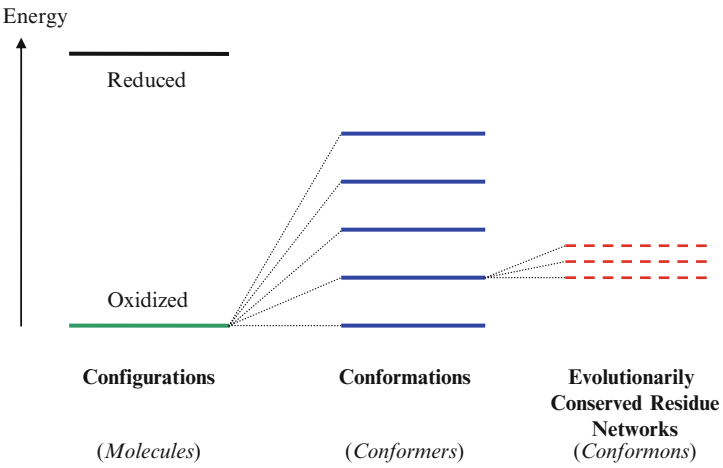


Fig. 11.21 A diagrammatic representation of the relations among *configurations* and *conformations* on the one hand and between *conformers* and *conformons* on the other. Multiple conformational energy levels are also available for the reduced configuration of a molecule but are not shown for brevity. The energy scale is approximate

freedom (or the *bioinformation or bioinformatic* dimension) is thought to be manifested in the form of evolutionarily conserved amino acid residues as indicated on the right-hand side of Fig. 11.21. That there indeed exists such an internal degree of freedom in enzymes was strongly suggested by the finding that many families of enzymes, receptors, and DNA-binding proteins are characterized by unique networks of a small number (10–25% of the total) of amino acid residues that are evolutionarily conserved and coevolved (Lockless and Ranganathan 1999; Süel et al. 2003; Poole and Ranganathan 2006).

Another distinguishing feature between these two classes of molecules is that micromolecules are too small to harbor any long-lived internal conformational strains or kinks, whereas biomacromolecules are large and complex enough to retain relatively stable internal *conformational strains* produced either during their syntheses on the ribosomes (Klonowski and Klonowska 1982) or during their catalytic cycles. Such conformational strains have been variously referred to as *conformons* (Green and Ji 1972a, b; Ji 1974b, 2000, 2004a), *frustrations* (Anderson 1983, 1987), *mobile defects* (Lumry 1974; Lumry and Gregory 1986), or *SIDDs* (Stress-Induced Duplex Destabilizations; Benham 1992, 1996a, b). It is here suggested that the concept of the conformational *gates* that are postulated to control the rates of enzymatic reactions in the *stochastic model of enzymic catalysis* proposed by Kurzynski (1997, 2006) can also be viewed as equivalent to *conformons*, since no *gate* can be opened or closed at right times for right durations without utilizing *mechanical energy* and *control information* both stored in local conformational strains in proteins. There are other interesting commonalities between the *conformon theory of molecular machines* (Ji 1974a, b, 2000, 2004a) and *the stochastic model of protein machines* proposed by Kurzynski (1993, 1997, 2006).

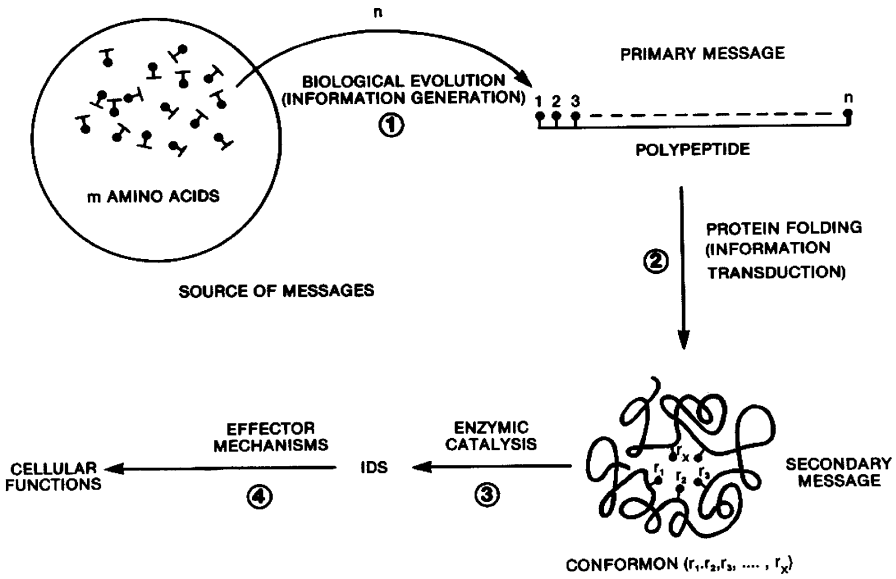


Fig. 11.22 A theoretical model of the communication system responsible for generating biological information (Ji 1990, 2000). The message source = biological evolution; the channel = conformons and IDSs (intracellular dissipative structures such as ion gradients); the receiver = the cell. Conformons are the packets of mechanical energy or conformational strains entrapped in local sites within biopolymers, thus carrying free energy and genetic information that are both necessary and sufficient to drive all goal-directed molecular processes inside the cell (Ji 1974a, b, 2000) (Sect. 8.1). The key postulate underlying the model is that the information generated in Step 1 is utilized to produce *n* conformons in an enzyme, each of which being capable of driving one elementary step in enzymic catalysis, Step 3, leading to the production of IDSs, Intracellular Dissipative Structures (Chap. 9), which are postulated to be the immediate causes (or driving forces) for all cell functions

It was postulated in Ji (1985a, b) that the genetic information of an enzyme is not *homogeneously* distributed within the enzyme but *heterogeneously* distributed as a part of *conformons*, defined as the discrete units of *mechanical energy* and *genetic information* (i.e., the information that is transmitted from one cell generation to the next). Conformons are postulated to be responsible for all goal-directed molecular motions (e.g., chromosome remodeling) and processes (e.g., enzymic catalysis, active transport, muscle contraction) in the cell (Chap. 8). Based on a protein-centered model of biological evolution schematized in Fig. 11.22, it was possible to derive Eq. 11.19 that can be used to estimate the number of amino acid residues constituting one conformon within an enzyme (Ji 1990, pp. 198–200) (see Table 11.8 for more details):

$$n!/(n-x)! = 20^{n/p} \tag{11.19}$$

Table 11.8 The components of the communication system modeling biological evolution

System components	Identification (see Fig. 11.22)
Source of messages	Biological evolution regulating the linear sequence of amino acids of enzymes through DNA and RNA (see Step 1)
Channel	Polypeptides, conformons, IDS (see Steps 2 and 3)
Receiver	The living cell (see Step 4)

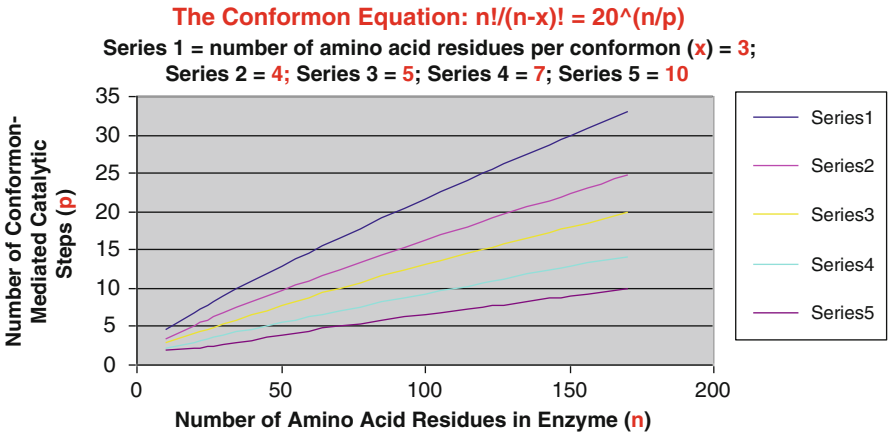


Fig. 11.23 A numerical simulation of the *conformon equation* derived from the model of biological evolution shown in Fig. 11.22. See text for more details

where n = the number of the amino acid residues of an enzyme; x = the number of the amino acid residues constituting a conformon that participates in (or are essential for) a catalytic act such as binding, de-binding, covalent rearrangement, free energy storage, and free energy transfer; and p = the maximum number of the conformon-mediated catalytic steps within an enzyme molecule. For convenience, Eq. 11.19 will be referred to as the "conformon equation." Inserting into the *conformon equation* a set of reasonable numerical values for a typical enzyme, i.e., n = 150 and p = 10, it is found that the average number of the amino acid residues constituting one conformon is approximately nine (see Table 2 in Ji 2000). This appears to agree with the number of the evolutionarily conserved residues involved in numerous enzymic functions described in Lockless and Ranganathan (1999), Süel et al. (2003), Poole and Ranganathan (2006). The results of a more systematic calculation based on Eq. 11.19 are depicted in Fig. 11.23, from which it is clear that the following generalization can be made:

> The number of conformon-mediated catalytic steps are directly proportional to the number of the amino acid residues constituting an enzyme and inversely proportional to the number of the amino acid residues constituting a conformon. (11.20)

According to Fig. 11.23, a polypeptide with 40 amino acid residues catalyzing three catalytic processes will have three *conformons*, each comprising 10 amino acid residues (see the lower left region of Series 5 in Fig. 11.23). If there is no overlap among the amino acid residues that constitute two different conformons, the maximum number of amino acid residues required to generate three conformons would be 30. If an overlap is allowed, the maximum number would be less than this number, leading to the prediction that at most 75% of the amino acid residue of the 40-mer polypeptide should be evolutionarily conserved. This prediction seems to be in agreement with the observation reported by Socolich et al. (2005): Multiple sequence alignments of the 120 members of the WW domain family revealed that about 50% (i.e., 17 out of 36) of the amino acid residues of WW domains is evolutionarily conserved. These conserved residues exhibited the SCA (statistical coupling analysis) conservation scores greater than 0.5, the background level (see Fig. 1b in Socolich et al. 2005). The discrepancy between the predicted value of 75% and the observed one of 50% may simply indicate that

> An amino acid residue at a given locus on a polypeptide chain can participate in producing more than one conformons. (11.21)

Statement 11.21 is reminiscent of the piano keys (*amino acid residues*) which can be struck (at different times) to produce more than one musical sounds or melodies (analogous to *conformons*). We may refer to Statement 11.21 as the *conformon composition rule*, which can be more generally stated as follows:

> Conformons are generated in a biopolymer from a set of evolutionarily conserved elements (amino acid residues or nucleotides) that are combinatorially arranged in space and time, just as musical melodies are generated from the combinatorial arrangements of musical notes in time. (11.22)

Just as producing melodies requires a pianist's expending energy by striking a select set of right keys in a right temporal order, it is clear that generating a conformon in a conformer of an enzyme by selecting a set of right amino acid residues arranged in space and time must be paid for by some exergonic processes such as ligand binding/de-binding and electronic rearrangements (known as chemical reactions). From the bioenergetics point of view, the production of a conformon requires coupling two partial processes – one endergonic (free energy-consuming) and the other exergonic (free energy supplying) (see Fig. 11.30 for more details).

The fundamental assumption made in deriving the *conformon equation* simulated in Fig. 11.23 can be stated as follows:

> The information (secondary message) required to order amino acid residues in space and time to produce conformons within an enzyme cannot be greater than the amount of the genetic information (primary message) encoded in the primary structure of the enzyme. (11.23)

Statement 11.23, if proven to be true, may be referred to as the *Principle of Information Conservation Principle* (PIC), in analogy to the *Principle* of *Energy Conservation* (PEC) in thermodynamics.

In view of the importance of the concept of the *conformon* in interpreting single-molecule data of Lu et al. (1998) to be presented in Sect. 11.3.3, the step-by-step derivation of the *conformon equation*, Eq. 11.19, is thought to be important enough to be reproduced below from Ji (1990, pp. 197–200) (replacing the original figure numbers with the corresponding ones from this chapter and adding a new table):

> To estimate the information content of conformons, it is necessary to postulate a communication system that links the source of message to the receiver through a channel (Pierce 1980). The communication system of our interest is schematically shown Fig. 11.22, and the various components of the systems are identified in Table 11.8.
>
> To calculate the Hartely information content of any message, it is necessary to know the number of all possible messages (W_0) and the number of messages actually selected (W). Then the average information content (I) of a message is given by
>
> $$I = \log_2(W_0/W) \tag{1}$$
>
> Equation (1) can be derived from Shannon's formula (Pierce 1980) by assuming that all messages have equal probability of selection. I is maximum when W = 1;
>
> $$I = \log_2 W_0 \tag{2}$$
>
> Applying Eq. (2) to Step 1 in Fig. 11.22, it is clear that the maximum information content of the primary message (I_p) is
>
> $$I_p = \log_2 m^n \tag{3}$$
>
> where m = the number of different amino acids and n = the number of amino acid residues constituting an enzyme. We assume that all of the information contained in the primary message, I_p, is transduced into the information content of conformons, each conformon consisting of an alignment of x amino acid residues (out of n) into a transient (i.e., kinetically labile and metastable) structure at the active site of an enzyme (see Step 2). The maximum information content of one conformon can then be estimated on the basis of two further assumptions: (1) all conformons are unique (i.e., no degeneracy) and (2) the maximum number of conformons consisting of x amino acid residues out of a polypeptide chain of n amino acid residues can be calculated as
>
> $$W_0 = n!/(n - x)! \tag{4}$$
>
> Inserting Eq. (4) into Eq. (2) leads to the maximum information content of one conformon:
>
> $$I_{conformon} = \log_2[n!/(n - x)!] \tag{5}$$
>
> If all the primary information is transduced into p conformons, we have
>
> $$\begin{aligned} I_p &= p \cdot I_{conformon} \\ &= p \cdot \log_2[n!/(n - x)!] \end{aligned} \tag{6}$$
>
> From Eqs. (3) and (6), one obtains
>
> $$[n!/(n - x)!]^p = m^n \tag{7}$$

If the value of the number of amino acids has been stable at 20 during most of the biological evolution, Eq. (7) can be rewritten as

$$[n!/(n-x)!]^p = 20^n \tag{8}$$

Using Eq. (8), the maximum number of conformons, p, that can be generated within a typical enzyme of 150 amino acid residues can be estimated, if the value of x is taken to be typically 5–10, in agreement with the recent findings of A. Fehrst (1985) that 12 amino acid residues participate in the active site of tyrosyl t-RNA synthase.

$$[150!/(150-10)!]^p = 20^{150} \tag{9}$$

Eq. (9) is satisfied when $p = 9.02$, or 9. Therefore, the maximum information content of one conformon, from Eq. (6), is

$$\begin{aligned} I_{conformon} &= I_p/p \\ &= \left(\log_2 20^{150}\right)/9 \\ &= 653/9 = 73 \text{ bits} \end{aligned} \tag{10}$$

If we assume that the value of x is 5 instead, the same calculation leads to

$$I_{conformon} = 36 \text{ bits} \tag{11}$$

Therefore, we conclude that the information content of one conformon may be in the range of 40–80 bits.

Equation (8) is the same as Eq. 11.19, the *conformon equation*, which has allowed us to estimate the maximum information content of a conformon to be 40–80 bits.

The maximum *free energy* content of a conformon can also be estimated. Since the synthesis of one molecule of ATP in mitochondria is known to require about 16 kcal/mol of free energy and since it takes at least one conformon to couple the redox reaction of the respiratory chain and the phosphorylation reaction of ADP catalyzed by ATP synthase, it would follow that the maximum free energy content of one conformon is 16 kcal/mol (Ji 2000). If the number of steps coupling respiration and phosphorylation is x, then the average free energy content of one conformon would be reduced to 16/x kcal/mol. With $x = 10$, the free energy content of one conformon would be 1.6 kcal/mol. Hence it may be reasonable to conclude that the free energy content of one conformon ranges between 2 and 16 kcal/mol (see Table 2 in Ji 2000).

11.3.3 Isomorphism Between Blackbody Radiation and Enzymic Catalysis

At a first glance, there seems to be little connection between *blackbody radiation* (i.e., the study of the relation between the intensity of the light emitted from an object as a function of wavelength and temperature) and *enzymic catalysis*. The distance between these two topics is so vast that it is not surprising that more than one

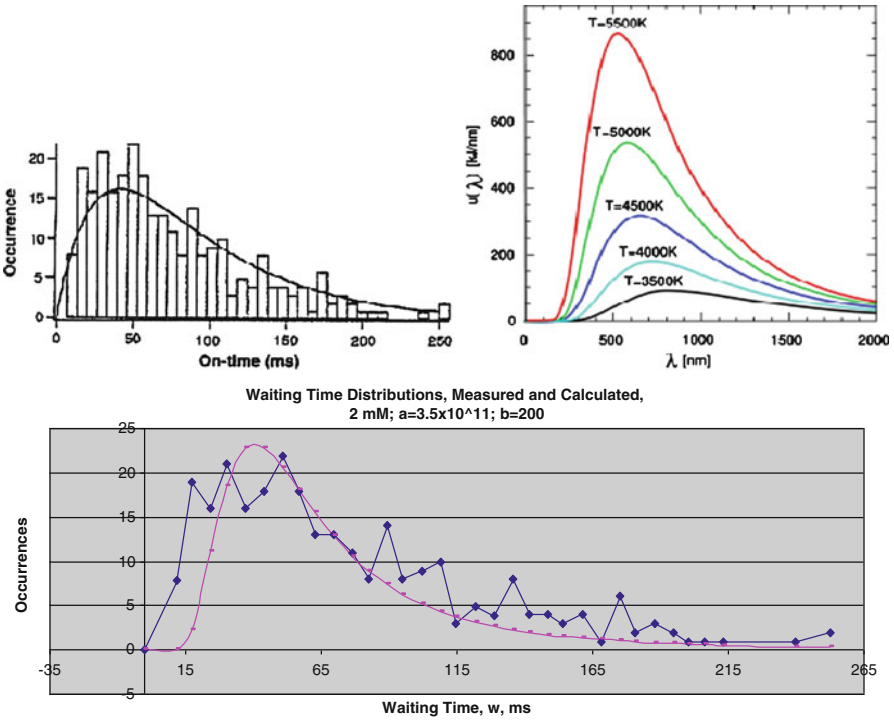


Fig. 11.24 The waiting time distribution (or histogram) of one molecule of cholesterol oxidase (COx) at the substrate concentration of 2 mM (Adapted from Fig. 1d in Lu et al. 1998). (*Upper*) The *solid line* (*left panel*) was derived from Eq. 11.25 with $k_1 = 33 \pm 6\ s^{-1}$, $k_2 = 17 \pm 2\ s^{-1}$, and $k_1 = 0$. The blackbody spectrum (*right panel*) was reproduced from *http://schools-wikipedia.org/images/705/70552.png.htm*. (*Lower*) The *smooth curve* derived from Eq. 11.27, with $a = 3.5 \times 10^5$, $b = 200$, and $X(w) = 0$. [Cholesterol] = 2.0 mM

statistical mechanicians with whom I had occasions to discuss this topic at the 100th Statistical Mechanics Conference held at Rutgers in 2008 (Ji 2008b) showed either no interest or even negative reactions. The purpose of this section is to present theoretical and experimental evidence that supports the following two conclusions:

1. Both blackbody radiation and enzymic catalysis can be viewed as resulting from *thermal excitation* of systems of *molecular oscillators*. Viewing an enzyme as a collection of oscillators is in agreement with the prediction made in Ji (1974a):

   Given all the vibrational frequencies of the individual bonds in an enzyme, as well as their three-dimensional arrangements, we can in principle deduce the thermodynamic and catalytic properties of the enzyme under any conditions. (11.24)

2. The waiting time distribution data of Lu et al. (1998), Figs. 11.18 and 11.24, can be accounted for in terms of a *quasi-deterministic* equation, Eq. 11.27, consisting of (a) a deterministic (or synchronic; see Table 4.2 for the definition of "synchronic" and "diachronic") term isomorphic with the Planck's radiation

formula, Eq. 11.26, and (b) a nondeterministic (or diachronic) term reflecting the genetic information embodied in *conformons* (discussed in Sect. 11.3.2).

The key observations reported by Lu et al. (1998) on cholesterol oxidase (COx) are as follows:

(A) The rate constant (or turnover time) of a COx molecule is not constant (as was generally believed prior to the Lu et al. 1998 experiments) but changes after each cycle of catalysis more or less randomly, ranging from tens of milliseconds to seconds (Figs. 11.18, 11.24). This phenomenon is known as "dynamic disorder" (Zwanzig 1990) or "dynamic heterogeneity." The histogram of these waiting times is *asymmetric* and *rugged* (uneven, zigzag, saw tooth-shaped) as evident in Figs. 11.18 and 11.24. The *ruggedness* of the waiting time histogram (defined as the difference between the measured waiting times and the theoretical waiting times calculated from a *smooth curve* that best fits the histogram) can be either due to *experimental error* or , at least in part, to *biological causes*. Lu et al. (1998) found one *smooth* mathematical function called the probability distribution function, p(t), i.e., Eq. 11.25, that fits the waiting time histogram reasonably well (see the upper left-hand panel in Fig. 11.24) but cannot model the ruggedness of the histogram. The conformon-based theory of single-molecule enzymology to be described below can account for both the *smooth* and *rugged* portions of the waiting time histograms.

(B) Increasing the cholesterol concentration by tenfold from 0.2 to 2.0 mM decreased the longest waiting times measured by tenfold and the mode (i.e., the ordinate value under the peak of the distribution curve) of the waiting time by about fourfold (from 150 to 40 ms).

(C) Pairs of waiting times separated by m turnovers are correlated as long as m is less than about 10 (see Fig. 3 in Lu et al. 1998). This observation is known as the "memory effect."

(D) The spectral mean (i.e., the average wave number or wavelength of the fluorescence emission of FAD) of a COx molecule fluctuates by about 1.5% around the mean (see Fig. 5a in Lu et al. 1998).

(E) The autocorrelation function of *waiting times* and that of the *spectral means* are similar (see Fig. 4a, b in Lu et al. 1998).

The clue to explaining these observations mechanistically was provided by the unexpected finding that the waiting time distributions of cholesterol oxidase, Observations **A** and **B**, could be modeled using an equation similar in form to *Planck's radiation formula* derived from the blackbody spectrum (see the lower panel of Fig. 11.24). A detailed analysis of this finding (as outlined in Table 11.9 below) led me to conclude that the *conformon theory of enzymic catalysis* developed in Ji (1974a, b, 1979, 2000, 2004a) applies to cholesterol oxidase. In other words, the single-molecule enzymological data on cholesterol oxidase reported by Lu et al. (1998) can be accounted for by the conformon theory of molecular machines as detailed in Table 11.10. Again, conformons are defined as the sequence-specific conformational strains of biopolymers (proteins, RNA, and

Table 11.9 A comparison between blackbody radiation and enzymic catalysis. For a more detailed discussion of this table, see Footnote 5 in Table 11.10

	Blackbody radiation	Enzymic catalysis
1. Experimental observation	Asymmetric bell-shaped distribution of radiation intensity as a function of wavelengths, $\lambda \sim 1{,}860$	*Asymmetric* bell-shaped and *rugged* histograms of the frequency of catalytic rate constants as a function of waiting times, w. (Lu et al. 1998)
2. System of	$\sim 10^{27}$ oscillators	$\sim 10^{3}$ oscillators
3. System dimension	~1 m	~1 nm
4. Temperature, K	3,000 ~ 5,000	~300
5. Difference	Heat energy, E, absorbed (or emitted) by blackbody under measurement	Rate constant, k, of the enzyme molecule inferred from the measured lifetimes of the fluorescence of the COx coenzyme, FAD
6. Variables[a]	$\lambda \sim 1/E$, or $E = hc/\lambda$	$k \sim 1/w$, or $w \sim 1/k$
7. Formula[a]	$u(\lambda) = (8\pi hc\lambda^{-5})/(e^{hc/\lambda k\_BT} - 1)$	$f(w) = (aw^{-5})/(e^{b/w} - 1)$ $a = 3.5 \times 10^{11}$(or 4.0×10^{14}) $b = 2.0 \times 10^{2}$ (or 6.5×10^{2})
8. Theory[a]	$n(E)\Delta E = g(E)f(E)\Delta E = g(E)e^{-E/k\_BT}\Delta E$	$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$ $k \approx e^{-\Delta G\ddagger/k\_BT} = e^{\Delta S\ddagger/k\_B}e^{-\Delta H\ddagger/k\_BT}$
9. Density of states determined by	External constraints (i.e., the geometry of the blackbody cavity, i.e., boundary conditions)	Internal constraints (i.e., the primary, secondary and tertiary structure of the COx molecule)
10. Isomorphism	λ E g(E) e^{-E/k_BT}	w k $e^{\Delta S\ddagger/k\_B}$ $e^{-\Delta H\ddagger/k\_BT}$
11. Conclusion	*Quantization* of radiation energy (*photons*)	*Selection/quantization* of conformational strains, called *conformons* (Ji 1974a, b), based on their ability to control both (a) the size of rate constants of the enzymic reactions they catalyze and (b) the probability of the occurrence of the rate constants. It is assumed that (a) is determined by the *energy content* and (b) by the catalytic *information content* of *conformons*

[a]Symbols are defined as follows: λ = wavelength, E energy, h = Planck constant, c = the speed of light, k = rate constant, w = waiting time, u = a function, k_B or k_B = the Boltzmann constant, f = another function, a, b = constants, T = temperature, $\Delta S^{\ddagger}$ = the entropy of activation, $\Delta H^{\ddagger}$ = the enthalpy of activation, $\Delta G^{\ddagger}$ = the Gibbs free energy of activation, and g = a function

Table 11.10 The suggested explanations of the single-molecule enzymological observations on cholesterol oxidase based on the conformon theory of molecular machines. Extensive footnotes are provided below, numbered 1–10

Observations of Lu et al. 1998	Explanations based on the Conformon Theory of Molecular Machines (Ji 1974b, 2000)
A *Asymmetric waiting time distribution, or dynamic disorder* (Zwanzig 1990)	1. The enzymic activity of COx is supported in part by the heat absorbed by its covalent and non-covalent bonds acting as molecular oscillators just as the blackbody radiation is supported by a system of molecular oscillators, both obeying the Bose-Einstein statistics rather than the Boltzmann statistics (see 5) 2. The *deterministic* shape (or the smooth portion) of the waiting time distribution is due to different content of the *mechanical energy* stored in the conformons of the COx molecule in its ground state (Fig. 11.28) 3. *The nondeterministic* shape (or the rugged portion) of the waiting time distribution (see Fig. 11.24) is attributed to the different *catalytic negentropy* (Ji 1974a) encoded in the evolutionarily conserved amino acid residues constituting conformons (see 2)
B *Concentration dependence of waiting times*	4. The formation of the *real* conformons in COx at the Franck-Condon state depends on the substrate binding–induced stabilization of *virtual* conformons, an example of the *Circe* effect (Jencks 1975) (see Fig. 11.30), and binding interactions are concentration dependent
C *Autocorrelation among waiting times*	5. Within the lifetime of a conformer, more than one cycle of catalysis can take place, each cycle involving the thermal activation of a ground-state (or *static*) conformon to *dynamic* conformons at the Franck-Condon (FC) state and the relaxation of the *dynamic* conformon back to its original or closely related *static* conformons or to another conformer. "Static" and "dynamic" conformons are defined in (**7**) below
D *Fluctuations of the spectral mean*	6. The fluorescence efficiencies of FAD and $FADH_2$ (Fig. 11.16) depend on the conformational states of FAD and $FADH_2$ which are in turn influenced by the conformational state of the binding pocket of the COx molecule
E *Similarity between the autocorrelation functions of waiting times and spectral means*	7. The conformational state of the binding pocket of the COx molecule affects not only the spectral means of the fluorophores but also the cycling between *static* and *dynamic* conformons at the active site of the COx molecule

DNA) deemed *necessary* and *sufficient* to drive all goal-directed molecular motions inside the cell (see Chap. 8 and Sect. 11.3.2).

1. Lu et al. (1998) derived a mathematical equation, Eq. 11.25, to fit the waiting time distribution data of cholesterol oxidase shown in Figs. 11.17, 11.18, and 11.24. More recently Prakash and Marcus (2007) attempted to provide possible molecular mechanisms underlying the *dynamic disorder* phenomenon and the similarity

between the autocorrelation functions of waiting times and spectral means utilizing the concepts of "electrostatic interaction energy" and "solvatochromism." The theory of the COx waiting time distribution proposed here based on the *analogy between blackbody radiation and enzymic catalysis* (Ji 2008a) can provide qualitative molecular mechanistic explanations for all of the observations listed in Table 11.10.

Both the Xie and the Marcus groups agree that the waiting time fluctuations of COx are the result of the conformational fluctuations of the COx molecule. The Xie group made the assumption that different conformations of the COx molecule somehow give rise to different waiting times, without proposing any realistic molecular mechanisms responsible for coupling COx conformational states and the waiting time variations of its coenzyme, FAD. Given this assumption and the additional assumption that the Michaelis-Menten mechanisms shown in Schemes (11.16) and (11.17) hold for single-molecule enzymes, Xie and his coworkers derived the *probability distribution function* for waiting times:

$$p(t) = k_1 k_2/(k_2 - k_1)\left(e^{-k\_1t} - e^{-k\_2t}\right) \tag{11.25}$$

where p(t) is the probability of observing turnover time t and k_1 (or k_1) and k_2 (or k_2) are the time-dependent rate constants appearing in Scheme (11.16). The fitting of Eq. 11.25 to measured waiting time distribution is shown in the upper left panel of Fig. 11.24 (Lu et al. 1998).

Prakash and Marcus (2007) assumed that the *conformations* (i.e., the three-dimensional structure of a protein that can be altered without breaking or forming covalent bonds, Sect. 11.3.2) of a COx molecule, denoted as X(t), can fluctuate on the milliseconds to seconds timescale, despite the fact that the dynamics of proteins in general occurs on timescales ranging from tens of femtoseconds (10^{-15} s) to seconds (Prakash and Marcus 2007, p. 15984; Kurzynski 1997, Fig. 1). Their reasoning proceeds as follows:

(a) Fluctuations in X(t)

⇩

(b) Fluctuations in the "local electrostatic interaction energy at the active site, E(t)"

⇩

(c) Dynamic disorder and fluctuations in spectral means,

where the symbol "⇩" reads "leads to" or "causes." Given these assumptions, Prakash and Marcus (2007) derived the autocorrelation functions for waiting time distributions and for spectral mean fluctuations that are similar, in agreement with observation **E** (Table 11.10). However, it should be pointed out that Prakash and Marcus (2007) did not provide any explanation as to (a) how the slow conformational fluctuations of COx, namely, X(T), can arise in the first place in

view of the rapid oscillatory motions of peptide bonds, and (b) how X(t) mediates the reduction of FAD to $FADH_2$, which probably takes place on the femtosecond timescale, thus implicating the coupling between two events whose time constants differ by a factor of about 10^{10}. In contrast, the theory based on (a) the analogy between blackbody radiation and enzymic catalysis and (b) the generalized Franck-Condon principle (discussed in Sect. 2.2.3) can provide qualitative answers to both these questions (see **D** and **E** in Table 11.10 and (5) below).

2. In 2008, I noticed the similarity between the waiting time distribution of COx enzymic activity reported by Lu et al. (1998) and the blackbody spectrum (see the upper two panels in Fig. 11.24). (http://www.nationmaster.com/encyclopedia/Planck%27 s-law-of-blackbody-radiation). The similarity between the histogram given on the upper left-hand corner and the blackbody spectrum measured at 4,500 K shown in the upper right-hand corner of Fig. 11.24 is particularly striking. This observation motivated me to use Planck's radiation formula (Nave 2009), Eq. 11.26, generalized in the form of Eq. 11.27 (with the X(w) term set to zero), to model the waiting time distribution of Lu et al. (1998), leading to the result shown in the lower portion of Fig. 11.24 (see the smooth curve marked with squares).

The Planck radiation formula which successfully accounted for the blackbody spectrum in 1900 is given in Eq. 11.26 (Nave 2009):

$$u(\lambda, T) = \left(8\pi hc/\lambda^5\right)/\left(e^{hc/\lambda k_B T} - 1\right) \tag{11.26}$$

where $u(\lambda, T)$ is the *spectral energy density*, i.e., the intensity of radiation emitted or absorbed at wavelength λ by the blackbody wall when heated to T K; h is the Planck constant; c is the speed of light; and k_B is the Boltzmann constant.

The equation derived in Ji (2008b) on the basis of the analogy between blackbody radiation and enzymic catalysis is given in Eq. 11.27:

$$p(w) = \left(aw^{-5}\right)/\left(e^{b/w} - 1\right) + X(w) \tag{11.27}$$

where p(w) is the frequency (or probability) of the occurrence of waiting time w, a and b are constants with numerical values of 3.5×10^5 and 2×10^2, respectively, and X(w) is a *nondeterministic* function of w.

It should be noted that Eq. 11.26, which is based on the Bose-Einstein statistics, reduces to Eq. 11.28, known as the Wien's law (Kragh 2000), which is based on the Boltzmann statistics, if the exponential term is much greater than unity:

$$u(\lambda, T) = \left(8\pi hc/\lambda^5\right)e^{-hc/\lambda k_B T} \tag{11.28}$$

Equation 11.27 can also be reduced to a form similar to Eq. 11.28, if $X(w) = 0$ and the $e^{b/w}$ term is much greater than unity, but calculations showed that the exponential term was not much greater than 1 and hence Eq. 11.27 could not be simplified. As explained by Kragh (2000), the Wien's law fitted the short-wavelength portion

of the blackbody spectrum perfectly but underestimated the emission intensities at the long-wavelength regions. It was in an attempt to remedy this shortcoming that Planck was led to invoke the concept of "energy quanta," which allowed him to derive his radiation law, Eq. 11.26. In effect, Planck demonstrated that the blackbody radiation data are better explained in terms of the Bose-Einstein statistics than in terms of the Boltzmann statistics.

Equation 11.27 consists of two terms, referred to as the "deterministic" and "nondeterministic" terms. These could be equally well referred to as "synchronic" and "diachronic" terms, respectively (for the definitions of "synchronic" versus "diachronic" information, see Table 4.1). The deterministic term is isomorphic with Planck's radiation formula, Eq. 11.26. It is important to point out that neither Lu et al. (1998) nor Prakash and Marcus (2007) discussed the possibility of including any *nondeterministic* (also called *diachronic* or *arbitrary*) term, X(w), in their equations, probably because they assumed, as most biological theorists do, that all biological data, including the waiting time distribution histogram, should fit *deterministic equations* as long as they are noise free. Under such an assumption, any experimental data that do not fit deterministic equations such as Eqs. 11.25 and 11.26 would be *logically* regarded as noise and hence automatically excluded from any theoretical considerations. In contrast, it is here assumed that:

(a) The nondeterministic (or *diachronic* or *arbitrary*) term, X(w), which is defined by Eq. 11.27 as the difference between the measured and the predicted values of w, is too large to be discounted as noise (as seems evident in the lower panel of Fig. 11.24).
(b) The nondeterministic term, X(w), in fact carries biological information (yet to be determined and hence the symbol X), most likely encoded in the *evolutionarily conserved set of amino acid residues* constituting conformons. By "evolutionarily conserved set of amino acid residues," I mean something similar to the "evolutionarily coevolving amino acid residues" found in the WW domains by Lockless and Ranganathan (1999), Süel et al (2003), Socolich et al. (2005), and Poole and Ranganathan (2006).

3. One possible mechanism by which the *evolutionary information* encoded in a conformon can influence the probability of the occurrence of a given waiting time w is described in Table 11.11. This table is constructed on the basis of the relations among *configurations*, *conformers*, and *conformons* described in Fig. 11.21. Waiting time, w, is postulated to be determined by *conformers* denoted as $(\ldots)_A$, $(\ldots)_B$, and $(\ldots)_C$ in Column (2), which is consistent with the postulated mechanism of enzymic catalysis described in the right-hand panel of Fig. 11.28. Please note that three different conformers, A, B, and C, are associated with three different waiting times, 51, 56, and 63 ms, as shown in Column (2), and Column (4) lists the numerical value of the deterministic component of the probability of the occurrence of w calculated from Eq. 11.27 with X(w) set to zero. Column (5) lists the numerical values of the nondeterministic component of Eq. 11.27 calculated as the difference between the measured probability value minus the deterministic component, and these differences are attributed to the differences in (or the arbitrariness of) the *evolutionary*

Table 11.11 The catalytic function of the *evolutionary information* carried by conformons generated in different conformers of an enzyme consisting of *n* amino acids. The numerical data appearing in Columns (2), (4), and (5) are experimental values read off from the *x*- and *y*-coordinates of the three pairs of p(w) values centered at the *x*-coordinate of 56 in the lower panel of Fig. 11.24, except the numbers in parentheses in Column (5).N = the number of amino acid residues in Cox. The numbers in Column (3) indicate the position of the (arbitrarily chosen) amino acids in a protein that are thought to constitute a conformon. The number in green indicates the amino acid residue thought to be common to the conformons belonging to a set of functionally related conformers. The numbers in the parentheses in Column (5) are hypothetical

1. Configuration[a]	2. Conformers (w)	3. Conformons[a]	4. Deterministic component of p(w)[b]	5. Nondeterministic component of p(w)
1, 2, 3, . . ., *n*	$(1, 2, 3, \ldots, n)_A$ (51)	(. . . 12, 35, 60, 100, 120, . . .)$_A$	20	(+1.9)
		(. . . 10, 35, 60, 100, 120, . . .)$_A$	20	+2.0
		(. . . 10, 35, 60, 100, 125, . . .)$_A$	20	(+1.8)
	$(1,2, 3, \ldots, n)_B$ (56)	(. . . 45, 55, 60, 111, 128, . . .)$_B$	18	(0)
		(. . . 45, 55, 60, 111, 155, . . .)$_B$	18	0
		(. . . 50, 55, 60, 111, 155, . . .)$_B$	18	(0)
	$(1, 2, 3, \ldots, n)_C$ (63)	(. . . 6, 10, 60, 125, 142, . . .)$_C$	15	(−1.3)
		(. . . 6, 10, 60, 125, 110, . . .)$_C$	15	−2.0
		(. . . 9, 10, 60, 125, 110, . . .)$_C$	15	(−1.9)

[a] See Sect. 3.2 for the definitions of "configurations" and "conformations"
[b] Read off from Fig. 11.24

information carried by conformons depicted as different patterns of amino acid sequences organized in the active site of an enzyme in a given conformation, as illustrated in Column (3). The following points are important to note in connection with Column (3):

(a) A protein consisting of n amino acid residues can generate more than one conformers, designated as $(1, 2, 3, \ldots, n)_A$, $(1, 2, 3, \ldots, n)_B$, etc., in Columns (2) and (3) in Table 11.11, where values within parentheses symbolize the three-dimensional arrangement of the amino acid residues.

(b) *A conformer can generate more than one conformon*, each generated by activating or spatiotemporally ordering a set of, say, five amino acid residues at the active site (see the different sets of five numbers listed within the parentheses in Column 3). All the conformons belonging to a conformer share a subset of say three amino acid residues in common (residues 35, 60, and 100 for Conformer A; residues 55, 60, and 111 for Conformer B; etc.). The conformons belonging to the set of functionally related conformers given in Column (2) share one amino acid residue in common, i.e., residue 60.

(c) A *conformer* is associated with one waiting time as indicated in Column (2) and hence with one value of the probability of occurrence, p(w), as shown in Column (4), thus giving rise to the deterministic component of Eq. 11.27. In contrast, *conformons*, depending on their amino acid residues shown in Column (3), can modulate the probability of the occurrence of w either positively (Rows 2 and 4 in Column 5), negatively (Rows 8 and 10, Column 5), or not at all (Rows 5 and 7, Column 5), thus engendering the nondeterministic term in Eq. 11.27. That is, it is suggested here that *conformers* account for the deterministic term while the genetic information determines the non-deterministic term. This introduces an *extra degree of freedom* for an enzyme to regulate its activity and this extra degree of freedom is identified as a part of the "evolutionary information" discussed by Socolich et al. (2005), "catalytic information," or "catalytic negentropy" discussed in Ji (1974a) (more at (7) below).

(d) The similarities among the numbers in Column (4) of Table 11.11 reflect the similarities among the amino acid sequences of the conformons in Column (3). Thus the amino acid sequence constituting the core of conformons belonging to Conformer A (i.e., 35, 60, 100) is more similar in structure (or closer in what may be referred to as the *conformon space*, an abstract space wherein each point represents one conformon within an enzyme) to Conformon B (i.e., 55, 60, 111) than is Conformon C (i.e., 10, 60, 125), and so are the corresponding p(w) values given in Column (4), i.e., 20 is closer to 18 than is 15. Similar correlations hold between Column (3) and Column (5): The amino acid residues constituting conformons belonging to Conformer A are more tightly centered on (35, 60, 100) than are those constituting the conformons belonging to Conformer C around (10, 60, 125). Consequently, the values of the nondeterministic component of Eq. 11.27 due to the conformons belonging to Conformer A are more tightly centered around +2.0 than are those due to the conformons belonging to Conformer C centered around −2.0.

(e) In calculating the numerical values given in Columns (4) and (5) in Table 11.11, it is assumed that

The closer the *conformers* are in the *conformon space*, so are the values of the *deterministic component* of p(w); the closer the *conformons* are in the conformon space, so are the values of the *non-deterministic* component of p(w). (11.29)

The *conformon space* is characterized by both *energy* (expressed in terms of the familiar Gibbs free energy, $G = E + PV - TS$) and *information* (expressed in terms of the "evolutionary information" of the kind discussed by Socolich et al. (2005), i.e., "sequence information", or "genetic information") and hence belong to the general class of what was referred to as Gnergy Space, gnergy being defined as a complementary union of information and energy (Sects. 2.3.2 and 4.9).

(f) The amino acid sequences given in Column (3) specify the conformons belonging to a conformer, C_i, of an enzyme at its ground state, which undergoes thermal excitation/activation in the time span of t_{ie} (e standing for excitation or

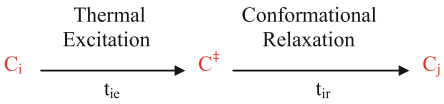


Fig. 11.25 The thermal excitation of ground-state and the relaxation of the transition-state conformations of an enzyme during a catalytic cycle. C_i and C_j are the ith and jth conformational states (or conformers), respectively, and $\mathbf{C}^{\ddagger}$ is the *common* transition state of the enzyme (Fig. 11.28). The symbols t_{ie} and t_{jr} stand for, respectively, "the ith excitation time" or the time required for the conformational transition from C_i to $C^{\ddagger}$ and "the jth relaxation time" or the time taken for the conformational transition from $C^{\ddagger}$ to C_j

activation) to reach the common transition state, $C^{\ddagger}$ (see Fig. 11.28). After catalysis, $C^{\ddagger}$ must relax, in the time span of t_{jr} (r standing for relaxation), back to a ground state, C_j, where j can be equal to or different from C_i (see Fig. 11.25). If the lifetime t_i of C_i is longer than the sum of t_{ie} and t_{jr}, i.e.,

$$t_i = a\left(t_{ie} + t_{jr}\right) \tag{11.30}$$

where a is a positive constant greater than unity, there is a high probability that $C^{\ddagger}$ will relax back to C_i or to C_j where j is in the neighborhood of i. This would provide one possible mechanism to account for the "memory effect," Observation C, in Table 11.10, the observation that long waiting times are likely to be followed by long waiting times and short waiting times are likely to be followed by short waiting times, since $C^{\ddagger}$ is more likely to relax back to C_i than to C_j.

4. Assumption (a) in (2) is experimentally testable. If this assumption is proven to be invalid, the waiting time distribution of Lu et al. (1998) can be completely accounted for *deterministically*, i.e., based on the laws of physics (see Row 3, Table 4.1), either by Eqs. 11.25 or 11.27 with X(w) set to zero. If Assumption (a) is proven to be valid, then the waiting time distribution of Lu et al. (1998) cannot be completely accounted for based on the laws of physics alone (i.e., in terms of *synchronic* laws alone as defined in Table 4.1) but entails invoking additional laws or principles (e.g., *diachronic rules* in Table 4.1) reflecting the evolutionary history of living systems. In other words, if Assumption (a) can be validated by further experiments, it would be possible to conclude that the waiting time distribution of Lu et al. (1998) embodies two orthogonal sets of regularities referred to in Table 4.1 as *synchronic laws* and *diachronic rules*. Generalizing Eq. 11.27, it may be possible to make the following statements:

$$\text{Biological Phenomena} = \text{Synchronic Laws} + \text{Diachronic Rules} \tag{11.31}$$

Biological phenomena embody synchronic laws and diachronic rules that are orthogonal to each other. (11.32)

Evidently, Eq. 11.31 and Statement 11.32 combine both *inexorable* laws of physics and the *arbitrary* rules of biological evolution, reminiscent of the theory

of the *matter-symbol complementarity* advocated by Pattee (1996, 2001, 2008), which has alternatively been referred to as the *von Neumann-Pattee principle of matter-sign complementarity* (Ji 1999b). It is tempting to suggest that Statement 11.32 and similar generalizations be referred to as the *First Law of Biology* (FLB) in analogy to *First Law of Thermodynamics*. The so-called PCS (physics, chemistry, and semiotics) paradigm that is emerging in biology as discussed in Ji (2002a) and Barbieri (2003, 2008a, b, c) may also be viewed as an expression of FLB.

If FLB is true, it may provide a possible answer to the question raised by Frauenfelder in "Plenary Debate: Quantum Effects in Biology: Trivial or Not?" (Abbott et al. 2009):

> If we find a general law that determines or explains life, is it quantum mechanical or classical? (11.33)

If we assume that both quantum mechanics and classical mechanics have *synchronic* and *diachronic* aspects and that FLB indeed represents a general law of biology, applying Eq. 11.31 to the Question 11.33 would lead to the following answer:

> The general laws of life are compatible with both quantum mechanics and classical mechanics. (11.34)

In the thought-provoking debate reported in (Abbott et al. 2009), several participants raised questions of the same type as (11.33), namely, "Is it A or B?," when the most likely answer is "Both A and B." For convenience, we may refer to such questions as the *Frauenfelder questions*. In a less obvious way, the title question itself of the Gran Canaria Debate "Quantum Effects in Biology: Trivial or Not?" may be viewed as a *Frauenfelderian question*, and one possible answer to it may be stated as follows:

> Quantum effects in biology are both trivial and non-trivial, depending on the time and spatial scales involved. (11.35)

More specifically, since the spatiotemporal scales involved here are most likely related to quantum mechanical tunneling, the following generalization may be made:

> Quantum effects in biology are fundamental below the critical threshold of the space and time scales where quantum mechanical tunneling occurs and trivial above this threshold. (11.36)

A specific example of quantum mechanical tunneling playing an essential role in enzymology is provided by the electron transfer reaction between an electron donor, AH_2, and an electron acceptor, B, when they are brought close enough to each other through thermal fluctuations for the electron tunneling to occur (see b in Fig. 8.1).

Statement 11.36 can be viewed as an extension of the concept of the *thermal barrier* that separates macroscopic and molecular machines (Ji 1991, pp. 29–35) to the concept of what is here called the *quantum barrier* that separates molecule machines and quons (Herbert 1987) (i.e., the material entities that exhibit the

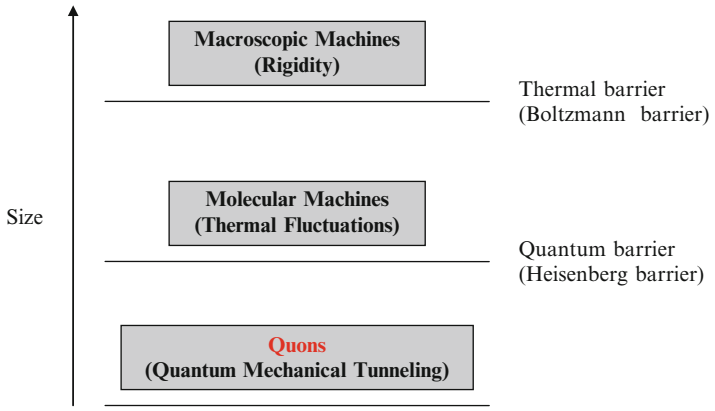


Fig. 11.26 The importance of the size of particles or material systems in determining their physical properties under physiological conditions. Macroscopic machines (e.g., computer) must be large enough to resist the thermal fluctuations of their component parts (to avoid short circuiting) but molecular machines (e.g., enzymes) must be (1) small enough to undergo thermal fluctuations under physiological conditions and yet (2) large enough to prevent, when necessary, the quantum mechanical tunneling of quons (e.g., electrons, protons, etc.) at their active sites. Thus *molecular machines* can be said to be separated from macroscopic machines by what has been referred to as the *thermal (or Boltzmann) barrier* (Ji 1991, pp. 29–35) and from quons by what may be referred to as the *quantum* (or *Heisenberg*) *barrier*

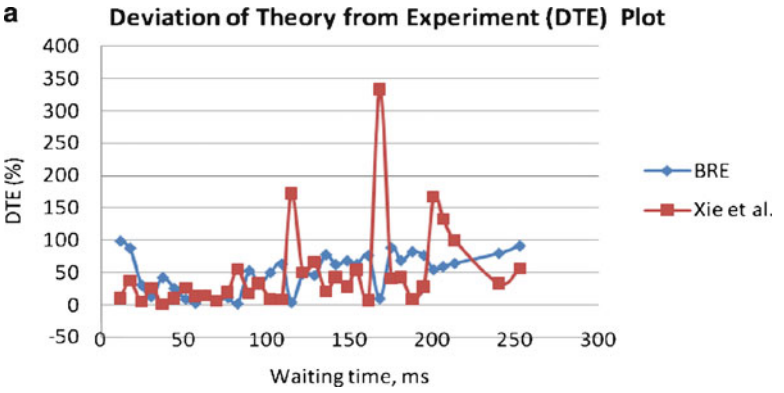
wave-particle duality and the quantum mechanical tunneling, including molecules, atoms, and subatomic particles). This idea is diagrammatically represented as shown in Fig. 11.26.

5. Having discussed the meaning of the nondeterministic term of Eq. 11.27 in some detail, we are now ready to tackle the meaning of the deterministic term of the equation, which will reveal, among other things, the fundamental role of *thermal fluctuations* in enzymic catalysis. As already pointed out, Eq. 11.27 with X(w) set to 0 fits the waiting time distribution fairly well, at least as well as Eq. 11.25 derived by Lu et al. (1998). To quantitatively compare the capabilities of Eqs. 11.25 and 11.27 to fit the experimentally measured waiting time distribution, the following quantity was defined as a measure of the *deviation of the theoretical predictions from measured data* called DTE (*Deviation of Theory from Experiment)*:

$$\mathrm{DTE} = \left(\left(\left(\text{Calculated w} - \text{Measured w}\right)/\text{Measured w}\right)^2\right)^{1/2}\Big) \times 100 \qquad (11.37)$$

DTE represents the absolute value of the deviation of the theoretically predicted w from the measured w expressed as a fraction of the measured w. Figure 11.27 shows the results of applying Eq. 11.37 to Eqs. 11.25 and 11.27. The average DTE values are about the same for these two equations but the standard deviations and the coefficients of variations are about twice as large for Eq. 11.25 as

a



b

Parameters	BRE	Xie et al.
Mean DTE (%)	49.0	49.5
Standard Deviations	30.5	65.9
Coefficient of variations (CV)	62.2	133.2

Fig. 11.27 The deviation of theory from experiment (DTE), the distances between the waiting times measured and those predicted as defined by Eq. 11.35. (**a**) (*Diamond*) Calculations were performed using the blackbody radiation-like equation (BRE) given in Eq. 11.27 with X(w) = 0. (*Square*) Calculations based on the distances between the measured and predicted values read off from Fig. 1d in Xie and Lu (1999). (**b**) A statistical comparison between the BRE and Xie et al. models

for 11.27 (see the table in Fig. 11.27b), indicating that BRE fits the single-molecule enzymological data better than the bi-exponential function of Lu et al. (1998).

The results shown in Fig. 11.27 indicate that Eq. 11.27 derived on the basis of the analogy between blackbody radiation and enzymic catalysis is superior to Eq. 11.25 derived on the basis of the Michaelis-Menten mechanism (Lu et al. 1998).

The interesting question that now arises is:

> What is the theoretical rationale, if any, for the apparent analogy between blackbody radiation and enzymic catalysis? (11.38)

The most important reason for the similarity between *blackbody spectrum* and the *waiting time distribution* of COx may be traced to the fact that both the blackbody wall and the enzyme molecule consist of *systems of molecular oscillators* (see Row 2 in Table 11.9). A blackbody is a system of approximately 10^{27} oscillators that are vibrationally and electronically excited from their common ground-state energy level, E_0, to various excited states denoted as E_i, where i runs from 0 to n, the total number of energy levels available to each oscillator (see the left panel in Fig. 11.28). On the other hand, the COx molecule is a system of about 10^5 atoms linked to form a three-dimensional network of covalent bonds forming

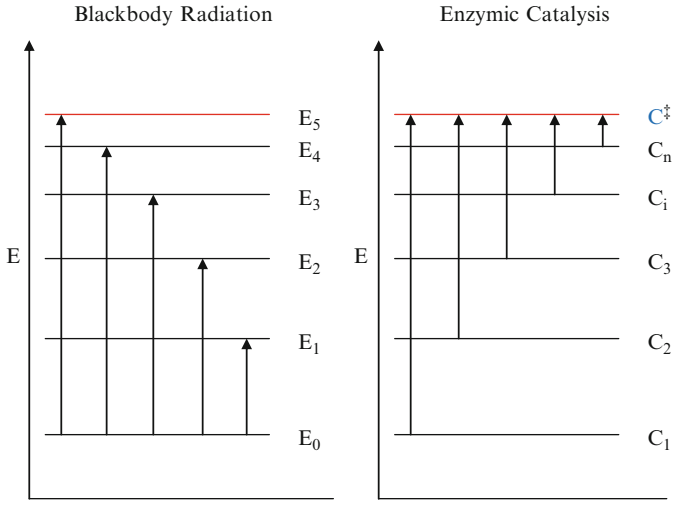


Fig. 11.28 A comparison between *blackbody radiation* and *enzymic catalysis*. (*Left*) Blackbody radiation involves promoting the energy levels (vibrational, electronic, or vibronic, i.e., both vibrational and electronic) of oscillators from their ground state E_0 to higher energy levels, E_1–E_5. The wavelength of the radiation (or quantum) absorbed or emitted is given by $\Delta E = E_i - E_0 = hf$, where E_i is the ith excited-state energy level, h is the Planck constant, f is the frequency, and ΔE is the energy absorbed when an oscillator is excited from its ground state to the ith energy level. Alternatively, blackbody radiation can be thought of as resulting from the transitions of electrons from one energy level to another within matter, e.g., from E_1 to E_0, from E_2 to E_0, etc. (*Right*) A single molecule of cholesterol oxidase (COx) is postulated to exist in n different conformational states (i.e., conformers, also called *conformational substates* by Frauenfelder et al. 2001), denoted here as C_i with i running from 1 to n. Each *conformational state* (or *conformer*) is thought to carry a set of sequence-specific conformational strains, or *conformons*, as explained in Fig. 11.20 and can be excited to a common transition state (denoted as $C^{\ddagger}$) by thermal fluctuations

the skeleton of a *globular protein*, each covalent bond acting as an oscillator (with vibrational frequencies in the range of 10^{14}/s [Kurzynski 1997, 2006]) which, when coupled properly, can lead to low-frequency *collective modes* of oscillations with frequencies as low as 10^3/s or less (according to the Fourier theorem [Herbert 1987]), thus accounting for the genesis of the so-called the slow protein coordinate, X(t), of Prakash and Marcus (2007).

One crucial difference between *blackbody radiation* and *enzymic catalysis* is thought to be this: Although both the *blackbody* and the *enzyme molecule* absorb heat or energy from their environment (see the upward arrows in Fig. 11.28) and reemit it to their environment in equal amounts at equilibrium, what is experimentally measured from these two systems is different: From the blackbody, the energy reemitted is measured (see the blackbody spectrum in the upper right-hand corner of Fig. 11.24), while from COx, the disappearance of the fluorescence emission is measured that results from enzymic catalysis, the *precondition of which being energy absorption* (see the histogram in the upper left-hand corner of Fig. 11.24).

In other words, what is measured from the blackbody is what it absorbs from its environment, but what is measured from the COx molecule is not what it absorbs from its environment but what *that absorbed energy helps the enzyme molecule to accomplish (e.g., a → b transition in Fig. 11.19), namely, the removal of the fluorescence from its coenzyme, FAD, by catalyzing its reduction to the non-fluorescent* $FADH_2$. It is important to point out that the heat absorbed by an enzyme cannot perform any molecular work, including catalysis, *since no thermal energy can drive any work under isothermal conditions*, according to the Second Law of thermodynamics (see Sect. 2.1.4). However, according to the new version of the Second Law as formulated by McClare in 1971 (see Statement 2.5 in Chap. 2), an enzyme can utilize thermal energy if it can be paid back or returned to its environment within its turnover time, leading to the following generalization:

> An enzyme can utilize thermal energy to facilitate catalysis without violating the Second Law, if the chemical reaction being catalyzed can release heat to the environment within the times shorter than τ, the turnover time of the enzyme. (11.39)

We may refer to Statement 11.39 as the *First Law of Enzymic Catalysis*, to emphasize the fundamental role that thermal energy, as manifested in molecular motions (or Brownian motions), plays in enzymic catalysis, the foundational process of the phenomenon of life.

The blackbody spectrum measures all the thermal photons absorbed by the blackbody wall, but the waiting time distribution of COx measures only a small fraction of the thermal photons absorbed by the COx molecule that helps COx to reach its transition state, $C^{\ddagger}$. This difference is visualized in Fig. 11.28 in terms of the *multiple levels* (labeled E_1 though E_5) of thermal excitations for blackbody radiation on the one hand and the *fixed level* of thermally activated transition state in the COx molecule labeled $C^{\ddagger}$ that triggers catalytic event on the other.

The reason that Planck's radiation formula, Eq. 11.26, can account for the waiting time distribution of COx, in the form of Eq. 11.27 with X(w) set to zero, is probably because of the mechanistic isomorphism between blackbody radiation and enzymic catalysis as indicated by the similar distributions of the upward arrows in the two panels in Fig. 11.28: A set of arrows starting from a common ground state reaching different activated states on the one hand and a similar set of arrows starting from different ground states arriving at the common activated state, $C^{\ddagger}$, on the other. The rationale for invoking different ground states for the thermal activation in COx is given in (6) below. Due to the varying levels of conformational energy associated with C_i, the thermal energies required for C_i to reach the common transition state, $C^{\ddagger}$, differs as indicated by the varying lengths of the upward arrows in the right-hand panel of Fig. 11.28.

6. It is well known that a protein molecule contains many internal mechanical (i.e., conformational) strains variously referred to as "mobile defects" (Lumry 1974; Lumry and Gregory 1986), "frustrations" (Anderson 1983, 1987), or conformons (Green and Ji 1972a, b; Ji 1974b, 2000) as already indicated in Sect. 11.3.2. The number and locations of these mechanical strains within an enzyme probably vary from one conformer to another (Fig. 11.21). The conformers of a protein

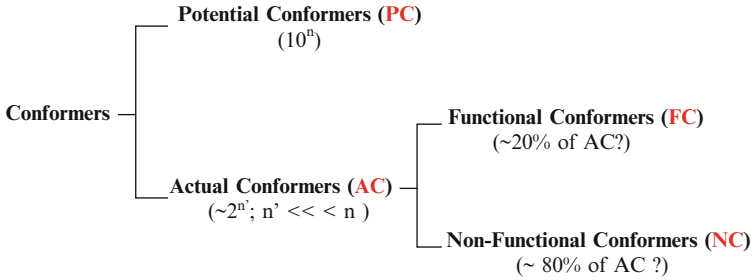


Fig. 11.29 The postulated hierarchical organization of the conformers of a protein. The number of PC is estimated to be 2^n, where n is the number of the amino acid residues, and the number of AC is thought to be far less than that of PC, i.e., AC <<< PC, and those of FC and NC are probably comparable: FC ~ NC. The number n appears in both Figs. 11.23 and 11.28, but Fig. 11.23 deals with the number of all possible linear sequences of *n nucleotides* (i.e., configurations) whereas Fig. 11.28 is concerned with the number of all possible three-dimensional arrangements of a given linear sequence of n amino acid residues (i.e., conformations or conformers). The number of potential n-nucleotide sequences is probably smaller than the number of the conformers theoretically possible for a protein with n amino acid residues, because the former is 4^n whereas the latter is x^n where x is the number of possible orientations that an amino acid residue can assume as it is being added to the growing polypeptide chain during protein synthesis, x being most likely larger than 4

are denoted as C_i in Fig. 11.28, where i runs from 1 to n, the total number of conformers belonging to a molecule of COx which can be astronomically large. Since COx has 504 amino acid residues, n could be as large as 2^{504} or about 10^{152}, assuming that each amino acid residue added during protein synthesis on the ribosome leads to at least two new conformational states for the resulting polypeptide. Of these theoretically predicted large number of conformers of COx, it is expected that only a small number, n′, would be selected by evolution to be realized in COx under the intracellular environmental conditions: i.e., n′ <<< n. It is difficult to estimate the precise magnitude of n′. Whatever the actual size of n′ will turn out to be, it is probably reasonable to assume that most, if not all, of these n′ conformers serve some biological functions in order for them to be evolutionarily conserved. Thus n′ conformers may be divided into two classes – *functional* and *nonfunctional* under a given environmental condition. The n conformers that are theoretically predictable, whether realized or not in cells, represents a third class to be referred to as *potential* conformers in contrast to *actual* conformers which divide into *functional* and *nonfunctional* ones. Thus, conformers can be classified as shown in Fig. 11.29.

As discussed in Sect. 11.3.2, the three terms *molecules, conformers,* and *conformons* are distinct and their mutual relations may be simply summarized as follows:

A molecule is a set of confomers; a conformer is a set of conformons. (11.40)

A conformer of an enzyme may contain one or more conformons belonging to two different classes: (a) the conformons (i.e., conformational kinks) introduced into an enzyme during its biosynthesis on ribosomes and (b) the conformons

generated from exergonic processes (i.e., binding, de-binding, covalent bond rearrangements, etc.) catalyzed by the enzyme itself such as the myosin head during muscle contraction (see (d) (3) in Fig. 11.33). We will refer to the former as *static* (or *intrinsic*) *conformons* (also called the Klonowski-Klonowska conformons in [Ji 2000]) and the latter as *dynamic* (or *extrinsic*) *conformons*. These terms were already employed in Rows (C) and (E) in Table 11.10 and are further discussed in Sect. 11.4.2. It is postulated here that the nonzero ground energy levels of the conformers postulated in Fig. 11.28 result from the presence of one or more *static conformons* in each conformer.

A functional *conformer* is postulated to carry as many *conformons* as the number of elementary processes it catalyzes (see Figs. 11.23, 11.28), which may be at least two, namely, binding and de-binding processes. In order for a conformer to carry out its catalytic act (be it binding, de-binding, or electronic rearrangement, singly or in combinations), it must satisfy the following two requirements: (a) a conformer must be thermally activated/excited to reach the transitions state $C^{\ddagger}$ (as indicated in Fig. 11.28) and (b) a conformer must recruit the right set of x out of its n amino acid residues obeying the conformon equation, Eq. 11.19.

Satisfying these requirements is tantamount to generating a set of *dynamic* conformons by a conformer within its lifetime.

It is natural to associate with COx the so-called slow protein coordinate, X(t), that plays a central role in the theory of waiting time distribution of COx proposed by Prakash and Marcus (2007). COx can be viewed as a system of atoms linked by covalent bonds, each of which acts as an oscillator with vibrational periods in the 10^{-14} s range (or vibrational frequencies in the 10^{14}/s range), as already indicated. According to Fourier's theorem (Herbert 1987, pp. 79–92; http://en.wikipedia.org/wiki/Fourier_series), it is possible to generate low-frequency collective vibrational modes by appropriately coupling these high-frequency primary oscillators. Nature may *slow down* molecular oscillations by increasing the effective mass of oscillators through compactifying or "chunking" lower-level molecular systems to higher level ones in steps of about 5 (Ji 1991, pp. 52–56), as exemplified by the chunking of a DNA double helix into a chromosome (Fig. 2.9) reducing the linear size of DNA by a factor of about 10^{10} and therefore its effective mass by a factor of 10^{30}. This in turn should decrease oscillatory frequency by a factor of $(10^{30})^{1/2}$ or 10^{15}, since frequency, f, is inversely proportional to the square root of the mass, m, according to the equation for simple harmonic oscillators,

$$f = (1/2\pi)(k/m)^{1/2} \tag{11.41}$$

where k is the spring constant. Eq. 11.41 also suggests that the oscillatory frequency can be reduced by reducing the spring constant, k. Thus, when large domains of a protein oscillate with respect to one another, the frequency of oscillation can be reduced not only by increasing effective mass but also by weakening the spring constant k by, say, changing local electric fields by protonation-deprotonation, phosphorylation-dephosphorylation, and acetylation-deacetylation reactions involving critical amino acid residues.

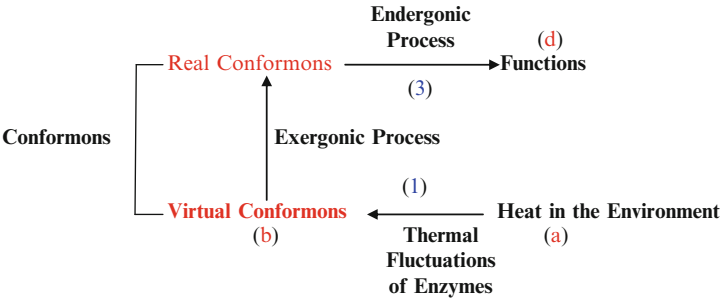


Fig. 11.30 A network representation of *the architectonics of the conformon*. The network consists of four nodes, (a)–(d), and three edges, (1)–(3), all of which are indispensible in defining the structure and function of the conformon, *sequence-specific conformational strains of biopolymers that are postulated to drive all goal-directed molecular motions in the living cell* (Ji 1974b, 1985b). Thermal fluctuations are alternatively referred to as *Brownian motions*

7. Indirect evidence gleaned from the studies carried out by molecular biologists, e.g., Socolich et al. (2005), Lockless and Ranganathan (1999), and by enzyme kineticists, e.g., Northrup and Hynes (1980) and Kurzynski (1993, 1997, 2006), suggests that within the lifetime of a conformer, more than one conformons are likely to be produced. The relation among a *conformer,* a *conformon*, and *amino acid residues* is triadic in that the production of a conformon requires (a) a set of amino acid residues, (b) the mechanical energy associated with (or stored in) their nonequilibrium arrangements in space and time, and (c) the function associated with the conformer harboring the conformon under consideration.

We may summarize the relation among these three entities as follows:

A conformer (at the $(n + 1)^{th}$ level) provides the biological meaning of the conformons (at the n^{th} level) that are generated within it utilizing a subset of its amino acid residues (at the $(n-1)^{th}$ level) through their interactions with an exergonic process such as ligand binding or chemical reactions. (11.42)

We may refer to Statement 11.42 as the *triadic architectonics of the conformon* (TAC), the term "architectonics" referring to the *design principles of an architecture or a building* as already alluded to previously. The molecular mechanisms implementing TAC require introducing two more concepts – *virtual conformons* and *thermal fluctuations* (see (1) and (b) in Fig. 11.30):

The heat or thermal energies supplied by the environment of living systems (see (a) in Fig. 11.30) are essential for thermal fluctuations (also known as Brownian motions) (1) which are in turn prerequisite for all living processes, which leads to the following generalization:

No thermal fluctuations, no life. (11.43)

To emphasize the fundamental significance of *thermal fluctuations* in understanding the phenomenon of life on the molecular level, Statement 11.43 may be referred to as the *Second Law of Biology,* the First Law of Biology being given in Statement 11.32.

Virtual conformons (b) are those conformational strains that are produced spontaneously and transiently as the result of the thermal fluctuations of a conformer of an enzyme. Because of the constraints imposed by the Second Law of Thermodynamics, *virtual conformons* cannot be utilized to do any molecular work, and this is ultimately because they are produced under isothermal environment without any sustained thermal energy gradient. However, if, during their transient life times, virtual conformons can participate in some exergonic processes such as ligand bindings and electronic rearrangements in substrates, *virtual conformons* can be converted to *real conformons* (see Process 2 in Fig. 11.30) as long as the following conditions are satisfied:

(1) The rate of free energy release from the exergonic process (e.g., ligand binding or electronic rearrangement) is fast relative to the conformational relaxation times of the enzyme so that the *generalized Franck-Condon principle* is not violated (see Sect. 2.2.3)
(2) A part of the energy released from the exergonic process pays back to the environment the thermal energy borrowed by virtual conformons during their thermal genesis.
(3) The exergonic process produces effects (e.g., reaction products) that stabilize virtual conformons (Ji 1979).

If Step (2) involves a ligand binding, the rate of the formation of real conformons (c) would depend on the concentration of the ligand. Observation B in Table 11.10 that a tenfold decrease in cholesterol concentration led to a tenfold increase in the largest waiting time supports Step (2). *Real conformons*, once formed, can persist for arbitrarily long times until they are utilized to drive some *goal-directed endergonic process* (3) otherwise known as *functions* (d). In contrast, the lifetimes of *virtual conformons* are limited (due to the Second Law of Thermodynamics) to times shorter than the enzyme turnover times (Sect. 2.1.4) (McClare 1971, 1974; Welch and Kell 1986).

It is clear from Fig. 11.30 that the so-called Second Law of Biology, Statement 11.43, is only one of the many necessary conditions for the production and utilization of the conformon, which was postulated to be the quantum of life (Ji 2000). Another necessary condition may be stated as follows:

No coupling between exergonic and endergonic processes, no life. (11.44)

Examples of the coupling between exergonic (i.e., free energy supplying) and endergonic (i.e., free energy consuming) processes include the coupling between the exergonic respiration and endergonic phosphorylation of ADP to produce ATP (Ji 1974b, 2000). Statement 11.44 may well deserve to be referred to as the *Third Law of Biology*. Finally, since all of the first three laws of biology are necessary to generate conformons, according to Fig. 11.30, it may be logical to refer to the following statement as the *Fourth Law of Biology*:

No conformons, no life. (11.45)

8. A conformer of COx can contain or harbor one or more conformons (whose number can be estimated from the *conformon equation* discussed in Sect. 11.3.2

and Fig. 11.21; see also Column (3) in Table 11.11). Each conformon is thought to catalyze one elementary step of a goal-directed process for which a conformer of COx is postulated to have been selected by evolution. It is also assumed in Fig. 11.21 that each conformer of COx must be thermally activated/excited to reach the transition state, $C^{\ddagger}$, which is essential for catalyzing the overall process of the electron transfer from cholesterol to FAD to produce $FADH_2$. Because different conformers are at different distances from the transition state $C^{\ddagger}$ (Fig. 11.28) and hence associated with different activation free energy, $\Delta G^{\ddagger}$, different conformers are associated with different *waiting times, w,* for catalyzing the FAD reduction by cholesterol. (For the relation between $\Delta G^{\ddagger}$ and w, see Rows 6 and 8 in Table 11.9 and Eq. 11.46.)

According to Eq. 11.27, waiting time is determined by a deterministic component which is the function of $\Delta G^{\ddagger}$ as indicated in Rows (6) and (8) in Table 11.9 and a nondeterministic component which is thought to result from the genetic information of the conformons (also called "catalytic negentropy" in Ji 1974a) or "evolutionary information" in Socolich et al. (2005) and Poole and Ranganathan (2006) (see further explanation given below).

The probability of a photon with wavelength λ to be absorbed or emitted by the blackbody at equilibrium is given by the product of two terms: (a) the *Boltzmann factor*, $e^{-E/kT}$, giving the probability of an energy level, E, to be occupied, and (b) the statistical weight of the energy level E (i.e., the *density of states*, n(E) in Row 9, Table 11.9), which is determined by the number of modes of the standing waves that can be accommodated by the blackbody cavity (Nave 2009).

Similarly, it is postulated here that the deterministic portion of Eq. 11.27 specifying the frequency of the occurrence of waiting time w is given by the product of two factors:

(a) The *Bose-Einstein factor* (which applies to conformons assumed to be members of the boson family of quons), $1/(e^{b/w} - 1)$, where b is a constant and w is related to activation free energy as shown in Eq. 11.46
(b) The density of states determined by the aw^{-5} term, where a is another constant reflecting the geometrical properties of COx including the "internal constraints" of the primary, secondary, and tertiary structure of COx (see Row 9 in Table 11.9) which differs from the "external constraints" such as size of the reaction vessel

Based on the transition state theory of reaction rates (Frost and Pearson 1965, pp. 97–102; Kurzynski 2006, pp. 169–171), the waiting time, w, can be related to the rate constant k, which in turn is related to the thermodynamic variables as shown in Eq. 11.46:

$$w = 1/k = (h/k_B T)e^{\Delta G^{\ddagger}/RT} = (h/k_B T)(e^{-\Delta S^{\ddagger}/R})(e^{\Delta H^{\ddagger}/RT}) \qquad (11.46)$$

where $\Delta G^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta H^{\ddagger}$ are the activation free energy, activation entropy, and activation enthalpy, respectively; k_B is the Boltzmann constant; T is the absolute

temperature; h is the Planck constant; and R is the gas constant. Since $\Delta H^{\ddagger} = \Delta E^{\ddagger} + P\Delta V^{\ddagger}$, where P is the pressure and $\Delta V^{\ddagger}$ is the activation volume of COx, $\Delta H^{\ddagger} = \Delta E^{\ddagger}$ if $\Delta V^{\ddagger}$ is zero, which is generally assumed to be true, thus transforming Eq. 11.46 to 11.47:

$$w = 1/k = (h/k_B T)(e^{-\Delta S^{\ddagger}/R})(e^{\Delta E^{\ddagger}/RT}) \tag{11.47}$$

Equation (11.47) is equivalent to Eq. 2 in Ji (1974a, p. 420), based on which the following postulate was made in Ji (1974a, pp. 434–435):

> . . .the enzyme can control the rate of chemical reactions by affecting either $\Delta E^{\ddagger}$ or $\Delta S^{\ddagger}$. The enzyme can alter the magnitude of $\Delta E^{\ddagger}$ by changing the curvature of the potential energy hypersurface of the substrate, which it does by undergoing appropriate conformational transitions . . .. I now postulate that the catalytic negentropy stored in the enzyme can regulate the rate of enzymic reactions by modulating the magnitude of $\Delta S^{\ddagger}$. I regard the enzyme as a negentropy reservoir from which the substrate can borrow negentropy (i.e., negative entropy) change [Sect. 2.1.5]to reach the transitions state. At the end of an elementary chemical reaction, the negentropy withdrawn from the enzyme can be returned to the protein, so that no net changes in the negentropy content of the enzyme may result. Although the vast kinetic energies stored in the enzyme cannot be localized on the substrate as a means of catalysis, because of the second law, I believe that the transfer of negentropy from the enzyme to the substrate can be invoked for the purpose of catalysis without violating the second law. The molecular mechanism of negentropy transfer from the enzyme to the substrate may be identified with the ordering of the catalytic groups in the reaction cavity in the Franck-Condon state and the disordering of structures elsewhere in the enzyme. (11.48)

The *negentropy transfer* from domain A to domain B, the active site, in an enzyme to reach the transition state can affect $\Delta S^{\ddagger}$ (and hence alter the associated waiting time, w; see Eq. 11.46) in three ways" (a) *positively*, increasing $\Delta S^{\ddagger}$; (b) *negatively*, decreasing $\Delta S^{\ddagger}$; and (c) *neutrally*, having no effect on $\Delta S^{\ddagger}$. Although some negentropy transfer from A to B may not affect $\Delta S^{\ddagger}$ and associated w, it can still affect the probability, p(w), of the occurrence of w, again in three ways – (d) *positively*, increasing p(w); (e) *negatively*, decreasing p(w); and (f) *neutrally*, having no effect on p(w) – depending on the amino acid sequence of the conformons involved, as illustrated in Column (5) in Table 11.11.

The term "negentropy" should be interpreted with caution. This term is paradoxical in the sense that when defined as "negative entropy change (NEC)," negentropy signifies or is associated with "order" and "information," but, when defined as "negative entropy (NE)," it violates the Third Law of thermodynamics, according to which entropy of a thermodynamic system can never be less than zero (or negative). This situation was referred to as the *Schrödinger's paradox* in Sect. 2.1.5. Please note that NEC is a *differential* concept whereas *NE* is an absolute one.

Therefore the phrase "negentropy reservoir" appearing in Statement 11.48 can be interpreted as those regions or domains of an enzyme serving as storage sites for negentropy in the form of *ordered* or *low-entropy conformational structures*. The key message of Statement 11.48 is that an enzyme can utilize the negentropy stored in one region of an enzyme to organize the catalytic residues at the active site to reach the transition state, and this process can be viewed as a form of *negentropy*

Table 11.12 The *garage-door metaphor* of enzymic catalysis

	Garage door	Enzyme
1. Storage device	Mechanical spring	Nonactive site domains (domain A or negentropy reservoir, NR)
2. What is stored	Mechanical energy	Negentropy (low-entropy local structure)
3. Mechanism of storage	*Gravitational potential energy* of the door is transduced into the *mechanical energy* of the spring as the door closes	Negentropy is generated at domain A allosterically (in the form of a *conformon*) as the substrate binds to domain B, the active site
4. Mechanism of utilization	*The mechanical energy* of the spring is transferred to the raised door as its *gravitational potential energy*	The negentropy stored in domain A is transferred to domain B, the active site, as a low-entropy conformation of the catalytic residues needed for catalysis, without *necessarily* changing the overall activation entropy, $\Delta S^{\ddagger}$ of the enzyme-substrate complex
5. Net result	Less energy is required to open the garage door	The observed probability of the occurrence of waiting times can deviate from the deterministic values (due to the ruggedness of the histogram) either positively, negatively, or neutrally, thereby increasing the variety of the probabilities, p(w), of the occurrence of w

transfer from domain A (i.e., the negentropy reservoir) to domain B (i.e., active site), leading to the disordering of A and ordering of B without changing the total amount of the negentropy stored in A and B during the transfer process. This idea can be conveniently expressed using the *garage door* as a metaphor:

> Just as a part of the gravitational potential energy of the garage door is stored in mechanical springs as the door closes and the stored energy is subsequently re-utilized when the garage door opens, so the negentropy generated (allosterically) within domain A in an enzyme when a substrate binds to domain B, or the active site, can be transferred to B as "catalytic negentropy" which organize the amino acid residues to effectuate catalysis, returning the catalytic negentropy back to A as the activated enzyme relaxes to its ground state. (11.49)

Statement 11.49 will be referred to as the *garage-door mechanism* of enzymic catalysis or the *garage-door postulate of enzymic catalysis*, and its salient features are summarized in Table 11.12.

Two features of the garage-door postulate deserve special attention:

(a) The existence of a group of amino acid residues that is postulated to function as a *negentropy reservoir* (NR) (Row 1, Table 11.12) at domain A. Domain A need not be located at the active site (domain B) making direct contact with a bound substrate but can involve a part or the whole of the enzyme other than the

active site, as long as domain A is allosteric (i.e., mechanically coupled) to domain B. Because of their postulated role in catalysis, it can be predicted that these *NR residues* in domain A will be evolutionarily conserved and coevolve with the *catalytic residues* in domain B, similar to the critical residues found in the WW domain proteins (Lockless and Ranganathan 1999; Süel et al 2003; Socolich et al. 2005, and Poole and Ranganathan 2006). It is postulated here that the NR residues are responsible for the *ruggedness* of the waiting time histograms (Fig. 11.24). Therefore *it can be predicted that mutating one or more of the NR residues of COx will remove the ruggedness of the waiting time histograms* (see the lower panel of Fig. 11.24). (This prediction was suggested to me on July 28, 2009, by one of my undergraduate students at Rutgers, Ms. Julie Bianchini.)

(b) The *iso-entropic nature* (i.e., no change in $\Delta S^{\ddagger}$) postulated for the negentropy transfer process from NR to the active site of the enzyme (Row 4, Table 11.12) is the most salient feature of the *garage-door postulate*. Lumry and Gregory (1986, p. 23) discussed enzymic mechanisms similar to the garage-door mechanism described here (Lumry 1974; Lumry and Gregory 1986).

If these conjectures are correct, we can conclude that *blackbody radiation* and *the waiting time distribution of COx* are isomorphic with each other as summarized in Row (10) of Table 11.9.

9. Armed with the conclusions drawn above, we can return to Eq. 11.7 with a new perspective, namely, the view that the X(w) factor does not merely reflect experimental noise but also carries biological (i.e., genetic or evolutionary) information. We will refer to this view as the "X factor hypothesis," which may be expressed as follows, among others:

   The waiting time distribution of COx contains both deterministic and non-deterministic (or stochastic) components. (11.50)

   The waiting time distribution of COx contains the deterministic and non-deterministic components, the former being constrained by, and the latter harnessing, the laws of physics and chemistry. (11.51)

   The waiting time distribution of COx contains the deterministic and non-deterministic components, the former being constrained by the *laws of physics and chemistry* and the latter embodying the *evolutionary information* that harness the laws of physics and chemistry. (11.52)

   Enzymic catalysis embodies two complementary aspects – the *energy/matter aspect* obeying the laws of physics and chemistry and the *bioinformatic aspect* embodying the evolutionarily selected amino acid residues capable of harnessing the laws of physics and chemistry. (11.53)

It should be noted that the adjectives "deterministic" and "nondeterministic" appearing in the above statements can be replaced by their synonyms, "synchronic" and "diachronic," respectively, as already indicated (see Row 3 in Table 4.1).

10. The *waiting time distribution* of COx measured by Xie and his colleagues in Lu et al. (1998) may be comparable to the *blackbody spectrum* measured by Otto Lummer and Ernst Pringsheim in 1899 (Kragh 2000). Also the probability

Table 11.13 A suggested historical analogy between blackbody radiation and single-molecule enzymology. COx = cholesterol oxidase

	Blackbody radiation	Single-molecule enzymology
1. Data	Blackbody spectrum	Waiting time distribution of COx
2. Early theory	Wien's law Rayleigh-Jeans law	Probability distribution function for waiting times derived on the basis of the *Michaelis-Menten kinetics* (Lu et al. 1998; Kurzynski 2006; Qian and Xie 2006; Prakash and Marcus 2007)
3. Final theory	Planck's law	Probability distribution function for waiting times derived from the *blackbody radiation-enzymic catalysis analogy* (Ji 2008b)
4. Improvement	*Better fit* in the low frequency region of the blackbody spectrum	Better fit for the "noisy" or "rugged" portions of the waiting time distribution by introducing the *X(w) factor as a measure of evolutionary information carried by catalytic residues*
5. New concept	Energy quantization (photons)	Conformons as carriers of (a) quantized energy and (b) catalytic information or catalytic negentropy (Ji 1974a)

distribution for waiting times derived by Lu et al. (1998), Eq. 11.25, may be comparable to Wien's law and Rayleigh-Jeans law (Kragh 2000; Nave 2009), just as that derived on the basis of the analogy between blackbody radiation and enzymic catalysis, Eq. 11.27 (Ji 2008b), is comparable to Planck's law, Eq. 11.26. These and other analogies between *blackbody radiation* and *enzymic catalysis* are summarized in Table 11.13.

If the *blackbody radiation-enzymic catalysis* analogy turns out to be true, the single-molecule waiting time distribution measured by Lu et al. (1998) may be viewed as the first direct experimental evidence for demonstrating that an enzyme molecule must absorb heat before it can carry out catalysis, *thus establishing the fundamental role of heat in molecular biology*, consistent with the "thermal barrier" hypothesis of molecular machines (Ji 1991, pp. 29–31) and the Second Law of Molecular Biology, Statement 11.43. Although biochemists have known for a long time that raising temperature leads to an increase in catalytic rates (the so-called Q_{10} value of an enzymic reaction being in the 2–4 range), these rates are ensemble averages that are affected by many physicochemical steps, making it difficult to pin down the precise catalytic process affected by heat. This difficulty is largely overcome in single-molecule kinetic experiments where one elementary step (e.g., the electron transfer from cholesterol to FAD, Scheme 11.16) can be studied.

Unlike in chemical reactions where heat provides all of the energy required to overcome the activation energy barrier, an enzyme molecule appears to supplement the heat energy absorbed from its environment with its *intrinsic* ground-state potential energy stored in local conformational strains (called *static* or *intrinsic conformons*; see (6) above) in activating its substrate to form the product. A similar

conclusion was reached by Rufus Lumry in his "The Protein Primer" available online (Lumry 2009).

If the content of Table 11.9 is true, there may be an interesting historical analogy between *blackbody radiation* in physics and *enzymic catalysis* in biology as summarized in Table 11.13. Just as the blackbody spectrum led Max Plank in 1900 to postulate the existence of *quantized energy packets* (later called "photons"), so the single-molecule kinetic data of COx suggest that:

(a) There exists a minimal unit of *c*atalytically *e*ffective *c*onformational *s*trains (CECS) of an enzyme molecule
(b) The minimal unit of CECS is characterized by its mechanical energy and *evolutionarily conserved amino acid residues* encoding genetic information (Row 5, Table 11.13)

The CECSs invoked above can be identified with *conformons* since conformons are defined as the conformational strains localized at sequence-specific sites within biopolymers carrying both *mechanical energy* and *genetic information* to drive goal-directed molecular motions in the cell (Chap. 8) (Ji 1974a, b, 2000). In other words, the *blackbody radiation-enzymic catalysis analogy* entails invoking two complementary factors underlying catalysis" (a) the *conformational energy* stored in an enzyme (see Fig. 11.28) and (b) the *catalytic information* (or negentropy Ji 1974a) encoded in the select set of the amino acid residues constituting the active site of an enzyme which may be similar to the *evolutionarily coevolving amino acid residues* of enzymes (Poole and Ranganathan 2006), and Socolich et al. (2005). The former is necessary to account for the deterministic component of Eq. 11.27, and the latter is necessary to account for the nondeterministic, stochastic, and arbitrary component, X(w). Together, these two factors – *conformational energy* and *genetic information* – completely account for the waiting time distribution of COx measured by Lu et al. (1998).

In conclusion, the *conformon theory of molecular machines* first invoked to account for the molecular mechanisms underlying the phenomenon of oxidative phosphorylation in mitochondria (Green and Ji 1972a, b; Ji 1974a, b, 2000) appears to provide a most comprehensive and mechanistically and evolutionarily realistic explanation to date for the single-molecule enzymological data on cholesterol oxidase measured by Lu et al. (1998).

11.4 The Conformon Model of Molecular Machines

The living cell is a system (or "renormalizable" network; see Sect. 2.4) of molecular machines that self-organizes to carry out its varied functions using the free energy supplied by exergonic chemical reactions or light absorption. Molecular machines playing essential roles in the cell include ordinary enzymes, molecular motors (e.g., myosin, kinesins, dyneins), ion pumps and channels, signal transducing proteins, DNA polymerase, RNA polymerase, and chaperones. Like macroscopic machines

such as cars, molecular machines must be driven by free energy derived from chemical reactions, but the mechanism by which these processes manage to drive molecular machines is not yet fully understood. One possibility is suggested by the *conformon theory*, according to which all molecular machines are driven by chemical reaction–derived or ligand binding/de-binding-induced *mechanical strains* stored in sequence-specific sites in biopolymers known as the *conformons* (see Sects. 8.2 and 11.4.1 for the mechanisms of conformon generation).

11.4.1 The Conformon Model of "Biomotrons"

There are several related terms used in the fields of molecular biology and the emerging field of single-molecule enzymology (Xie 2001; Deniz et al. 2008) such as "molecular energy machines" (McClare 1971, 1974; Welch and Kell 1986), "molecular machines," "molecular motors" (Astumian 2000, 2001), "molecular rotors," "molecular switches," "Brownian ratchets," "molecular catalysts," and "protein machines" (Kurzynski 2006). We can regard all these terms as representing different *species* (or *tokens*) of the same *class* (or *type*) of objects which may conveniently be referred to as "biomotrons," a term coined by one of the pioneers of the single-molecule mechanics, T. Yanagida (http://www.wtec.org/loyola/word/erato/pendixbf.doc) (Douglas 1995). *Biomotrons* stands for "*bio*logical *mo*lecular mo*tor*s." The main purpose of this section is to present the following two assertions:

1. All *biomotrons* are driven by *conformons*.
2. Conformons are generated in *biomotrons* from exergonic chemical reactions or exergonic ligand-binding and de-binding processes, based on the generalized Franck-Condon mechanisms (Sects. 2.2.3 and 8.2).

Conformons are the mechanical energies stored in biopolymers in the form of conformational strains (Chap. 8 and Sect. 11.3.2). Since work or energy is defined as (*energy*) = (*force*)(*displacement*), force is the rate of change of energy with respect to displacement. In other words, *energy* and *force* are intimately related so that one can be used to derive the other, given the numerical value of the displacement and the associated potential energy function. It is for this reason that *conformons can be used to produce molecular forces inside biopolymers*. In addition, conformons can be generated from chemical reactions through the generalized Franck-Condon mechanisms as shown in Fig. 8.1, thus making *conformons* as the realistic molecular mechanisms for transducing *chemical energy* to *mechanical energy* in muscle contraction and other molecular motions or movements (Astumian 2000, 2001).

The conformon mechanism was first applied to muscle contraction in Ji (1974b), Fig. 6 on p. 223, reproduced in Fig. 11.34). The essential content of this mechanism is depicted in Fig. 11.31b in terms of symbols rather than pictures. In Fig. 6 of Ji (1974b) and Fig. 11.34, *conformons* are represented as a stretched spring attached to the myosin head (also called subfragment-1 of myosin, or S-1).

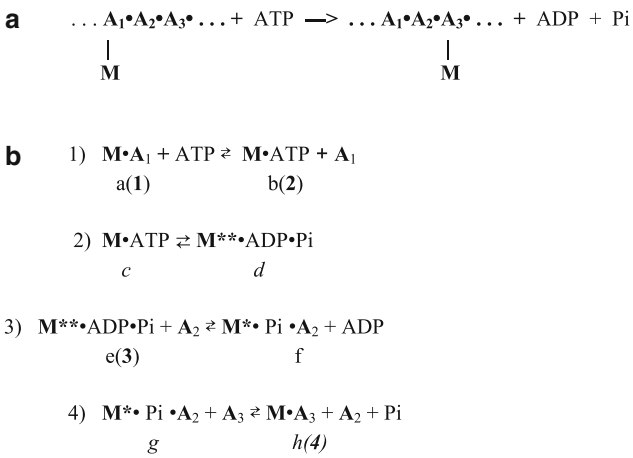


Fig. 11.31 A simplified version of the *conformon mechanism of muscle contraction* first proposed in Ji (1974b) on the basis of the generalized Franck-Condon principle (Sect. 2.2.3). (**a**) A schematic representation of one turnover of the actomyosin system. $\mathbf{A_1}$, $\mathbf{A_2}$, and $\mathbf{A_3}$ are the actin monomers that are linearly arranged, the center-to-center distance between adjacent actin monomers being about 5 nm. **M** stands for the myosin head (also called the S-1 subfragment of myosin) bound to an actin (**A**) through non-covalent bond indicated by a vertical bar, |. The figure indicates that the hydrolysis of one molecule of ATP to ADP and Pi results in the movement of the myosin head from $\mathbf{A_1}$ to $\mathbf{A_3}$ across a distance of about 10 nm or 100 Å. (**b**) The muscle contraction mechanism based on the conformon theory (see Sect. 8.2) consists of four main steps. *The numbers in the parentheses refer to the states of the actomyosin system that have been actually measured (see Fig. 11.33d) using the single-molecule manipulation techniques described in Fig. 11.32.* Step 1 = The actin ($\mathbf{A_1}$) bound to myosin (see State *a*) is displaced by ATP to produce the myosin-ATP complex (see State *b*). Step 2 = The myosin-actin complex fluctuates between two conformational states – the ground state, *c*, in which the potential energy is stored in ATP, and the energized state, *d,* in which the potential energy is stored in mechanical strains or conformons (denoted as two superscripts *, each symbol indicating one conformon). In other words, it is assumed that the hydrolysis of one molecule of the bound ATP to ADP and Pi generates two conformons in this step. Step 3 = One conformon is used to translocate the myosin head from $\mathbf{A_1}$ to $\mathbf{A_2}$, with a concomitant release of ADP into the medium. Step 4 = The second conformon is used to translocate the myosin head from A_2 to A_3, releasing Pi into the medium

Each of the steps shown in Fig. 11.31b can be expanded using the *pre-fit* (or generalized Franck-Condon) *hypothesis* discussed in Sect. 7.1.3. For example, Step (B) (1) may implicate the following processes: $\mathbf{M{\bullet}A_1}$ + ATP ⇄ $\mathbf{M'}$ + $\mathbf{A_1}$ + ATP ⇄ $\mathbf{M'{\bullet}}$ATP + $\mathbf{A_1}$, where $\mathbf{M'}$ represents a high-energy (or thermally excited) conformation whose shape is complementary to that of ATP. To account for some of the unexpected observations reported by Ishijima et al. (1998), e.g., the negative time values in the histogram of the temporal relation between actin displacement and the release of nucleotides from myonsin (see Fig. 7 in the above reference), it may be necessary to invoke a role of the pre-fit mechanisms in the operation of the actomyosin motor. More specifically, $\mathbf{M'}$ may have a long enough lifetime (without violating the Second Law of thermodynamics) to begin to exert force on the actin filament before receiving free energy input from ATP hydrolysis, thus accounting for the negative time values in Fig. 7 of Ishijima et al. (1998).

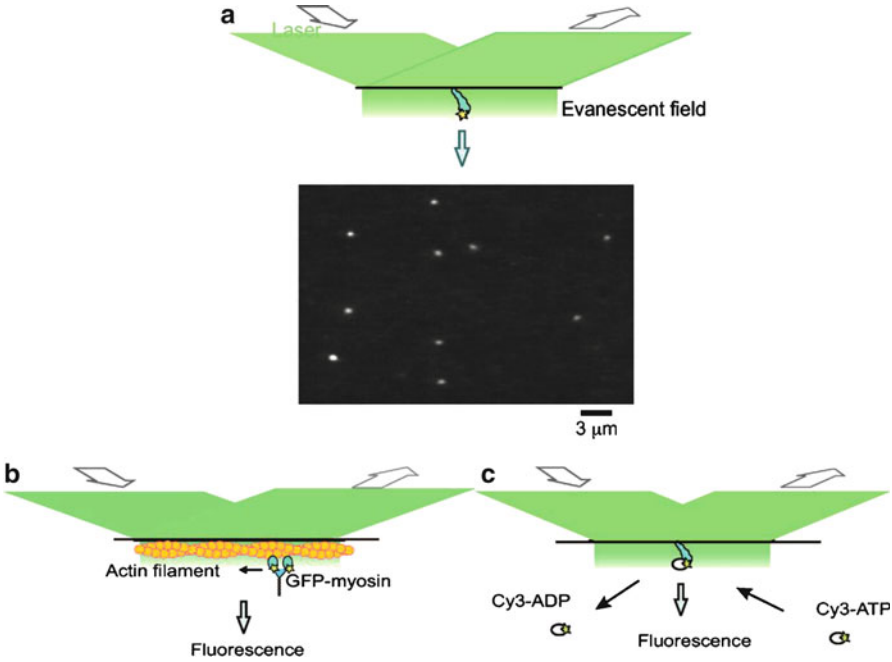


Fig. 11.32 Single-molecule fluorescence measurements using the total internal reflection fluorescence (TIRF) microscopy (Axelrod 1989). (**a**) The basic system of illuminating single fluorescent molecules on the glass surface (see the *black horizontal line*) using the *total internal reflection fluorescence (TIRF) microscopy*. Typical images of single molecules measured with TIRF microscopy are shown (see the *white dots* in the *dark background*). (**b**) Visualizing the sliding movement of a GFP (*Green* Fluorescent Protein)-tagged myosin molecule along an actin filament immobilized on the glass surface. (**c**) Visualizing the turnover of ATP hydrolysis by a single myosin molecule attached to a glass surface. Cy3-ATP and Cy3-ADP are labeled with a fluorophore (i.e., a portion of a molecule that absorbs light at one wavelength and emits a part of it as a longer-wavelength fluorescence; see Fig. 11.16). Cy3-ATP binds to the myosin head and stays bound until myosin head cleaves Cy3-ATP to produce Cy3-ADP and inorganic phosphate, Pi. Cy3-ADP then de-binds from the myosin head due to its low binding affinity and the fluorescent spot disappears. Thus, by using the methods employed in (**b**) and (**c**), it is possible to measure both single myosin molecular motions and the kinetics of ATP hydrolysis accompanying the myosin motion (see Fig. 11.33) (Reproduced from Ihsii and Yanagida 2007))

The conformon mechanism of muscle contraction proposed in Fig. 11.31 is supported by the data obtained from the single-molecule measurements of myosin moving along the actin filament in the presence of ATP. Such a single-molecule experiment was made possible because of the development of the optical (or laser) tweezers and the total internal reflection fluorescence (TIRF) microscopy (see Figs. 11.31 and 11.32). A 'laser tweezer', or 'optical tweezer' is a laser beam focused down to a diffraction-limited spot of about 1 μm in diameter. The laser beam provides an electric field with a gradient in every direction such that there is one point of maximum field strength. Due to the polarizing effect of the focused field,

any dielectric object feels a force proportional to the magnitude of the gradient that pulls the object into the region of maximum field strength. The laser beam therefore can be used to apply a force to any dielectric particle to manipulate its position (Ishii and Yanagida 2007). Employing optical tweezers, biophysicists during the past decade were able to measure simultaneously both the translational motion of the myosin head (which has the ATPase activity) along actin filament and the hydrolysis of ATP that powers the myosin movement (Ishijima et al 1998; Ishii and Yanagida 2007). A typical example of such experiments is shown in Fig. 11.33.

The single-molecule measurements revealed three distinct states for the ATP-actomyosin system as schematized in Fig. 11.33d. In State (1), actin is displaced from its equilibrium position as indicated by the upper trace in Fig. 11.33d due to myosin, free of ATP (as indicated by the low fluorescence level in the lower panel of Fig. 11.33d), exerting a force on it. In State (2), myosin rapidly dissociates from actin which causes a rapid return of actin to its equilibrium position and ATP begins to bind slowly to the dissociated myosin (which is not too far away from actin) causing an increase in fluorescence level. In the transient State (3), ATP is rapidly hydrolyzed by myosin and ADP leaves (as indicated by the precipitous drop in ATP fluorescence intensity), making the ATP-free myosin exert force on actin. In State (4), ATP-free myosin keeps actin displaced from its equilibrium position as in State (1).

In the lower portion of Fig. 11.33d, Ishii and Yanagida (2007) propose a four-state (labeled 1–4) mechanism of the myosin movement along the actin filament driven by ATP hydrolysis. In contrast, the *conformon-based mechanism* of muscle contraction shown in Fig. 11.31 contains eight steps (labeled *a*–*h*), some of which correspond to the four states invoked by Ishii and Yanagida (see the numbers in parentheses in Fig. 11.31). The Ishii-Yanagida and conformon mechanisms are compared in Table 11.14.

As evident in Table 11.14, the conformon-based mechanism of myosin-actin interactions can explain every observation accounted for by the mechanism proposed by Ishii and Yanagida (2000, 2007) and, in addition, provides reasonable explanations (i.e., two conformons generated per ATP hydrolysis event) as to why there are two 5.5-nm steps per turnover of the actomyosin system. The single-molecule mechanical measurements of the actomyosin system presented in Fig. 11.33 seem to support the conformon model of muscle contraction proposed in Ji (1974b). To evaluate the validity of this conclusion, the pictorial version of the conformon-based model of muscle contraction is reproduced in Fig. 11.34.

According to the conformon model, two processes are crucial in muscle contraction: (a) the transduction of the chemical free energy of ATP to conformons stored in myosin. In State a, one molecule of ATP is bound to S-1 and myosin is in its ground state (as symbolized by a relaxed spring). Brownian motions (also called thermal fluctuations) bring S-1 close to the myosin-binding site on the thin filament (see the upper bar with two indentations) that is located on the Z-line side of myosin (see a → b). Upon binding actin, myosin catalyzes the phosphoryl group transfer from the bound ATP to a hypothetical phosphoryl group acceptor X located in S-1 (see b). The exergonic nature of this reaction enables the following two events

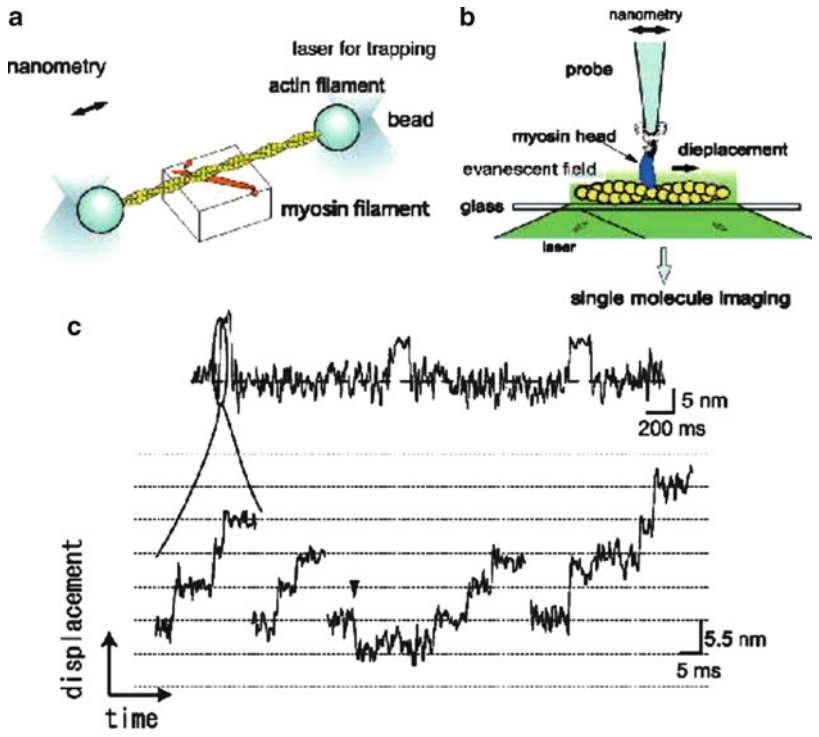


Fig. 11.33 Simultaneous measurements of the mechanical movement of the myosin head and the associated kinetics of ATP hydrolysis (Reproduced from Ishii and Yanagida 2007) with modification: I added the star symbol, *, to myosin in State (3) to indicate the presence of *conformational strains* or *the conformons postulated to be stored* in myosin. (**a**) In the presence of ATP, a molecule of myosin head immobilized on a block exerts a force on an actin filament attached to two beads on its ends. One of these beads is fixed with a laser tweezers and the movement of the other is measured with another optical tweezers. (**b**) An alternative way of measuring the myosin's mechanical activity. The myosin molecule attached to the tip of a micro-needle is brought to an actin filament fixed on a glass surface so that it can touch actin molecules. Given ATP in the medium, the myosin head exerts a force on the actin filament thereby producing an equal and opposite force on the tip of the micro-needle (following the Third Law of Newtonian mechanics), which causes the micro-needle to undergo displacements as recorded in (**c**). (**c**) Expanding the rising phase of the step movement in (**c**) revealed substeps of 5.5 nm, the diameter of the actin monomer. (**d**) The results of a simultaneous measurement of the mechanical movement of the myosin head and the hydrolysis of one molecule of a fluorescent ATP analogue. The upper trace records the movement of myosin along the actin filament, and the lower trace shows the binding activity of ATP to myosin. The high level of fluorescence indicates the binding of a molecule of ATP to the myosin head and the low level of fluorescence signals the desorption of ATP and ADP from myosin. It should be noted here that the superscript * added to the myosin head in State (3) (to denote the conformationally strained and hence mechanically energized state of the myosin head) is a modification proposed in this book for the first time based on the conformon theory of molecular machines (Green and Ji 1972a, b; Ji 1974a, b, 1979, 1991, 2000)

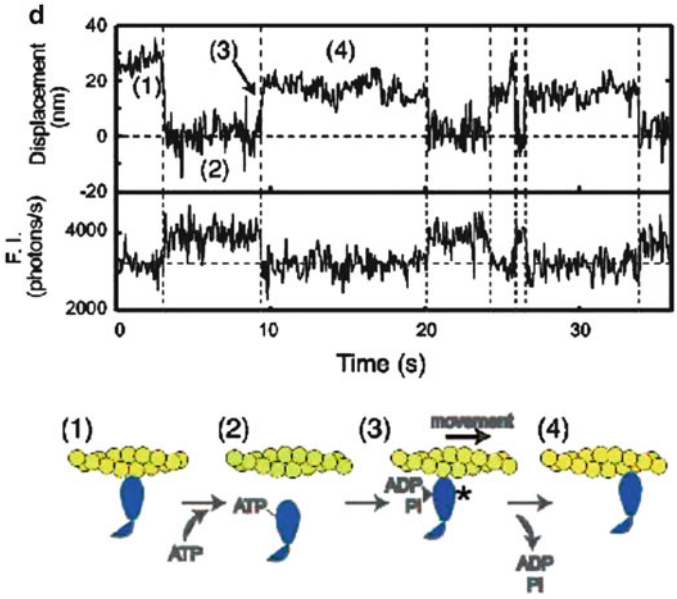


Fig. 11.33 (continued)

to take place: (a) the generation of a charge on myosin which increases the actin-binding affinity and (b) the paying back of the thermal energy borrowed from the environment to extend the S-2 subfragment in going from State a to State b. Actin and myosin are now tightly coupled electrostatically and mechanical energy is stored in myosin (which corresponds to State 3 in Fig. 11.33d). As S-2 relaxes, the thin filament is pushed toward left as indicated by the arrow in State b. When S-2 contracts to a critical distance, through allosteric interactions, the phosphoryl group in the myosin head (i.e., S-1) is thought to be transferred from X to Y (which could well be bound H_2O) (see State c) and the actin-binding affinity is drastically reduced so that myosin becomes detached from the thin filament (see c $\rightarrow$ d), thus completing one machine cycle.

It is known that one ATP split is capable of moving the thin filament by a maximum of about 100 Å or 10 nm (Huxley and Hanson 1960). This finding was the basis for the assumption that one turnover of ATP hydrolysis causes myosin to be displaced by about 100 Å (or 10 nm) in two steps, from States b to c (accompanied by the release of ADP from myosin) and from States c to d (associated with the release of Pi from the same). The sequential releases of ADP and Pi were postulated on the basis of the analogy drawn between the *electron* and the highly unstable phosphoryl group, $PO3^{-}$, which was conveniently termed the *phosphoron* (Ji 1974b). Just as the electron flow from carrier A to carrier B in Fig. 8.1 led to the generation of conformons (see the cocked spring stabilized by two opposite charges at State c), it was thought plausible to generate conformons in myosin by transferring the phosphoron from ATP to a hypothetical *phosphoron* carrier X and then to another *phosphoron* carrier, Y, thereby generating two conformons, each

Table 11.14 A comparison between the two explanations for the single-molecule measurement data on the myosin-actin interactions coupled to ATP hydrolysis (Fig. 11.33)

States in Fig. 11.33d	Mechanism proposed by Ishii and Yanagida (2007)	Mechanism based on the conformon theory (Green and Ji 1972a, b; Ji 1974b, 1991, 2000, 2004a, b; see Sect. 8.2)
1	*Myosin strongly interacts with actin and dissociates upon binding ATP*	The conformon stored in myosin exerts force on actin
2	*Myosin weakly interacts with actin*	Myosin dissociates from actin upon binding ATP
3	*Myosin generates mechanical motion when Pi and ADP dissociates from myosin*	1. ATP is hydrolyzed and a part of the chemical free energy supplied thereby is stored in myosin as mechanical energy or *conformons* (as denoted by the superscript * on the myosin molecule) 2. The mechanical energy stored in myosin is used to exert forces on actin in two steps, each step involving a 5.5-nm displacement (see Fig. 11.33c) 3. Each 5.5-nm displacement of actin is allowed if and only if one of the two products of ATP hydrolysis dissociates from myosin. For example, ADP can dissociate from myosin and the other product, Pi, remains bound to myosin to prevent its slippage from actin filament, thereby preventing the futile cycling (i.e., hydrolyzing ATP without producing any processive movement of actin), in agreement with the mechanism of muscle contraction proposed in Ji (1974b) (see Fig. 11.34)
4	*Myosin interacts with actin strongly*	After both ADP and Pi dissociate from myosin, myosin binds and exerts force on actin as in State (1)

carrying about 8 kcal/mol of free energy. Thus it was assumed that in States b and c in Fig. 11.34, myosin was phosphorylated at the hypothetical carriers X and Y, respectively (Ji 1974b, p. 221). *Thus, the conformon-based mechanism of muscle contraction proposed in Ji (*1974b*) predicted the two, 5 nm-step motion of the myosin along the actin filament which was confirmed by the single-molecule measurements of Ishijima et al. (*1998*) shown in Fig. 11.33c.*

From the point of view of the conformon hypothesis, the most important steps in Fig. 11.33d are States (2) and (3), since these steps represent the first *direct experimental evidence* for the conversion of *chemical energy* to *mechanical energy* stored in myosin, i.e., conformons. In State (2), ATP is bound to myosin and actin is relaxed as indicated by the two related traces labeled (2) in Fig. 11.33d. In State (3), ATP is

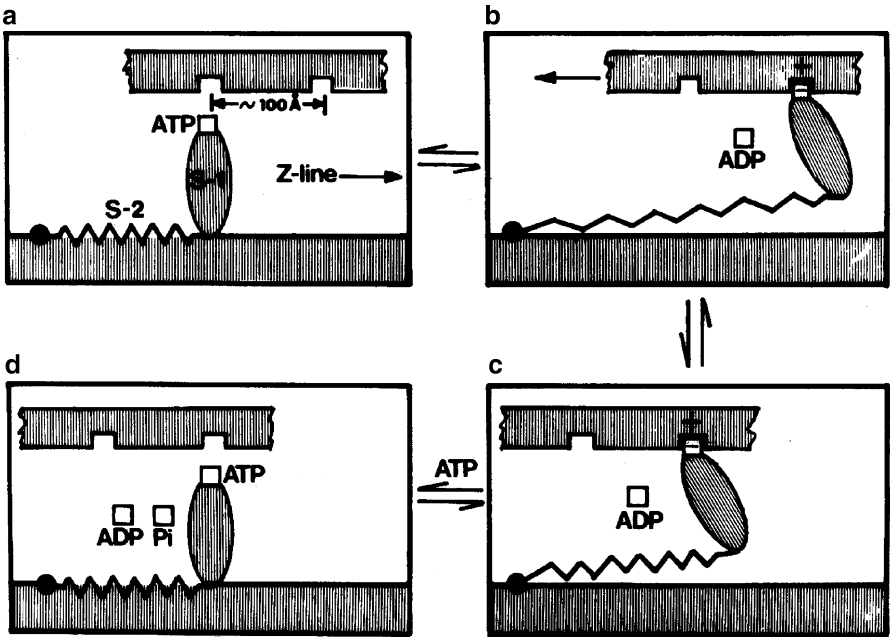


Fig. 11.34 A pictorial representation of the conformon model of muscle contraction discussed in Fig. 11.31 (Reproduced from Ji 1974b). The S-1 subfragment of myosin is depicted as an ellipsoid and the S-2 subfragment as a mechanical spring, but both are thought to be involved in storing mechanical energy, i.e., *conformons*. The *upper bar* represents the thin filament composed of a linear aggregate of actin monomers and the *lower bar* is the thick filament, an intertwined chain of myosin subfragments S-2 with subfragments S-1 protruding from the body of the thick filament. (**a**) ATP bound to the myosin head which is detached from the actin filament. (**b**) ATP is split into ADP and Pi and the Pi-bund myosin head attaches to the actin filament. (**c**) The S-2 subfragment contracts and pushes the actin filament to the left. (**d**) The myosin head releases Pi and detaches from the actin filament to restart the cycle. In some publications, the order of the release of ADP and Pi from the myosin head is the reverse of what is given in this figure, which will not substantially alter the basic mechanisms underlying the conformon-mediated coupling between chemical reactions and mechanical processes

hydrolyzed and the resulting ADP dissociates from myosin as indicated by the rapid decrease in the fluorescence signal at t = 10 s in Fig. 11.33d which is associated with the $a \rightarrow b$ transition postulated in Fig. 11.34, and the ADP-free myosin then exerts a mechanical force on actin as shown by the relatively slow displacement of actin around t = 10 s in Fig. 11.33d, supporting the c → d transition in Fig. 11.34. *The fact that the fluorescence drop in State (3) is faster than the velocity of the associated displacement of actin is consistent with the proposed mechanism where ATP hydrolysis leading to conformon generation in myosin precedes the displacement of actin by myosin.* Therefore, it may be concluded that *the experimental data presented in Fig. 11.33d provide the first direct experimental evidence to validate the following mechanism of free energy transduction in molecular biology that was proposed more than three decades ago (Ji* 1974b*):*

ATP Hydrolysis ⟶ Conformon Generation ⟶ Force Generation

Fig. 11.35 The conformon mechanism of chemical-to-mechanical energy transduction in biology proposed in Ji (1974b) which was supported by the single-molecule mechanical measurements made by Ishijima et al. (1998; Ishii and Yanagida 2007)

Figure 11.35 supported by the empirical data in Fig. 11.34 thus substantiates the following generalizations:

1. Motor enzymes are molecular machines that carry out chemical-to-mechanical (i.e., "chemo-mechanical") energy conversion/transduction at the microscopic level at physiological temperatures, similar to combustion engines at the macroscopic level at high temperature.
2. Motor enzymes convert chemical energy first to the intermediate form of conformational energy known as *conformons* before they are converted to mechanical forces acting on their environment to do work.

If this analysis turns out to be correct, it could be concluded that the conformon concept embodies the most fundamental characteristics of enzymes (both simple enzymes and molecular motors) at the microscopic level providing a theoretical foundation for single-molecule mechanics (Xie 2001; Ishii and Yanagida 2007; Deniz et al. 2008).

11.4.2 Static/Stationary *versus* Dynamic/Mobile *Conformons*

In Sect. 11.3, the single-molecule enzymological data of Lu et al. (1998), namely, the waiting time distribution of cholesterol oxidase (see Fig. 11.24) were analyzed on the basis of the postulated analogy between the *blackbody radiation* and *enzymic catalysis*. The net result of this analysis was the conclusion that the ground-state cholesterol oxidase (and presumably those of enzymes in general) contains a set of *conformons* with different free energy contents (See Fig. 11.28). In Sect. 11.4.1, the single-molecule mechanics data on the actomyosin system measured by Ishijima et al. (1998) were found to be consistent with the predictions made by the *conformon* model of muscle contraction proposed in Ji (1974b). In both analyses, the concept of the *conformon* played a key role, but with some difference. In cholesterol oxidase, the conformons are postulated to be present even before the catalysis takes place, most likely due to the *endogenous conformational strains* introduced into the protein as it is synthesized on the ribosome one amino acid at a time and folded into a globule before the last amino acid is added (see Klonowski and Klonowska 1982 for a related discussion). In contrast, the conformons postulated to be generated within the myosin molecule during muscle contraction are the result of ATP hydrolysis and are not thought to remain stored in myosin long, before they are used up in doing

molecular work on the actin filament. In other words, the conformons present in cholesterol oxidase are present from the birth of a protein while those generated from ATP hydrolysis (and other exergonic chemical reactions such as ligand binding, methylation, oxidation, reduction, etc.) are introduced later in the life cycle of a protein. For the lack of better terms, we will refer to the former as *static* (or *intrinsic*/*endogenous*) and the latter as *dynamic* (or *extrinsic*/*exogenous*) conformons. As pointed out in (6) in Sect. 11.3.3, "static" conformons are closely related to what is known as the Klonowski-Klonowska conformons (Ji 2000) and to "frustrations" of Anderson (Ji 2000).

In conclusion, the single-molecule enzymological and mechanical data measured by two independent groups in 1998 have been rationally accounted for in terms of the concept of the *conformon* introduced into molecular biology in 1972 (Green and Ji 1972a, b; Ji 1974b, 2000). If the explanations proposed in Sects. 11.3 and 11.4 turn out to be correct upon further investigation, we will be able to conclude that *it took a quarter of a century for the theoretical concept of the conformon to be experimentally confirmed with reasonable certainty*.

11.4.3 Stochastic Mechanics of Molecular Machines

In Sect. 4.9, the concept of "info-statistical mechanics" was introduced based on the *information-energy complementarity* as applied to statistical mechanics. In the present section, a related term, "stochastic mechanics," is introduced, motivated by recent emergence of single-molecule enzymology and mechanics (Xie and Lu 1999; Xie 2001; Ishii and Yanagida 2007; Deniz et al. 2008). Both these terms are closely related as forest and trees or as global and local views. In other words, we may regard "info-statistical mechanics" and "stochastic mechanics" as global (or forest) and local (or trees) views, respectively, of the same phenomenon of life on the microscopic level.

We can divide machines into *deterministic* and *stochastic* machines. *Deterministic machines* (e.g., computers, cars, washing machines) are macroscopic in size, robust against thermal fluctuations (i.e., machine component configurations are not destroyed/rearranged by Brownian motions) and obey deterministic rules. *Stochastic machines* in contrast are microscopic in size (e.g., enzymes, molecular motors, cells), depend critically on Brownian motions for their functions, and exhibit stochastic behaviors that can be represented as time-dependent functions of some random variables (e.g., enzymic activity).

As already mentioned, during the past decade a new field in molecular biology has emerged variously referred to as "single-molecule mechanics" (SMM) or "single-molecule enzymology" (SME) (see Sects. 11.3 and 11.4) as a result of the development of new experimental techniques such as optical tweezers and Foerster (or fluorescence) resonance energy transfer (FRET) methods that have enabled biophysicists to visualize and manipulate single biopolymer molecules (proteins, DNA, and RNA) and measure their motions in real time, involving forces and displacements in the ranges of piconewtons and nanometers, respectively (Ishii and

Yanagida 2000, 2007; Deniz et al. 2008). SME differs from the conventional ensemble-averaged enzymology (EAE) in one important respect: Whereas EAE studies time-dependent *concentrations* of materials involved in chemical reactions, SME investigates time-dependent *probabilities* of single-molecule events such as the activation or deactivation of an enzyme (Fig. 11.17), stochastic movements of molecular motors along DNA, actin filament (Fig. 11.33), or microtubules. It is here suggested that SMM and SME obey the same set of the principles and rules (described below) on which what is here called the "single-molecule stochastic mechanics" (SMSM) is grounded and hence are synonymous with it: i.e., SMM = SME = SMSM.

There appears to be only a small number of the physical principles and rules that underlie SMSM:

1. All molecular machines are driven by mechanical energy packets known as *conformons* that are stored in biopolymers as sequence-specific and mobile conformational deformations (Green and Ji 1972a, b; Ji 1974b, 1991, 2000, 2004a).
2. Conformons can be generated from chemical reactions in three steps (see Fig. 8.1 in Sect. 8.2 and Fig. 11.30):
   (a) Enzymes borrow thermal energies from their environment to produce *virtual conformons* (as a result of *thermal fluctuations*) lasting for less than the time, τ, required for enzymes to complete their machine cycles.
   (b) Virtual conformons mediate the catalysis of an exergonic (i.e., free-energy-supplying) physicochemical processes within their lifetimes.
   (c) Enzymes avoid violating the Second Law by "paying back" the thermal energy borrowed in Step (a) by letting the free energy released from the physicochemical processes equilibrate with its environment within times less than τ and also by synchronously stabilizing the virtual conformons with one or more products generated from the exergonic chemical reactions (Ji 1979).
3. All molecular machines perform work on their environment (e.g., actin filament in the case of myosin, ions in the case of ion pumps) through energy transfer during the coupled phase of the machine-environment interaction cycle, preventing slippage (Ji 1974b).

Items (2)(a) and (2)(b) may appear to violate the traditional formulation of the Second Law of thermodynamics, according to which no *thermal energy can be utilized to do work in the absence of temperature gradients*, but this is not the case, because these mechanisms obey the "molecularized" Second Law of thermodynamics (MSLT) formulated by McClare (1971) (see Statement 2.5 in Sect. 2.1.4).

Rule (2)(b) appears reasonable in view of the fact that *virtual conformons* can last for times much longer than the time required for electronic transitions (or covalent bond rearrangements) and hence the generalized Franck-Condon principle (GFCP) can be applied to them (Sect. 2.2.3). Single-molecule measurements indicate that conformational changes attending enzymic actions are slower than the

electronic rearrangements entailed by chemical reactions by a factor of 10^3–10^6 (see data in Ishii and Yanagida 2000, 2007; Xie and Lu 1999; Xie 2001). Therefore, Rules (1), (2), and (3) presented above appear to provide a sound theoretical framework for grounding the newly emerging *single-molecule stochastic mechanics* (SMSM).

11.4.4 Biopolymers as Molecular Machines*: Three Classes of Molecular Machines and Three Classes of Their Mechanisms of Action*

All biopolymers (proteins, RNA, and DNA) have two properties in common: (a) *sequence information* and (b) *sequence-preserving mechanical deformability* (also called "conformational changes"), which enables biopolymers to store mechanical energy as conformational strains. These properties were first clearly recognized in enzymes and were postulated to play essential roles in the molecular mechanisms underlying enzymic catalysis (Lumry 1974; Ji 1974a, b, 1991, 2000, 2012) as embodied in the concept of the *conformon*, the conformational strains storing mechanical energy and genetic information to drive all goal-directed molecular motions in living cells (see Chap. 8). The main objective of this section is to propose that

> The principles and mechanisms of molecular machines discovered in proteins are universally applicable to all biopolymers, including RNA and DNA to varying degrees. (11.54)

We may refer to Statement 11.54 as the *Principle of the Universality of Molecular Machines* (PUMM) and represent its content in a tabular form as shown in Table 11.15.

Molecular machines can be divided into *passive* and *active* machines depending on whether their outputs approach to or move away from equilibria, respectively. Examples of the former include voltage- and ligand-gated ion channels and those of the latter include active transporters such as the Na^+/K^+ ATPase, H^+ pumps and Ca^{++} pumps. The active machines in turn divide into two classes – primary active machines and secondary active machines – depending on whether the form of the free energy driving the machine is chemical (e.g., Na^+/K^+ ATPase) or nonchemical, i.e., osmotic (e.g., Na^+/Ca^{++} antiporter) or mechanical (e.g., DNA supercoil-driven regulation of gene expression; see Sect. 8.3), respectively. Thus these dual dichotomous divisions lead to three distinct types of molecular machines (a) primary active (or Type I) machines, (b) secondary active (or Type II) machines, and (c) passive (Type III) machines and each type is divided into three classes based on molecular types, i.e., proteins, RNAs and DNAs, on the one hand, and based on whether the processes involved are Victoria or scalar, thus resulting in a total of 18 classes of molecular machines as summarized in Table 11.15. The 9×2 matrix constituting the content of Table 11.15 may be viewed as the *periodic table of molecular machines* (PTMM), and, as was the case with its chemical counterpart, many cells or blocks are left vacant

Table 11.15 The Principle of the Universality of Molecular Machines (PUMM): three classes of molecular machines (proteins, RNA and DNA) and three classes of their mechanisms of actions (Types I, II, and III)

Molecular machines (principles and mechanisms)		Vectorial process (v)	Scalar process (s)
Type I *Primary active machines (conformons Ji* 1974a, b, 2000, *2011)*	Protein	Na^+/K^+ *ATPase*	*RNA polymerase*
		H^+ *pump*	*DNA polymerase*
		Ca^{++} *pump*	*Glycogen synthase*
		Actomyosin system	*ATP synthase*[a]
	RNA		*Riboswitch-ribozymes*, e.g., glmS riboswitch (Winkler et al. 2004)
	DNA		
Type II *Secondary active machines (generalized Franck-Condon principle, pre-fit hypothesis Ji* 1974a, b, 1991, *2011)*	Protein	Na^+/Ca^{++} *antiporter*	*Receptor tyrosine kinase*
		Na^+*/amino acid symporter*	*kinases*
	RNA		*Ribozymes*, e.g., RNA component of RNAse-P, and many introns of RNA (Kruger et al. 1982; Wochner et al. 2011; Tang and Breaker 2000)
	DNA		*Deoxyribozymes*
			DNA supercoils
			Self-regulatory genes (Ji et al. 2009c)
Type III *Passive machines (pre-fit hypothesis (Ji* 1974a, b, 1991, *2011)*	Protein	Voltage- and ligand-gated ion channels	*Esterases*
			Phosphatases
			G-protein-coupled receptors
			Cytokine receptors
			Other simple receptors
	RNA		*Riboswitches*, e.g., FMN riboswitch, glycine riboswitch, and TPP riboswitch (Nudler and Mironov 2004; Tucker and Breaker 2005; Vitreschak et al. 2004; Batey 2006; Nahvi et al. 2002)
	DNA		*Noncoding DNA* as regulators of gene expression (Mattick 2003, 2004)
			Deoxyriboswitches (?)

[a]According to the *chemiosmotic* hypothesis (Sect. 11.6), the respiratory ATP synthesis in mitochondria is driven by the proton gradient across the inner mitochondrial membrane. In contrast, the *conformon hypothesis*, the respiration-driven ATP synthesis is not mediated by any proton gradient but by *conformons*, i.e., the conformational strains of enzymes induced by respiration (Ji 1974b, 1976, 1977, 1979, 1991, 2011; Sect. 11.5). In other words, according to the chemiosmotic hypothesis, ATP synthase is a Type I(v) machine whereas, according to the conformon hypothesis, it is a Type I(s) machine

which may be filled in the future as our knowledge on molecular machines advance, especially with respect to the RNA and DNA varieties.

11.5 The Conformon Theory of Oxidative Phosphorylation

The molecular mechanism of oxidative phosphorylation described in Fig. 11.36 is reproduced from (Ji 1974b, 1979). To the best of my knowledge, it is the most comprehensive model of oxidation phosphorylation that accommodates most, if not all, of the key experimental findings on mitochondria, including the phenomenon of

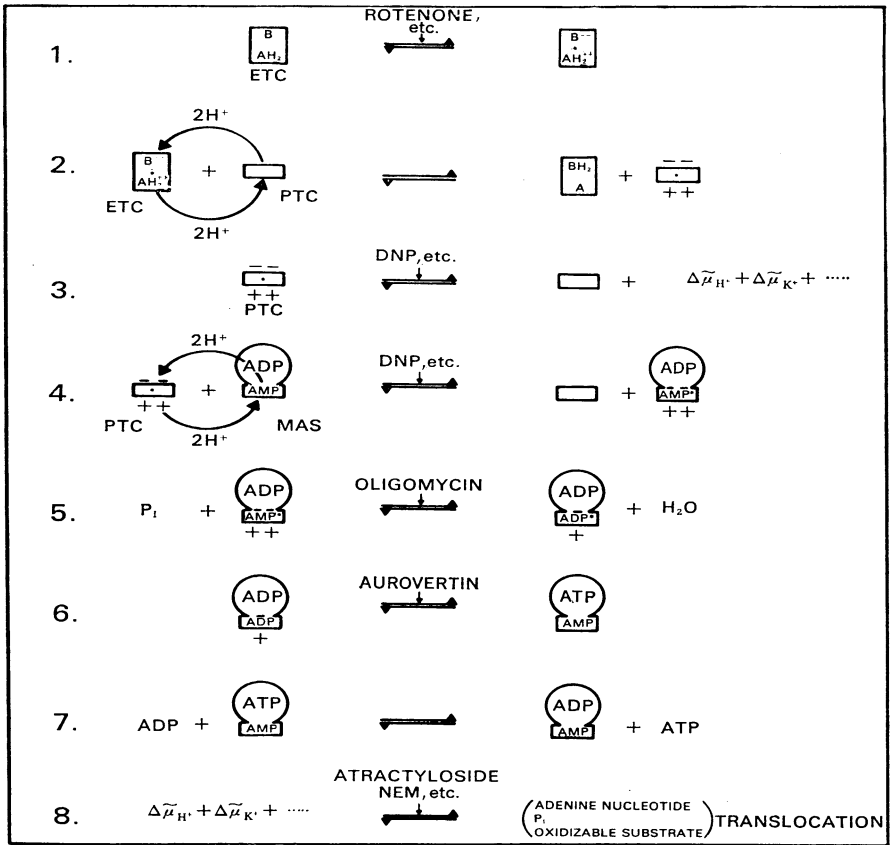


Fig. 11.36 *The Madisonator* – A molecular model of oxidative phosphorylation based on the theory of conformons as energy and information carriers in bioploymers (Reproduced from Ji 1974b, 1979). For detailed explanations for individual steps, see text. The symbol * appearing in Steps 1–5, e.g., AMP*, denotes conformons, i.e., the conformational strains of biopolymers (or their ligands) carrying mechanical strains at sequence- or stereo-specific sites (Chap. 8)

chemiosmosis (see Steps 1–3) (Mitchell 1961, 1968). What distinguishes the *conformon model* and the *chemiosmotic model* of oxidative phosphorylation (see Sect. 11.6) is that the former is rooted in the generalized Franck-Condon principle (Sect. 2.2.3) which has been found to account for not only oxidative phosphorylation but also enzymic catalysis (Sect. 7.2) and muscle contraction (Fig. 11.34). It is clear that the chemiosmotic hypothesis is inapplicable to both enzymic catalysis and muscle contraction, because these two processes can occur without any osmotic barrier, the essential requirement of chemiosmosis – the conversion of chemical energy to osmotic energy. In other words, the chemiosmotic hypothesis has little to say concerning the fundamental molecular mechanisms underlying enzymic catalysis and muscle contraction.

In Step 1, the electron transfer complex (ETC) catalyzes the separation of electrons and protons, storing a part of the free energy released from the redox reaction as conformons (denoted by the symbol *). In Step 2, the energized ETC collides with a hypothetical intra-membrane protein acting as a proton pump (and hence called proton transfer complex, PTC), and two protons are postulated to be donated to the matrix (or the lower) side of PTC and two protons are thought to be abstracted from the cytosolic (or the upper) side, resulting in a depolarized and de-energized ETC and a polarized and energized PTC. In Step 3, the polarized PTC utilizes its conformons to actively pump protons out from the matrix space to the cytosolic space to create a pH gradient and a membrane potential (as in the chemiosmotic hypothesis). Alternatively, the energized PTC can transfer its conformons (via asymmetric protonation-deprotonation reactions as in Step 2) to the mitochondrial ATP synthase (MAS), leading to the de-energization of PTC and energization of MAS as shown in Step 4. In Step 5, a part of the conformons is used to phosphorylate the AMP bound to the basepiece of MAS, and a second conformon is postulated to be used to transfer the phosphoryl group from the ADP bound to the basepiece of MAS to the ADP bound to the F_1 subunit (denoted as a circle) of MAS, thus generating one ATP bound to MAS (see Step 6). In Step 7, this ATP is exchanged for the ADP in the matrix space of mitochondria. Finally, in Step 8, the ATP in the matrix compartment of mitochondria is actively transported out into the cytosol, driven by the proton electrochemical gradient and membrane potential generated in Step 3. All the steps included in Fig. 11.36 are supported by experimental data on the actions of the inhibitors and uncouplers specific for them, except Steps 2 and 7 whose inhibitors and uncouplers appear not to have been discovered yet to the best of my knowledge.

11.6 Deconstructing the Chemiosmotic Hypothesis

The British biochemist, P. Mitchell (1920–1992), proposed the concept of *chemiosmosis* in 1960 (Mitchell 1961, 1968) in an attempt to explain how mitochondria, *the powerhouse of the cell,* synthesize ATP from ADP and inorganic phosphate, P_i, utilizing the free energy supplied by the oxidation of substrates such as

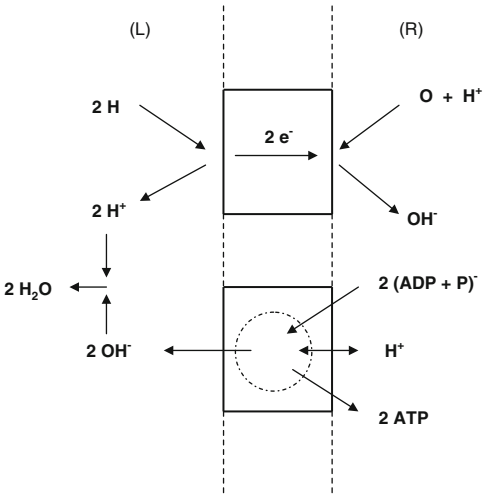


Fig. 11.37 The chemiosmotic hypothesis proposed by P. Mitchell in 1961 (adopted from Mitchell 1961)

NADH and succinate during respiration. His basic idea is that the *chemical* energy of, say, NADH is first converted into the *osmotic* energy (hence the adjective "chemiosmotic") of the proton gradient across the mitochondrial inner membrane (inside high pH and outside low pH) and associated membrane potential (inside negative and outside positive) which subsequently drives the synthesis of ATP (Scheme (11.55)):

$$(\textbf{Chemical Energy of NADH}) \xrightarrow{1} (\textbf{Proton Gradient}) \xrightarrow{2} (\textbf{ChemicalEnergy of ATP}) \tag{11.55}$$

where *Process 1* indicates the translocation of protons across the mitochondrial inner membrane driven by respiration (see the upper box in Fig. 11.37 below), and *Process 2* indicates the proton gradient-driven phosphorylation of ADP to ATP (see the lower box in Fig. 11.37). The key postulates of the Mitchell hypothesis are as follows:

1. The membrane-embedded respiratory enzymes (symbolized by the upper box in Fig. 11.37) *somehow* separate the electron (indicated by e^- the encircled negative charge) and the proton (H^+) from the hydrogen atom (H) and move the former across the membrane (from the left side, L, to the right side, R), leading to the generation of a transmembrane proton gradient and a membrane potential (not shown) and attendant acidification of the L compartment and alkalinization of the R compartment.
2. The osmotic energy stored in the proton gradient (also called the electrochemical gradient of protons or the "proton-motive force", PMF) then drives the abstraction of the hydroxyl ion (OH^-) from the L compartment and the proton from the R compartment to effectuate the synthesis of ATP from ADP and P_i at the reaction center embedded inside the M phase (see the lower box in

Fig. 11.37). But the realistic molecular mechanisms accomplishing such complex molecular processes were left undefined.

3. The respiratory enzyme system catalyzing Process 1 and the reversible ATPase system catalyzing Process 2 are coupled through the mediation of the common chemical species, i.e., *protons*, which are generated from respiration (upper box) and consumed by the ATP synthase (lower box) through as yet unknown mechanisms.

I have long expressed my doubt about the validity of the chemiosmotic hypothesis (despite the seemingly universal acceptance of the chemiosmotic theory by biochemistry textbook writers around the world), because it does not provide any realistic theoretical insights into the possible molecular mechanisms underlying oxidative phosphorylation (Ji 1974b, 1979, 1991). Even if the chemiosmotic hypothesis proves to be theoretically correct, it cannot represent a *universal* principle of *biological energy coupling* because there are membrane-independent (and hence *non-osmotic*) energy-coupled processes in biology, including *muscle contraction*, *molecular motors* moving cargoes along cytoskeletal tracks in the cytosol, and the *tracking of RNA polymerase* along DNA during transcription. In Ji (1991, pp. 60–61), I wrote:

> . . . The chemiosmotic hypothesis of oxidative phosphorylation proposed by P. Mitchell in 1961 (Nicholls 1982; Skulachev and Hinkle 1981) postulates that ATP synthesis is driven by the electrochemical gradient of protons across the inner mitochondrial membrane which is set up by respiration; in other words, in Mitchell's model the generation of the transmembrane electrochemical gradient of protons driven by respiration precedes the phosphorylation reaction. However, according to the Madisonator [i.e., Fig. 11.36], the respiration-driven generation of the transmembrane proton gradient (step 3 in Fig. 1.3) [which is Fig. 11.36 here] and the phosphorylation reaction (steps 5 and 6) are parallel events that are driven by a common free energy precursor generated from respiration, namely conformons (see steps 1 and 2). The primary biological role of the active transport in mitochondria is thought to be not the synthesis of ATP as P. Mitchell assumes but most likely the *communication between mitochondria and metabolic events* going on in the cytosol. If this interpretation turns out to be correct, then the phenomenon of the proton gradient-driven ATP synthesis, well-known in the literature, may have no general biological significance in mitochondria, except perhaps that such a process may contribute to the survival of cells under anoxic conditions when the cytosolic pH drops due to the accumulation of lactate produced by anaerobic glycolysis and that the resulting transmembrane proton gradient may drive ATP synthesis according to the chemiosmotic mechanism of P. Mitchell. (emphasis added)

R. J. P. Williams (1969) is another critic of the chemiosmotic coupling concept. His criticism, aired from the very beginning of the chemiosmotic conception, is based on the consideration of thermodynamic efficiency, which I find persuasive as discussed in (2) below. The following are my specific criticisms against the chemiosmotic hypothesis:

1. Mitchell's proposed mechanism for effectuating respiration-driven proton translocation across the mitochondrial membranes is based on what he calls *vectorial metabolism* or *anisotropy of membrane protein organization* (Mitchell 1961). This idea seems insufficient to account for oxidative phosphorylation, because structural organization alone, no matter how asymmetric, cannot cause an asymmetric transport of the products of chemical reactions without dissipating requisite free

energy. Without any *enzymologically realistic mechanisms* for coupling a down-hill reaction (e.g., oxidation of NADH to NAD^+) to an up-hill chemical reaction or physical process (e.g., the vectorial movement of protons and asymmetric removal of water or the hydroxyl group from the ATP synthesis center), structural asymmetry alone cannot achieve or cause asymmetric metabolism. In fact to cause a symmetry breaking in molecular processes without dissipating requisite free energy is tantamount to violating the First Law of thermodynamics, because the resulting gradients could be harnessed to do work, thereby producing energy.

2. According to the chemiosmotic coupling scheme, the protons generated from respiration are extruded from the membrane phase (with volume V_M) to the bulk phase (with volume V_B). As Williams (1969) correctly pointed out, this is an energy-dissipating process because V_B is much greater than V_M. (The situation is analogous to perfume molecules diffusing out of a perfume bottle into the vast space of a dancing hall.) In addition, at least the same amount of free energy must be dissipated during the proton-driven ATP synthetic step, because in order to bring the protons back into the ATP synthesis center in the M phase (Fig. 11.37), free energy must be dissipated in the amount proportional to the volume ratio, V_B/V_M, which would probably be greater than 10^9. This ratio can be estimated by measuring the areas occupied by the mitochondrial inner membrane relative to the cytoplasmic area in an electron micrograph of the cell and raising the resulting ratio to the power of 3/2.
3. As indicated in (1), structural asymmetry is necessary but not sufficient for effectuating asymmetric process or metabolism. In addition, it is critical for the chemiosmotic hypothesis that the ATP synthesizing reaction center (see the dotted circle in the lower box in Fig. 11.37) be located *within* the M phase, not in the R phase, since, in the latter case, the ATP synthesis cannot be driven by any osmotic energy of the transmembrane proton gradient. However, the recent X-ray crystallographic findings (Aksimentiev et al. 2004; Junge et al. 1997) clearly demonstrate that the ATP synthase is located not in the M phase as Mitchell assumed but outside the membrane phase attached to the proton pumping structure (i.e., F_0) in the M phase through a set of long polypeptide chains (designated as γ and ε subunits).
4. It is generally accepted that, when ATP synthase catalyzes the formation of ATP from ADP and P_i driven by the proton gradient, the electrochemical energy of proton gradient is first converted into the mechanical energy (in the form of "torque," i.e., the energy producing a rotatory motion) within F_0, which is then transmitted to F_1 (through the rotatory motion of the shaft composed of the γ and ε subunits) where the energy is utilized to release (or de-bind) ATP from F_1 (Aksimentiev et al. 2004). Thus, the sequence of events involved in the proton gradient–driven synthesis of ATP can be depicted as follows (Scheme (11.56)):

$$\begin{array}{c}(\textbf{Proton Gradient}) \overset{1}{\leftrightarrow} (\textbf{Mechanical Energy of the } \boldsymbol{\gamma} \textbf{ and } \boldsymbol{\varepsilon} \textbf{ Subunits}) \\ \updownarrow 2 \\ (\textbf{Chemical Energy of ATP})\end{array} \tag{11.56}$$

Scheme (11.56) is known to be reversible so that protons can be pumped across the mitochondrial inner membrane (producing osmotic energy) driven by the chemical energy of ATP hydrolysis. On the phenomenological level, therefore, the concept of chemiosmotic coupling proposed by Mitchell may appear validated since *chemical* and *osmotic* energies are indeed interconverted. But this way of looking at the problem is superficial. The heart of the problem concerns not so much *whether or not* the process of chemiosmosis occurs in mitochondria (which was known to take place in living systems long before 1961 when the chemiosmotic hypothesis was formulated) but exactly *how* such a process occurs on the molecular level. In other words, we must distinguish between the *phenomenon* of chemiosmosis and the *molecular mechanisms* underlying the phenomenon. *On the phenomenological level, the Mitchell hypothesis cannot be faulted. But it is on the level of molecular mechanisms of chemiosmosis that the Mitchell hypothesis fails as I have been pointing out over the past three decades* (Ji 1979, pp. 34–35; Ji 1991, pp. 60–61; Williams 1969).

Any mechanical (i.e., conformational) energy stored in biopolymers can be viewed as examples of *conformons*. Therefore we can rewrite Scheme (11.56) as follows:

$$\begin{array}{c}(\textbf{Proton Gradient}) \overset{1}{--}> (\textbf{Conformons Stored in the } \boldsymbol{\gamma} \textbf{ and } \boldsymbol{\varepsilon} \textbf{ Subunits}) \\ \downarrow 2 \\ (\textbf{Conformons Stored in } \mathbf{F_1} \leftrightarrow \textbf{Chemical Energy of ATP})\end{array} \tag{11.57}$$

Process 1 above is the step where conformons are generated from proton gradients, most likely by reversing the molecular steps postulated for the conformon-driven active transport described in Fig. 2 in Ji (1979) or Fig. 8.1 in this book. Process 2 involves conformon transfer from F_0 to F_1 through the γ and ε subunits, which probably occurs through the mechanism of conformon transfer proposed in Fig. 4 in Ji (1974b).

All the problems encountered by the chemiosmotic hypothesis as indicated above can be resolved simply by invoking the concept of *conformons* which can drive either active transport or ATP synthesis as indicated in Fig. 11.36, depending on the metabolic needs of the cell. The conformon theory of molecular machines accounts for not only membrane-dependent oxidative phosphorylation and active transport but also membrane-independent processes such as muscle contraction and DNA transcription and replication by RNA and DNA polymerases, respectively, DNA supercoiling, and cytoplasmic molecular motor movements – all through the common agency of the energy and information carried by conformons (Ji 1974b, 1979, 2000, 2004a). Thus the conformon concept provides a bioenergetic mechanism that can be applied *universally* to all energy-coupled processes in living systems, including chemiosmosis, but the chemiosmotic approach is limited to explaining membrane-dependent energy-coupled processes such as proton gradient–driven ATP synthesis – all on the phenomenological level.

A direct experimental evidence for the production of conformons from ATP hydrolysis in the F1-ATPase was recently reported by Uchihashi et al. (2011; Junge and Müller 2011). Using the high-speed AFM (atomic force microscopy), these authors succeeded in visualizing the propagation of the *conformational waves* of the β subunits in the counterclockwise direction around the isolated F_1 stator ring without the central γε subunits (see Fig. 2a in Uchihashi et al. 2011). These *conformational waves* are identical to what Green and I defined as *conformons* in 1972 (Green and Ji 1972a, b; Ji 1974b, 2000; also see Chap. 8) and thus provide *the best experimental evidence reported do date that verifies the theoretical concept of the conformon*.

11.7 Molecular Machines as Maxwell's "Angels"

In 1867, in a letter to Peter G. Tait, James C. Maxwell (1831–1879) described a microscopic "being" capable of separating fast moving molecules from slow moving ones into two compartments, thereby decreasing the entropy of the system, "without expenditure of work". Such a "being" was named "Maxwell's demon" in 1874 by William Thompson (1824–1907), implying the mediating, rather than the malevolent, connotation of the word. Maxwell describes his intelligent, microscopic "being" as follows:

> . . . if we conceive of a being whose faculties are so sharpened that he can follow every molecule in its course, such a being, whose attributes are as essentially finite as our own, would be able to do what is impossible to us. For we have seen that molecules in a vessel full of air at uniform temperature are moving with velocities by no means uniform, though the mean velocity of any great number of them, arbitrarily selected, is almost exactly uniform. Now let us suppose that such a vessel is divided into two portions, A and B, by a division in which there is a small hole, and that a being, who can see the individual molecules, opens and closes this hole, so as to allow only the swifter molecules to pass from A to B, and only the slower molecules to pass from B to A. He will thus, without expenditure of work, raise the temperature of B and lower that of A, in contradiction to the second law of thermodynamics. . . . (http://en.wikipedia.org/wiki/Maxwell's_demon)

To me, Maxwell's "being" violates the second law of thermodynamics basically because he "'opens' and 'closes' this hole . . . without expenditure of work". According to the second law of thermodynamics, no work of any kind can be performed without dissipating energy into heat, i.e., without increasing the entropy of the system which, in this case, consists of both gas molecules and Maxwell's "being". A more rigorous proof of a similar kind was formulated by Léo Szilárd in 1929. Many other proofs are now available to show that Maxwell's "being" violates the second law of thermodynamics (Leff and Rex 1962; Maruyama et al. 2009).

Maxwell's "being" can carry out his assigned task without violating the second law of thermodynamics *if and only if* he dissipates the requisite energy into heat – in other words, if and only if he receives energy from and dissipates heat into his environment while performing his molecular work. That is, Maxwell's "being" can

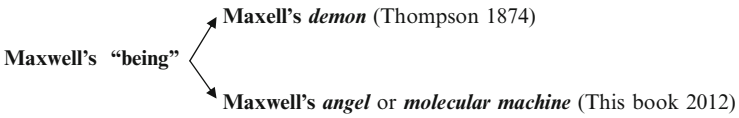


Fig. 11.38 The duality of Maxwell's "being." Maxwell's demon cannot exist because it violates the second law of thermodynamics, but Maxwell's angels exist because they do not violate the second law and act as molecular machines in all living systems

carry out his assigned task without violating the second law if he acts as or is a molecular machine, the concept well established in the molecular biology of the twentieth century (Alberts 1998). Thus, it seems logical to distinguish two kinds of Maxwell's beings – the original one that violates the second law, i.e., Maxwell's demon, and the other that obeys the second law, which I suggest here to be referred to as "Maxwell's angel" (see Fig. 11.38).

Maxwell's demon is of particular interest to us because it acts as the focal point of interaction between information (I) and energy (E), the two fundamental entities underlying the operation of all molecular machines. Therefore, in order to understand the I–E relation, it may be helpful to understand how Maxwell's demon works or does not work. According to Proposition I of the "dualogy" of Sabah Karam (2011), "In order to describe any single event, action, state of being, thought, or any other real or abstract concept it is necessary to identify two distinct complementary co-dependent entities that define the state (conjugate variables) and behavior (conjugate transformations) of the phenomenon under consideration." If Karam is right, the reason for the century-long debates about Maxwell's demon and the associated I-E relation (Leff and Rex 1962) may be traced to the failure on the part of the debaters "to identify two distinct complementary co-dependent entities" that define Maxwell's "being". In this book, I am suggesting that the "two distinct complementary co-dependent entities" that characterize Maxwell's "being" are *Maxwell's demon*, named by William Thompson in 1874, and *Maxwell's angel* that was born on December 1, 2011, during one of my lectures on the information-energy complementarity given to a group of interdisciplinary honors seminar students at Rutgers. Since *Maxwell's demon* and *Maxwell's angel* are conjugate entities, understanding one will inevitably lead to understanding the other, again according to the dualogy of Karam (2011). By identifying Maxwell's angel with the molecular machine of the twentieth-century molecular biology (Alberts 1998), it is claimed here that we will understand Maxwell's angel and its conjugate, Maxwell's demon, and hence the I-E relation if and when we understand how molecular machines work, the Holy Grail of the twenty-first-century molecular biology. Just as Maxwell himself succeeded in integrating *electricity* and *magnetism* into *electromagnetism* in the mid-nineteenth century, Maxwell's angles (or molecular machines) may contribute to integrating *information* and *energy* into *information-energy* (also called *gnergy*; see Sect. 2.3.2) in the twenty-first century. Figure 11.39 represents these ideas diagrammatically. In formulating these diagrams, two ideas emerged unexpectedly: (1) There may exists triadic categories composed of three

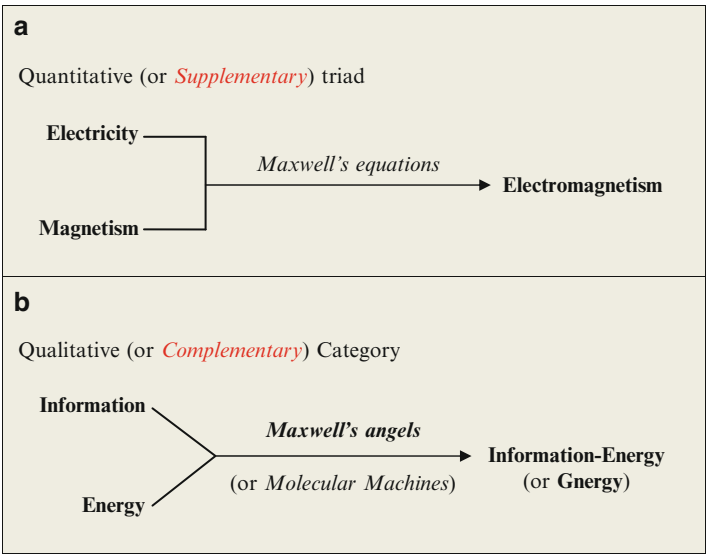


Fig. 11.39 Two kinds of "triadic" categories suggested by *Maxwell's equations* and *molecular machines* (or Maxwell's angels). The concepts of *supplementarity* and *complementarity* are defined in Sect. 2.3.1

nodes rather than the usual two and (2) there may be two kinds of triadic categories – the *quantitative* (or *supplementary*) category where the mapping can be expressed mathematically (e.g., Maxwell's equations), and the *qualitative* (or *complementary*) category where the mapping cannot be expressed in terms of mathematical equations. These two kinds of mappings are depicted with two different symbols in Fig. 11.39 (see Table 2.6 for related symbols).

Chapter 12
Whole Cells

12.1 DNA Microarrays: A Revolution in Cell Biology

The last decade of the twentieth century witnessed two revolutionary experimental techniques to emerge in molecular and cell biology – the *single-molecule mechanics techniques* discussed in Chap. 11 (Xie 2001; Ishii and Yanagida 2007; Deniz et al. 2008) and the *DNA microarray technique* to be discussed in this chapter.

The advent of the microarray technique in molecular biology in the mid-1990s (Pease et al. 1994; Schena et al. 1995; Eisen et al. 1998; Holter et al. 2000; Watson and Akil 1999; Alon et al. 1999; White et al. 1999) marks an important turning point in the history of cell biology, perhaps comparable to the discovery in 1953 of the DNA double helix in molecular biology. Although there remain many challenging problems, both methodological and theoretical (Weinstein 2008; Ji and Yoo 2005; Ji et al. 2009a), this novel technology has a great potential to make fundamental contributions to advancing our knowledge about the basic workings of the living cell which will lead to practical applications in medicine, biotechnology, and pharmaceutical industry (Chaps. 18, 19).

The advancement of the microarray technique, which was critically dependent on the molecular biology of DNA, has initiated a paradigm shift away from DNA toward a *system-based biology* by allowing biologists to study the cell as an *organized system of biopolymers* in contrast to the earlier studies centered on individual biopolymers (DNA, RNA, and proteins). In other words, DNA not only opened the era of *molecular biology* in the mid-twentieth century but also ushered in its own eclipse as the *prima dona* of biology in the last decade of the same century, by giving birth to the microarray technique that led to the emergence of *the systems biology*. It is becoming increasingly clear that the genome-wide expression data revealed by the DNA array technique can no longer be rationally accounted for solely on the basis of the principles and knowledge gained from molecular biology of individual biopolymers alone (Ji 2004a; Ji and Yoo 2005; Bechtel 2010) and that new approaches and perspectives are needed

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_12,

that are deep and powerful enough to enable cell biologists to correctly analyze and interpret the avalanche of DNA array data that is accumulating on the Internet.

12.2 The DNA Microarray Technique

cDNA fragments can be fabricated into either *microarrays* or *macroarrays* (Garcia-Martinez et al. 2004), but the term "microarrays" frequently refer to both *micro-* and *macroarrays*. A microarray consists of a microscopic slide (or its equivalent), about 2 × 2 cm in dimension, divided into, typically, 10,000 squares, each of which covalently binds hundreds of copies of a fragment of DNA (i.e., cDNA, or oligonucleotides) that is complementary to a stretch of the genome encoding a RNA molecule (Watson and Akil 1999). Thus, using one microarray, it is possible to measure simultaneously the levels of 10,000 RNA molecules in a biological sample. Before the development of the microarray technique, it was possible to study only a small number of RNA molecules at a time. The experimental procedures involved in DNA microarray measurements are (Watson and Akil 1999):

1. Isolate RNA from broken cells.
2. Synthesize fluorescently or radioactively labeled cDNA from RNA using reverse transcriptase and fluorescently or radioactively labeled nucleotides. When fluorescently labeled nucleotides are employed, the red fluorophore Cy5 is used to label the DNA synthesized from the RNA isolated from query samples and the green fluorophore Cy3 is used to label the cDNA synthesized from the RNA isolated from reference samples.
3. Prepare a microarray either with EST (expressed sequence tag, i.e., DNA sequences, several hundred nucleotides long that are complementary to the stretches of the genome encoding RNAs) or oligonucleotides (synthesized right on the microarray surface).
4. Pour the labeled cDNA preparation over the microarray surface to effect hybridization and wash off excess debris.
5. Measure the light intensity or the radioactivity of the labeled cDNA bound to individual squares (or spots) on a microarray surface using a computer-assisted microscope.
6. Display the final result as a table of numbers, each registering the signal intensity of a square on the microarray which is proportional to the concentration of cDNA (and ultimately RNAs in the cell before breaking the cell membrane) located at row x and column y. Row x indicates the identity of the genes encoding RNAs being measured, and column y indicates the time of measurement or the conditions under which the RNA levels are measured.

Typical results of microarray measurements of RNA levels are shown in Figs. 9.1, 12.1, and 12.2. These data were measured by Garcia-Martinez et al. (2004) from budding yeast *Saccharomyces cerevisiae* undergoing glucose–galactose shift at

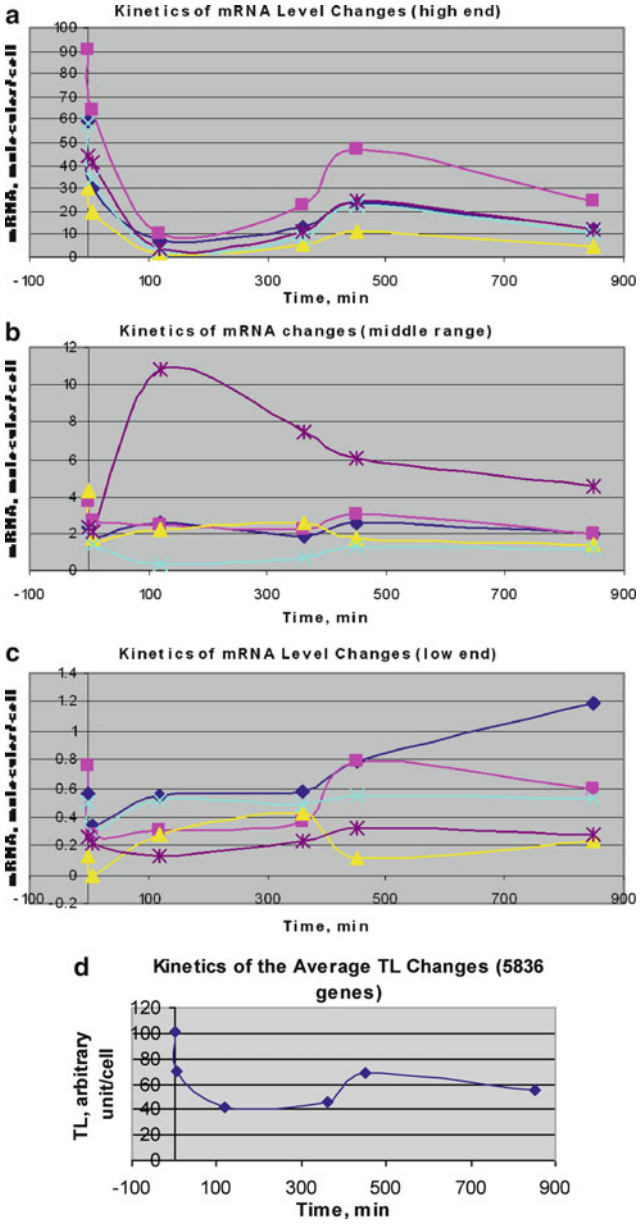


Fig. 12.1 Typical examples of the time-dependent RNA levels measured in budding yeast with DNA microarrays after switching glucose to galactose in the growth medium at t = 0 (Garcia-Martinez et al. 2004). Each data point is the average of three measurements. Panels **a**, **b**, and **c** show the RNA level trajectories of 15 genes chosen randomly out of over 6,000 genes in three different ranges on the *y*-axes, namely, between 0 and 60 RNA molecules per cell in Panel **a**, between 0 and 10 in Panel **b**, and between 0 and 1 in Panel **c**. Panel **d** depicts the average kinetics of the RNA molecules encoded by 5,836 genes. See Ji et al. (2009a) for the details involved in calibrating microarray signals in absolute units of RNA molecules per cell. A similar set of graphs are shown in Fig. 9.1

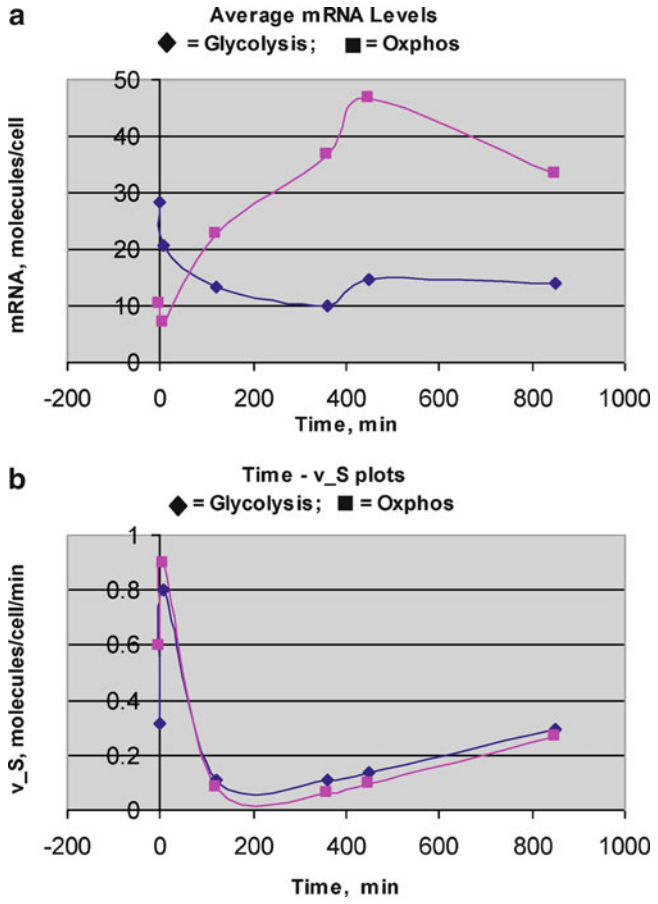


Fig. 12.2 The average time courses of the transcript levels (TL) and transcription rates (TR) of 14 each of the glycolytic and respiratory (also called oxidative phosphorylation, or ox phos) genes (Garcia-Martinez et al. 2004; Ji et al. 2009a)

6 time points: 0, 5, 120, 360, 450, and 850 min after the nutritional shift. Except two trajectories in Fig. 12.1b (brown and yellow trajectories) and one in Fig. 12.1c (yellow), most of the 15 transcripts show kinetic behaviors that are similar to the genome-wide average kinetic behavior shown in Panel in Fig. 12.1d, despite the fact that the scale of the y coordinates varies over two orders of magnitude. The overall quality of the kinetic data, as evident in the smooth and coherent trajectory exhibited by each gene, increases our confidence in the microarray experimental method. The three unusual trajectories seen in Figs. 12.1b, c are most likely not artifacts of measurement but most likely reflect genuine biological responses of the associated genes to the nutritional stress.

12.3 Simultaneous Measurements of Transcript Levels (TL) and Transcription Rates (TR) in Budding Yeast

Both the *transcript level* (TL) and *transcription rate* (TR) of individual genes were measured with DNA arrays at the same time by Garcia-Martinez et al. (2004). The *S. cerevisiae* yeast strain BQS252 was grown overnight at 28°C in YPD medium (2% glucose, 2% peptone, 1% yeast extract) to exponential growth phase. Cells were recovered by centrifugation, resuspended in YPGal medium (2% galactose, 2% peptone, 1% yeast extract), and allowed to grow in YP Gal medium for up to about 14 h after the glucose–galactose shift. Cell samples were taken at 0, 5, 120, 360, 450, and 850 min after the glucose–galactose shift. Two different aliquots were taken from the cell culture at each sampling time. One aliquot was processed to measure transcription rates (TR) using the *genomic run-on protocol*, the scaled-up version of the usual nuclear run-on method (Hirayoshi and Lis 1999), and the other was processed to measure transcript levels (TL) using the same DNA macroarrays recovered from the associated TR measurements. Two examples of the TL and TR measurements are shown in Fig. 12.2.

One striking feature of the curves shown in Fig. 12.2 is the contrasting kinetic behaviors of the glycolytic and oxidative phosphorylation (or oxphos) transcripts in Panel a and the close similarity of the transcription-rate profiles in Panel b of these two metabolic pathways. It is important to keep in mind that at least a part of the reason for this difference is attributable to the fact that Panel a deals with RNA concentrations whereas Panel b is concerned with the rates of RNA synthesis.

12.4 RNA Trajectories as Intracellular Dissipative Structures (IDSs) or *RNA Dissipatons*

The temporal trajectories of individual transcripts (i.e., RNA molecules) shown in Fig. 12.1 are dynamic structures whose existence depends on dissipating free energy and hence can be referred to as *dissipative* structures of Prigogine (1977, 1980) (see Sect. 3.1). These RNA trajectories (or waves) are also frequently referred to as "gene expression profiles," which is an inaccurate statement because RNA trajectories reflect not only *gene expressions* (understood here as transcription) but also *transcript degradation* (see Step 2 in Fig. 12.4 below). The general decline in the average RNA levels shown in Fig. 12.1d during the first 360 min after switching glucose to galactose is primarily due to the depletion of intracellular ATP caused by the removal of glucose, the preferred energy source of budding yeast. The subsequent rise in RNA levels beginning around 360 min is most likely due to galactose-induced expression of the genes coding for the Leloir enzymes (Berg et al. 2002) needed to metabolize the new substrate, galactose, to generate ATP (Ji et al. 2009a). This interpretation is supported by the finding that the Leloir transcripts began to increase at about 120 min after the nutritional shift (see Fig. 12.3).

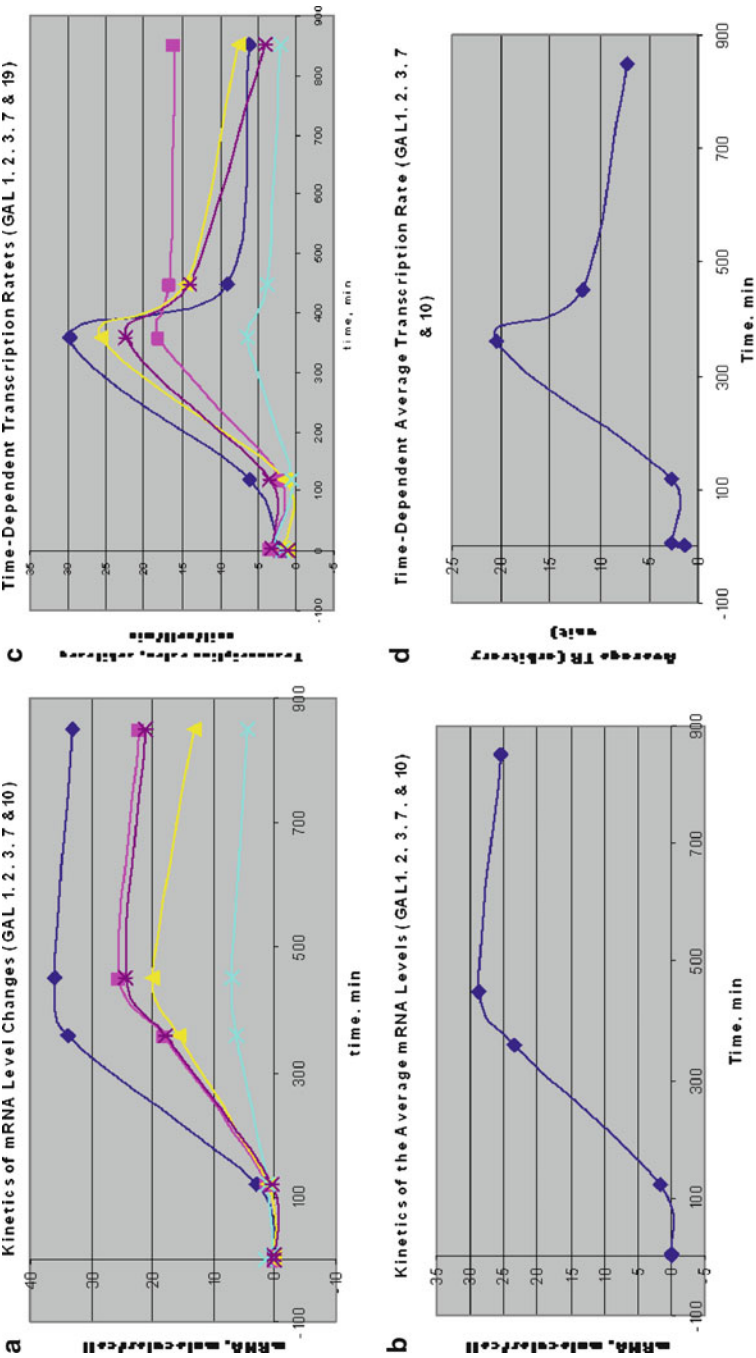


Fig. 12.3 The RNA trajectories and time-dependent rates of transcription of the Leloir genes. (**a**) The kinetics of the transcript levels of the Leloir genes. (**b**) The average kinetics of the LeLoir transcripts. (**c**) The average time course of the transcription rates of the Leloir genes. (**d**) The average of (**c**)

Table 12.1 A summary of the kinetics of the TL (transcript level) and TR (transcription rate) depicted in Fig. 12.2a, b. The upward and downward arrows indicate an increase and a decrease, respectively

Time, min		0–5	5–120	120–360	360–450	450–850
Phase (or time period)		I	II	III	IV	V
Transcript level (*TL*)	Glycolysis	↓	↓	↓	↑	No change
	Oxidative phosphorylation	↓	↑	↑	↑	↓
Transcription rate (*TR*)	Glycolysis	↑	↓	↓	↑	↑
	Oxidative phosphorylation	↑	↓	↓	↑	↑

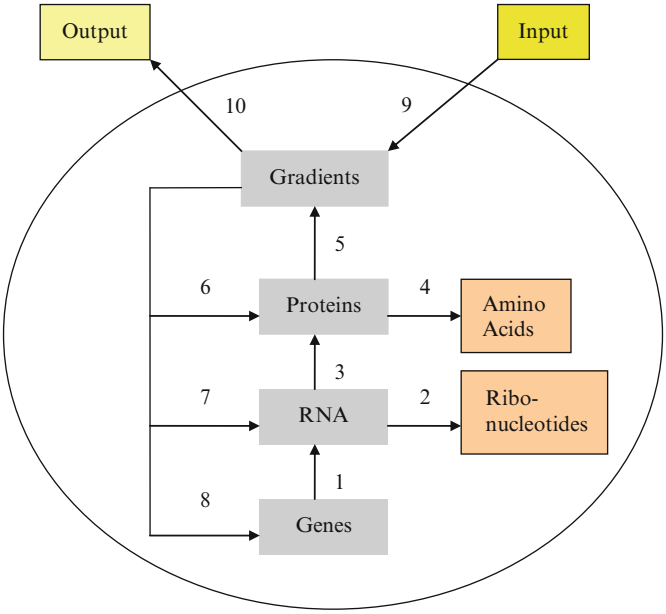


Fig. 12.4 A simplified version of the Bhopalator model of the cell (see Fig. 2.11). Gradients in this figure can be equated with "Dissipative Structure of Prigogine" in the Bhopalator or Intracellular Dissipative Structures (IDSs) (Ji 1985, 2002). It is important to note that what DNA arrays commonly measure is not the *rates* of transcription or gene expression (Step 1), as is widely believed, but the intracellular *levels* of RNA molecules (the balance between Steps 1 and 2) at any given time. In other words, the latter is determined by both the rate of synthesis (Step 1) and the rate of transcript degradation (Step 2). Ignoring this simple fact has led to erroneous interpretations of DNA microarray data since the beginning of the DNA microarray era in the mid-1990s (see Sect. 12.6) (Ji et al. 2009a)

The qualitative features of the temporal behaviors of TL and TR displayed in Fig. 12.2a, b are summarized in Table 12.1. In order to understand the molecular mechanisms underlying these dynamic behaviors of TL and TR, it is necessary to have a simplified model of the cell as shown in Fig. 12.4. As indicated in the first two rows in Table 12.1, the total observational period of 850 min can be divided into five phases, labeled I–V. During Phase I, the transcript levels of both glycolytic and respiratory genes decrease precipitously although the corresponding transcription

rates increase, most likely because the stress induced by glucose–galactose shift increases transcript degradation rates (see Step 2 in Fig. 12.4) more than what can be compensated for by increased transcription. During Phases II and III, the glycolytic transcript levels decrease by twofold, whereas the oxidative phosphorylation (oxphos) transcript levels increase by fourfold. Since the corresponding transcription rates of both the glycolytic and respiratory genes decline rapidly followed by a plateau, the increased respiratory (also called oxphos) mRNA levels cannot be accounted for in terms of transcriptional control alone but must implicate degradational control as well. That is, just as the removal of glucose "de-induces" glycolytic mRNA molecules (leading to the declining TL and TR trajectories for glycolysis seen in Fig. 12.2a, b), so it might repress (or de-induce) the degradation of respiratory mRNA molecules, leading to a rise in respiratory mRNA levels as seen in Fig. 12.2a between 5 and 360 min. This hypothetical phenomenon may be referred to as *glucose de-induction* in analogy to *glucose induction* (Winderickx et al. 2002; Ronne 1995). During Phase IV, both TL and TR for glycolytic and respiratory genes increase, and this may be attributed to galactose induction of the Leloir transcription (Fu et al. 1995; Leuther and Johnston 1992). In support of this interpretation, it was found that glucose–galactose shift induced an increase in both TL and TR of the Leloir genes (GAL 1, 2, 3, 7, and 10) between 120 and 450 min by more than tenfold (see Fig. 12.3). The Leloir genes code for the enzymes and transport proteins that are involved in converting extracellular galactose to intracellular glucose-1-phosphate (Berg et al. 2002), which is then metabolized via the glycolytic and respiratory pathways. Finally, during Phase V, the glycolytic mRNA levels remain constant while the respiratory mRNA levels decline slightly, the latter likely due to galactose repression (in analogy to the glucose repression [Winderickx et al. 2002]) of respiration following the formation of glucose-1-phosphate via the Leloir pathway (Berg et al. 2002). The transcription rate of glycolytic genes continue to increase during Phase V probably due to galactose induction (Fu et al. 1995; Leuther and Johnston 1992), although the corresponding transcript levels remain unchanged, which may indicate the degradational control of glycolytic mRNA molecules. That is, budding yeast seems capable of keeping glycolytic TL constant in the face of increasing TR, by increasing the transcript degradation rates (TD). The TR trajectory of respiratory genes also continue to increase during Phase V despite the fact that their TL trajectory decline, which can be best explained in terms of the hypothesis that respiratory mRNA levels are controlled by transcript degradation during this time period. It is evident that the TL and TR data presented in Fig. 12.2a, b cannot be adequately accounted for in terms of TR alone but requires taking into account both TR and TD (transcript degradation) on an equal footing (Ji et al. 2009a).

12.5 The IDS-Cell Function Identity Hypothesis: Experimental Evidence

Since RNA levels reflect the dynamic metabolic states of cells (or *cell states*) resulting from the interaction between two opposing processes – *transcription* and *transcript degradation* (see Fig. 12.4) – their maintenance requires free energy dissipation.

Consequently, the time-dependent patterns of the changes in RNA levels (i.e., RNA trajectories or RNA waves) qualify as species (or tokens) of *intracellular dissipative structures* (IDSs) (Ji 1985a, b, 2002b) as already indicated.

S. cerevisiae has the capacity to metabolize both glucose and galactose but prefers the former as the carbon and energy source over the latter. In the presence of glucose, the organism turns on those genes coding for the enzymes needed to convert glucose to ethanol, the phenomenon known as *glucose induction*, and turns off those genes needed for galactose metabolism, which is known as *glucose repression* (DeRisi et al. 1997; Johnston 1999; Ashe et al. 2000; Jona et al. 2000; Kuhn et al. 2001). The detailed molecular mechanisms underlying these phenomena are incompletely understood at present (Gasch and Werner-Washburne 2002; Winderickx et al. 2002). When glucose is depleted, *S. cerevisiae* increases its rate of metabolism of ethanol to produce ATP via the Krebs cycle and mitochondrial respiration (Ronne 1995; Gasch 2002; Winderickx et al. 2002). This metabolic control is exerted by reversing the glucose repression of the genes encoding the enzymes required for respiration (or oxidative phosphorylation). This process is referred to as *glucose de-repression* (Gasch 2002).

The fact that the trajectory of the average glycolytic RNA molecules decreases (presumably because these transcripts are no longer needed in the absence of glucose as the substrate) while that of the average respiratory RNA molecules increases (presumably because these transcripts are needed to produce the corresponding enzymes to metabolize ethanol left over from previous glucose fermentation and the new substrate, galactose) during the first 3 h in Fig. 12.2 provides a strong experimental support for the notion that the *intracellular dissipative structures* (e.g., the RNA gradients in the time dimension under discussion) are correlated with *cell functions,* thus providing one of the first experimental evidences for Step 10 in Fig. 12.4 (or Step 20 in Fig. 2.11). Thus, IDSs reflect metabolic functions (see the opposite changes in the glycolytic and respiratory RNA trajectories in Fig. 12.2a), leading to the hypothesis that IDSs can be employed as reliable molecular signs (or signatures) for the metabolic and functional states of the living cells. This makes RNA trajectories or waves measured with microarrays convenient *biomarkers* for monitoring the *functional* state of metabolic pathways in whole cells whose de-regulation can lead to various diseases, including cancer (Watters and Roberts 2006). These observations have motivated me to formulate the *IDS-Cell Function Identity Hypothesis* as follows:

> There is a one-to-one correlation between IDSs and cell functions because IDSs are the immediate driving forces for all cell functions. (12.1)

The question as to what regulates the intracellular levels of RNA is not simple to answer because of the complex interactions taking place among the myriad components of the cell (see Fig. 12.27 for a further discussion). It may well turn out that what ultimately regulates the intracellular concentrations of any metabolites, including RNA molecules, is *the living cell itself* in interaction with its environment (see Step 9 in Fig. 12.4 or Step 19 in Fig. 2.11) and not any component processes of the cell metabolism such as transcription or translation

steps individually, and this conclusion may be viewed as a corollary of the postulate that the cell is the smallest DNA-based molecular computer (Ji 1999a), or *the computon* (see Row 9 of Table 6.3 in Sect. 6.1.2).

12.6 The Transcription-Transcript Conflation

The DNA microarray technique can be used to measure either DNA or RNA inside the cell (Fig. 12.5). Measuring DNA is relatively simple, since all that needs to be done in this case is to break the cell membrane, transfer the cellular DNA (see D_C in Fig. 12.5) into a test tube (see Step 9), and hybridize it with the DNA (called the *probe* DNA) covalently attached to the surface of a microarray (see Step 5). But measuring RNA is much more complex, involving at least eight key steps or processes (see Steps 1–8 explained in the legend to Fig. 12.5). In other words, the signal S measured with microarray from an RNA sample isolated from a cell population is a function of at least eight parameters as shown in Fig. 12.5:

$$S \propto [R_C] \tag{12.2}$$

$$= K[R_C] \tag{12.3}$$

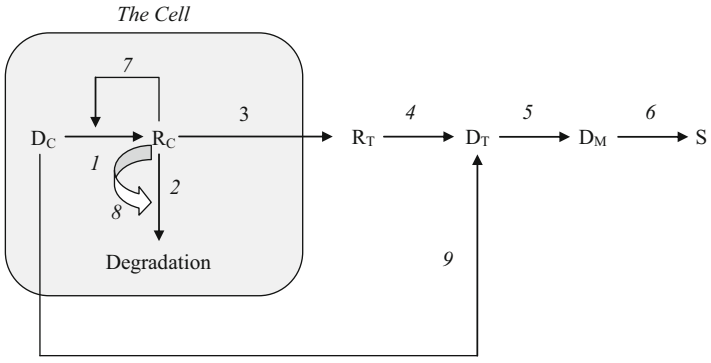


Fig. 12.5 The key steps involved in measuring intracellular RNA levels (R_C) with microarrays. D_c = DNA inside the cell; R_c = RNA inside the cell; R_T = RNA isolated in a test tube; D_T = DNA reverse transcribed from R_T inside a test tube; D_M = DNA hybridized to the probe DNA on the surface of a microarray; S = the fluorescence signal measured form D_M. 1 = transcription; 2 = transcript degradation; 3 = isolation of RNA from cell (C) into a test tube (T); 4 = DNA synthesis from RNA catalyzed by reverse transcriptase in test tube; 5 = hybridization of D_T to DNA *probes* covalently attached to the microarray (M) surface; 6 = measuring the fluorescence signal from the *target* DNA hybridized to the probe DNA on the microarray surface; 7 = an RNA molecule affecting the transcription of its own or other genes, either directly (via microRNA, for example) or indirectly through protein synthesis; 8 = an RNA molecule influencing its own degradation either directly as RNA or through protein synthesis; 9 = measurement of cellular DNA after isolation into a test tube

where $\propto$ symbolizes a proportionality and K is a function, denoted as f in Eq. 12.4, of at least eight parameters, denoted as P_i, each reflecting the characteristics of one of the eight arrows or Steps 1–8, in Fig. 12.5:

$$K = f(P_i) \tag{12.4}$$

where the index i runs from 1 to 8.

Combining Eqs. 12.3 with 12.4 leads to:

$$S = f(P_i)[R_C] \tag{12.5}$$

Equation 12.5 indicates that the microarray signal S would be proportional to the intracellular RNA levels, if and only if all the P_i values remain constant where the index i runs from 1 to 8. As evident in Fig. 12.5, the eight parameters that connect R_C to S can be divided into two groups – (1) the *biological parameters*, P_1, P_2, P_3, P_7, and P_8, and (2) what may be called the *measurement parameters*, P_4, P_5, and P_6. The reproducibility of the measurement parameters from one experiment to another can be readily gauged by repeating a measurement three or more times using the same biological samples. The accuracy and reproducibility of the DNA microarray technique has been improving since its invention in the mid-1990s so that, under ideal conditions, the measurement parameters can be kept constant within 30–50% (as exemplified by the microarray data reported by Garcia-Martinez et al. 2004). When signal S varies more than 30–50% under such experimental conditions, then (and only then) the signal variations observed could be attributed to *biological changes* occurring in the cell under investigation.

Interpreting the results of the measurement of intracellular RNA levels using the DNA microarray technique even under ideal settings is not simple because it involves at least four biological steps, i.e., Steps 1, 2, 7, and 8, in Fig. 12.5. (See also Fig. 12.22.) It is generally safe to assume that there exists a 1-to-1 correlation between S and R_C: When S increases, so does R_C, and whenever S decreases, so does R_C. But the common error committed by many users of the DNA microarray technique has been to assume that a 1-to-1 correlation exists between R_C and the rate of Step 1, namely, the transcription (or gene expression) step. Such an interpretation of the R_C level is invalid because R_C levels are determined not by Step 1 alone but also by Step 2 or the transcript degradation (Ji et al. 2009a).

Since the mid-1990s when the era of the DNA microarray technology began, cell biologists have been interpreting changes in the RNA levels measured with microarrays almost invariably in terms of *transcriptional activation,* or more generally called "expression," of corresponding genes, i.e., increased rate of Step 1 in Fig. 12.5 (Alon et al. 1999; Troester et al. 2004; Rhodes and Chinnaiyan 2004; Tu et al. 2005), ignoring *transcript degradation,* i.e., Step 2 in Fig. 12.5. This is surprising since it has been known for a long time that RNA molecules are unstable toward degradation (Shapiro et al. 1986; Hargrove and Schmidt 1989; Wang et al. 2002; Yang et al. 2003).

The direct experimental evidence for the critical role that the transcript degradation step plays in determining transcript level (TL) came to light when two groups – Fan

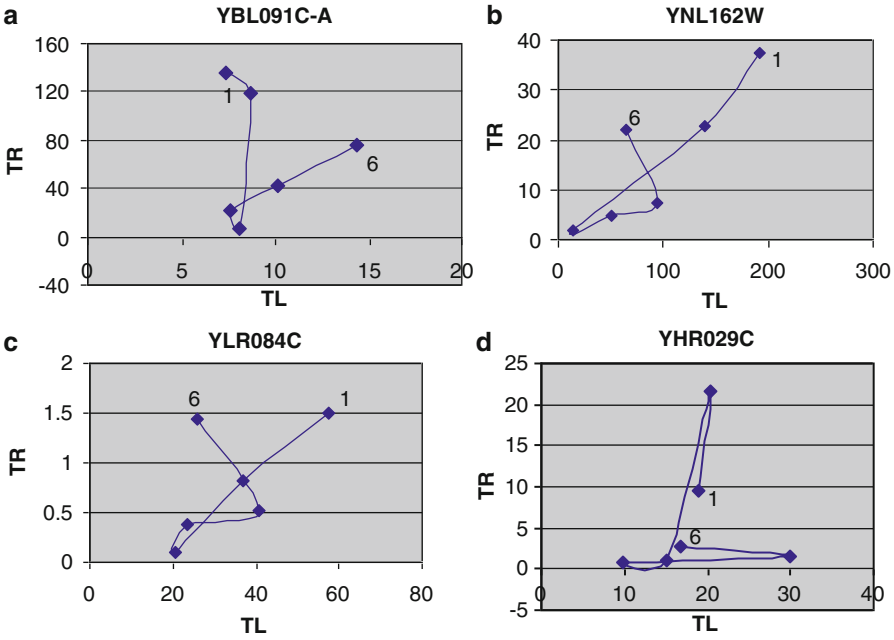


Fig. 12.6 The "TL-TR phase diagram": The plots of the transcription rates (TR) against transcript levels (TL) (in arbitrary units) measured in budding yeast at six time points ($1 = 0$ min, $2 = 5$ min, $3 = 120$ min, $4 = 360$ min, $5 = 450$ min, and $6 = 850$ min) after the glucose–galactose shift. Each point represents the average of triplicate measurements (Garcia-Martinez et al. 2004). The plotted genes were randomly chosen out of the 5,725 genes showing no missing values in their triplicate measurements of TL and TR. The notation given on the *top* of each figure is the name of the open reading frame (ORF) whose transcript was measured

et al. (2002) and Garcia-Martinez et al. (2004) – measured both TL (transcript *level*) and TR (transcription *rates*) simultaneously using DNA microarrays. Examples of the TL and TR data obtained by the latter group from budding yeast subjected to the glucose–galactose shift are presented in Fig. 12.6, which may be referred to as the "TL-TR phase diagram."

It is clear that TL and TR do not always change in parallel as most workers in the field have been assuming. The following quotations are typical of over 50 randomly selected papers that have been examined:

> Microarrays prepared by high-speed robotic printing of complementary DNAs on glass were used for quantitative expression measurements of the corresponding *genes*... (Schena et al. 1995). (12.6)

> Oligonucleotide arrays can provide a broad picture of the state of the cell, by monitoring the expression level of thousands of *genes* at the same time ... (Alon et al. 1999). (12.7)

> DNA microarrays, permits the simultaneous monitoring of thousands of *genes* ... (White et al. 1999). (12.8)

> DNA microarrays are used to monitor *changes in gene expression levels* ... expression is estimated by comparing the *relative amount of mRNA* in two distinct cell populations ....

Table 12.2 The multiple meanings of "gene expression" depending on context

Meaning of "gene expression"	Context of experiment
1. RNA level	1. Usual microarray experiments
2. Transcription	2. Microarray experiment using the "genomic run- on" protocol
3. Protein level	3. Protein microarrays
4. Pathway activation	4. Microarrays prepared with cDNAs encoding metabolic pathways
5. Cell morphology or properties	5. Microarrays designed to bind cell surface proteins characteristic of cell morphology

> The mRNA levels in control and test samples are ... compared and the *differential expression data given as a ratio or fold change*. (Okamoto 2005) (12.9)

These statements would be correct if the term "genes" (in bolds) are replaced by "RNA levels" or "transcripts." This is simply because:

> DNA microarrays, as normally used, measure RNA levels but not the rates of transcription. (12.10)

The phrase "gene expression" in the context of usual microarray experiments necessarily signifies "transcription" or Step 1 in Fig. 12.5. In other contexts, "gene expression" can mean *transcription rate*, *protein*, *metabolism, morphology,* or any other *phenotypes* being measured (see Table 12.2). In particular, if (and only if) microarrays are used in conjunction with the *genomic run-on protocol* (Garcia-Martinez et al. 2004), does "gene expression" mean "transcription" (see Row 2 in Table 12.2).

We commonly read Statement 12.11 in journal articles and advertisements or hear in seminars and lectures all over the world:

> Microarrays measure gene expression. (12.11)

Statement 12.11 can be true but not always so, since the phrase "gene expression" can mean any of the five different objects listed in the first column of Table 12.2, depending on the context of the experiment performed, leading to the following conclusion:

> The meaning of "gene expression" cannot be determined without knowing the experimental protocol employed in microarray experiments. (12.12)

The *critical dependence* of the meaning of *gene expression* on *protocol* as embodied in Statement 12.12 can be represented diagrammatically utilizing the *triadic definition of a sign* given by Peirce (see Sect. 6.2.1) (Fig. 12.7):

Combining Statements 12.11 and 12.12 leads to:

> Microarrays can measure any one of at least five different observables, including transcript levels and transcription rates, depending on the experimental protocol employed. (12.13)

A corollary of Statement 12.13 is:

> Microarrays cannot measure both transcript levels (TL) and transcription rates (TR) without using two independent experimental protocols. (12.14)

To many investigators who utilize microarrays, Statements 12.10 and 12.14 may come as a surprise because microarrays have been widely advertised in journals and

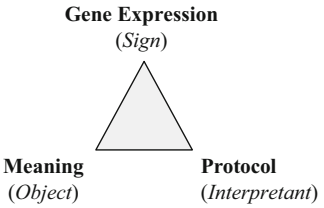


Fig. 12.7 The triadic definition of the sign "gene expression"

commercial media as the revolutionary tool for "measuring gene expression," interpreting "gene expression" arbitrarily as "transcription." To emphasize its importance, Statements 12.10 or 12.14 may be referred to as the *First Law of Microarray Data Interpretation (FLMDI)*.

A survey of the literature indicates that most investigators employing microarrays routinely violate FLMDI, since:

> Most biologists conflate the terms "gene expression" and "mRNA levels," or "transcription" and "transcript levels". (12.15)

Statement 12.15 will be referred to as the "transcription-transcript level conflation (TTLC)." The data obtained by Garcia-Martinez et al. (2004) and by Fan et al. (2002) clearly demonstrate that the mixing of these two terms can lead to false positive (Type I) and false negative (Type II) errors in interpreting microarray data (Ji et al. 2009a; Ji and Yoo 2005).

A gene, commonly defined as a DNA segment encoding proteins, is an *equilibrium structure* that is static (see Sect. 11.2). On the other hand, the level of an RNA molecule transcribed from its gene is a *dissipative structure*, because its maintenance requires dissipation of free energy. Many studies employing DNA arrays have been making the error of what may be referred to as "the gene-to-transcript misinterpretation," which would be equivalent to compressing both *transcriptomics* (the study of the whole set of the transcripts of a genome) and *genomics* (the study of the whole set of the genes of a genome) onto the same plane. As alluded to above, two types of errors have resulted from the misuse of the phrase, "gene expression." The Type 1 error (also called the false positive error) is committed when it is claimed that there is something when there actually is nothing; Type 2 error (or the false negative error) is committed when it is claimed that there is nothing when there actually is something. To help users of microarrays avoid making Types I and II errors, I recommend the following rules:

> It is impossible to identify a gene as a possible cause of a disease based only on the finding that its mRNA level changed in the diseased state relative to the control state without eliminating the possibility that the change in the mRNA level arose from the changes in transcript degradation rates rather than from changes in the transcription rates. (12.16)

Similarly:

> It is impossible to exclude a gene as a possible cause of a disease based only on the finding that its mRNA level did not change in the diseased state as compared to control without eliminating the possibility that the lack of changes in the mRNA level arose from the

coincidence of an increased transcription rate and a similarly increased transcript degradation rate or from the coincidence of a decreased transcription rate and a similarly decreased transcript degradation rate. (12.17)

Again, to emphasize the importance of Statements 12.16 and 12.17, they may be referred to as *the Second Law of Microarray Data Interpretation (SLMDI) and the Third Law of Microarray Data Interpretation (TLMDI),* respectively. Violating FLMDI leads to a false positive error (or Type 1 or α error), and violating SLMDI or TLMDI results in a false negative error (or Type 2 or β error).

In summary, I have formulated three laws of *microarray data interpretation* (MDI) in this section, i.e., Statements 12.10, 12.16, and 12.17. It is truly surprising to find that, even after almost one and a half decade following the invention of one of the most revolutionary experimental techniques in biology, namely, *DNA microarrays*, many workers in the field are still committing Types I and II errors in interpreting the data measured with this technique. In December, 2009, I had opportunities to attend two meetings, the *Regulatory Genomics, Systems Biology and DREAM 2009* held at the Broad Institute in Cambridge and the 102nd Statistical Mechanics Conference held at Rutgers, Piscataway. Having observed that several prominent participants in these meetings violated one or more of the laws of MDI described above, I was prompted to write several emails. I am taking the liberty of attaching two of these emails and related documents as Appendices C–F at the end of this book in the hope of stimulating *worldwide discussions on ways to avoid misinterpreting microarray data*, since misinterpreting microarray data can have far-reaching consequences in both basic and applied researches in cell biology, affecting drug discovery efforts in pharmaceutical industry and personalized medicine (Chaps. 18, 19)).

12.7 The Mechanistic Modules of RNA Metabolism

Each plot or trajectory in Fig. 12.6 can be divided into five segments or "component vectors" bound by two of the 6 time points labeled 1 through 6: First segment between 0 and 5 min measured after the glucose–galactose shift, the second segment between 5 and 120 min, the third segment between 120 and 360 min, the fourth segment between 360 and 450 min, and the fifth segment between 450 and 850 min. Each segment can be characterized in terms of the angle measured counterclockwise starting from the positive x-axis (see Fig. 12.8). For example, the segment between time points 5 and 6 in Fig. 12.6a is approximately 45° and that between time points 1 and 2 in Fig. 12.6b is approximately 225°, etc. These angles are conveniently divided into eight groups as explained in the legend to Fig. 12.8. Each group is associated with a distinct mechanism of RNA metabolism. For example Group 2 (with angles in the range between 4° and 86°) is associated with the mechanism in which both TL and TR increase (see the radial arrow in Fig. 12.8). In contrast, Group 8 (with angles in the range between 274° and 356°)

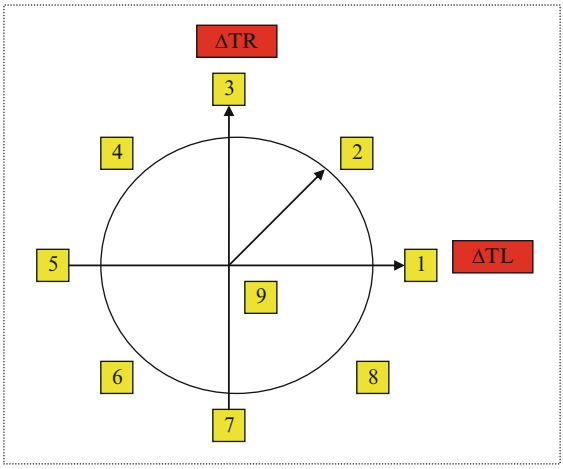


Fig. 12.8 The "unit circle" whose *x*-axis indicates the changes in TL values (ΔTL) and the *y*-axis indicates the changes in TR values (ΔTR) of a trajectory in the TL-TR plot (see Fig. 12.6). The direction of the radial arrow coincides with the direction of the component vector (or segment) of the trajectories in the TL-TR plot. The angle of the radial arrow is divided into eight ranges defined as follows: **1** = 357 ~ 3; **2** = 4 ~ 86; **3** = 87 ~ 93; **4** = 94 ~ 176; **5** = 177 ~ 183; **6** = 184 ~ 266; **7** = 267 ~ 273; **8** = 274 ~ 356. Range **9** indicates the situation where neither TL nor TR underwent any measurable changes (Reproduced from Ji et al. 2009a)

is associated with mechanism in which TL increases despite the fact that TR decreases, etc. Thus, it is logical to equate these groups with their underlying mechanisms (or modules) of RNA metabolism. We may refer to such modules as "mechanistic modules of RNA metabolism," "mechanisms of RNA metabolism," or "modules of RNA metabolism." These terms are related to "ribonomics" defined by Keene (2006) as the genome-wide study of RNA metabolism in cells.

The five angles characterizing the trajectory of each of the 5,725 genes were calculated from their TL and TR values as follows. The angle Θ determining the direction of the segment from the ith time point to the (i + 1)th time point in a TL vs. TR plot with coordinates (x_i, y_i) and (x_{i+1}, y_{i+1}), respectively, was calculated from the relation $\Theta = \tan^{-1}[(y_{i+1} - y_i)/(x_{i+1} - x_i)] + \alpha$, where $\alpha = 0^\circ$ if both the numerator and the denominator are positive, $\alpha = 180^\circ$ if either the numerator is positive and the denominator is negative or both the numerator and the denominator are negative, and $\alpha = 360^\circ$ if the numerator is negative but the denominator is positive. From the set of 5,184 pairs of TR and TL data measured at six time points, we calculated a total of $5 \times 5{,}184 = 25{,}920$ angles distributed over the eight modules, each over five different time segments. The results are given in Table 12.3 and Fig. 12.9 (Ji et al. 2009a).

The mechanisms of interaction between TL and TR that are associated with the nine modules appearing on the *x*-axis of Fig. 12.9 are listed in Table 12.4. Since there are three logical possibilities for the changes in TL and TR, namely, increase (+), no change (0) or decrease (−), there are a total of nine possible changes that can be assigned to the combined system of TL and TR, and these possibilities are listed

Table 12.3 The frequency distributions of the eight modules or mechanisms of RNA metabolism as the functions of the five time periods following the glucose–galactose shift. If the angles are homogeneously distributed over 360°, the expected distributions can be calculated as *(6/360) × 100 = 1.67%* for Mechanisms 1, 3, 4, and 7 and *(84/360) × 100 = 23.3%* for Mechanisms 2, 4, 6, and 8 (see the seventh row). The p-values for the difference between the *observed* and the *expected* distributions are given in the last row. The differences are all significant, except for Mechanism or Module 5 (Reproduced from Ji et al. 2009a)

Mechanism segments	1	2	3	4	5	6	7	8	Total
1	0	142	234	3,470	96	1,732	12	39	5,725
2	14	18	3	37	5	3,729	617	1,302	5,725
3	340	1,914	52	638	314	1,471	28	968	5,725
4	477	4,237	21	151	61	143	19	616	5,725
5	12	1,151	238	4,213	38	56	4	13	5,725
Total, observed	843	**7,462**	548	**8,509**	514	**7,131**	680	**2,938**	28,625
(%)	(2.94)	**(26.07)**	(1.91)	**(29.73)**	(1.80)	**(24.91)**	(2.38)	**(10.26)**	
Total, expected	477	**6,678**	477	**6,678**	477	**6,678**	477	**6,678**	28,625
(%)	(1.67)	**(23.33)**	(1.67)	**(23.33)**	(1.67)	**(23.33)**	(1.67)	**(23.33)**	
p-value	0	0	0.0011	0	0.0919	0.0000	0	0	

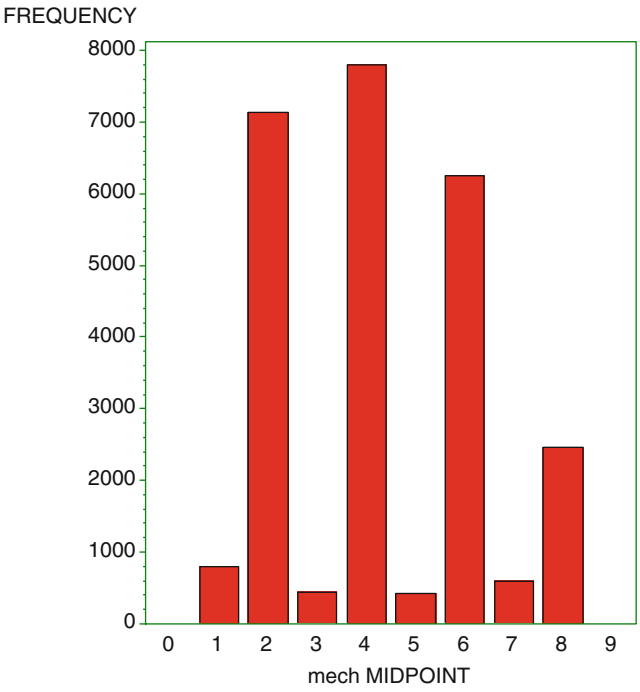


Fig. 12.9 The frequency distributions of the *RNA metabolic modules* in budding yeast undergoing the glucose–galactose shift. This histogram is a visual representation of the data shown in Table 12.3. The *y*-axis records the frequency of the occurrence of individual modules defined by the ranges of the angles of the component segments/vectors of the TL-TR trajectories in Fig. 12.6 and the *x*-axis lists the nine mechanisms or modules of RNA metabolism (Reproduced from Ji et al. 2009a)

Table 12.4 The nine mechanisms of interactions among transcript level (TL), transcription rate (TR), and transcript degradation rate (TD). ΔTR is + when the transcription rate is increased and – when the transcription rate is decreased. ΔTD is + when the transcript degradation rate is increased and – when the transcript degradation rate is decreased. The numerical labels of the Mechanisms in the fourth column are defined in Fig. 12.8

ΔTL	ΔTR	Relation between ΔTR and ΔTD	Mechanisms or modules
+	+	$\Delta TR > \Delta TD$	2
	0	$\Delta TR > \Delta TD$	1
	–	$\Delta TR > \Delta TD$	8
0	+	$\Delta TR = \Delta TD$	3
	0	$\Delta TR = \Delta TD$	9
	–	$\Delta TR = \Delta TD$	7
–	+	$\Delta TR < \Delta TD$	4
	0	$\Delta TR < \Delta TD$	5
	–	$\Delta TR < \Delta TD$	6

in the fourth column in Table 12.4. The third column in Table 12.4 indicates the range of changes for *transcript degradation rates*, TD, that are inferred from the associated changes in TL and TR.

The first three mechanisms reflect the case where the transcript level is increasing. Mechanism 2 is activated (or realized) when TL increases due to TR increasing more than TD. Mechanism 1 is activated when TL increases due to decreasing TD with no change in TR. Mechanism 8 is activated when TL increases due to TD decreasing more than TR. Similar explanations can be provided for the remaining six cases. Please note that there is a 180° rotational symmetry in the arrangement of the relational signs in the third column in the table, i.e., $> > >$, $= = =$, $< < <$, which indicates that the mechanistic explanations given in the table are logically coherent.

As evident in the second and third columns of Table 12.4, each of the nine possible mechanisms described entails a unique relation between the variations in transcription rates, ΔTR, and that of the transcript degradation rates, ΔTD. Such relations cannot arise from random interactions between these two processes, thus leading to the following conclusion:

> There exist mechanisms in living cells that control the interaction between transcription and transcript degradation rates. (12.18)

The enzyme system catalyzing transcription is known as *transcriptosome* (Halle and Meisteerernst 1996), and that catalyzing transcript degradation is referred to as *degradosome* in bacteriology which is here *commandeered* to represent transcript degradation in all cell types. Thus, the second column in Table 12.4 expresses the direction of the absolute changes in the activity of transcriptosome while the third column indicates the relative changes in the activities of *transcriptosome* and *degradosome*. The time-dependent patterns of the changes in TL (i.e., the RNA trajectories or waves) that result from controlled interactions between *transcriptosome* and *degradosome* will be referred to as

ribons. Thus, Statement 12.18 can be interpreted as the prediction of the existence of *ribons* as both the RNA trajectories in the living cell and as the cooperative or coordinated system of transcriptosome and degradosome underlying such trajectories:

$$\textbf{Ribons} = \textbf{Transcriptosome} + \textbf{Degradosome} \tag{12.19}$$

Defined in this manner, *ribons* are examples of dissipative structures or *dissipatons*, since ribons cannot exist without yeast cells dissipating free energy. Ribons are also examples of SOWAWN machines (Sect. 2.4.4) composed of *transcriptosome* and *degradosome*. Unlike transcriptosome and degradosome which can be isolated and purified, ribons cannot be isolated just as the flame of a candle cannot be isolated and studied. Interestingly, the term *ribons* tend to emphasize the shapes of RNA trajectories (i.e., kinematics) and *dissipatons* highlights the free energy cost of maintaining such trajectories (i.e., dynamics). Thus, ribons embodies two complementary aspects – kinematics and dynamics (see Sect. 2.3.5).

Since there are obviously many different *dissipatons* (RNA trajectories, protein trajectories, metabolite trajectories, ion gradients, cytoskeletal stress gradients, cell migratory path, etc.) (i.e., dynamics) (see Sect. 2.3.5), it would be necessary to have a means to differentially represent them as different species of *dissipatons*. One such method would be to attach a prefix to different kinds of dissipatons. For example, ribons may be referred to as "RNA-dissipatons" and the ion gradients across the cell membrane as "ionic dissipatons," etc.

12.8 Visualizing and Analyzing *RNA-Dissipatons*

12.8.1 ViDaExpert

The concept of dissipative structures (or *dissipatons*) has been around in the scientific literature for more than three decades (Prigogine 1977, 1980); Kondepudi and Prigogine 1998; Kondepudi 2008), but the experimental methods for studying them in the context of cell biology had been limited until the ViDaExpert became available about a decade ago (Zinovyev 2001; Gorban and Zinovyev 2004, 2005). My experience in analyzing budding yeast transcriptome (i.e., the genome-wide RNA metabolism) with this method (see below) induces me to speculate that *ViDaExpert* (and *equivalent computer programs*) may well turn out to be for the *cell biology* in the twenty-first century what the *X-ray crystallography* was to the *molecular biology* in the twentieth century. This speculation is based on one assumption – Cell biology is (and should be) mainly concerned with the study of *dissipative structures* (*dissipatons*) in contrast to molecular biology which has mainly been the study of *equilibrium structures* (*equilibrons*).

ViDaExpert is a stand-alone software that is freely available online at http://bioinfo-out.curie.fr/projects/vidaexpert/.ViDaExpert . It is a unique software tool for visualizing multidimensional datasets that was developed by A. Zinovyev in 2001 as his Ph.D. thesis under the supervision of the mathematician, A.N. Gorban, then at the Institute of Computational Modeling at the Siberian Branch of the Russian Academy of Science at Krasnoyarsk, Russia. The following description of ViDaExpert is largely based on the lecture that Zinovyev gave at Rutgers in 2006 and on the lecture slides that he generously made available to me.

ViDaExpert analyzes a finite set of objects in a multidimensional space endowed with some way of defining the distance (metrics) among the objects. ViDaExpert utilizes a form of the principal component analysis. One of the simplest objects that can be embedded in data space is a line that is aligned in the direction of a maximal dispersion of data. Such a line is referred to as *the first principal component* or *axis*. The second principal component can be calculated as the line passing through the middle of the first principal axis at a 90° angle, and the third principal component can be calculated as the line going through the intersection of the first and second principal axes at 90° to both, and so on to calculate higher principal components (Zinovyev 2006).

The principal component can be viewed as a generalization of the concept of the *mean*. The concept of the mean can be expressed in terms of a point, a set of points, or even an object with an arbitrary topology. The mean denoted as $< X >$ is defined as the sum of all the values, X_i, from $i = 1$ to m, divided by m, the number of the points or objects in the set. As a generalization of the mean value, we can define the *mean point* as a point which minimizes a functional, the sum of the squared distances between data points and the mean point. This definition is very general. Instead of the points used in K-means clustering, we can use any object or several objects which can be aligned in such a way as to make it the principal object or let it minimize the sum of the squared distances from data points to the object. After finding the principal object, we can project data points onto the surface of the object. When data points are so projected, we are in fact making a transition between two spaces – from data points in a high-dimensional space to a lower-dimensional space of the *principal object* (Zinovyev 2006).

The *principal object* (also called *principal manifold* or *principal grid*) is rather rigid. But ViDaExpert constructs a flexible principal object. To accomplish this goal, Zinovyev and Gorban employed the *elastic net* (Zinovyev 2006).

For simplicity, it is usually assumed that the stretching and bending coefficients are equal for all edges and ribs. This leaves only two parameters to be manipulated in constructing the principal manifold using ViDaExpert. The first parameter restricts the total length, or area, or the volume of the principal manifold. The second parameter tends to smooth out the topology of the manifold. One important point is that the energy functionals are all quadratic which means that they can be optimized in one step, solving a system of linear equations. And this makes ViDaExpert fast, in fact, one of the fastest methods now available to construct optimal principal manifolds (Zinovyev 2006).

There are two ways of projecting data points to the principal grid (i.e., the grid approximating the topology of the principal manifold calculated by ViDaExpert).

One way is to project data point to the nodes that are closest to them. The other is to project data points perpendicularly to the closest surface on the principal manifold. In analyzing the TL data from budding yeast using ViDaExpert, the "closest node" method of approximating the principal manifold was employed.

12.8.2 Ribonoscopy: Looking at RNA

In the following discussions, I will distinguish between *RNA molecules* which are equilibrium structures (i.e., *equilibrons*) and *RNA trajectories* or *waves* which are dissipative structures (i.e., *dissipatons*) by using two different stems – *ribo-* referring to the former and *ribono-* to the latter. Thus, "ribonoscopy" will denote the study of the time-dependent RNA concentrations in the cell (i.e., *RNA trajectories, ribons* or *RNA waves*) using DNA microarrays and computer-assisted analysis of microarray data, i.e., RNA waves.

About 1,000 genes were selected out of a total of over 6,000 genes whose transcripts were measured with DNA arrays in budding yeast after switching the nutrient glucose to galactose (Garcia-Martinez et al. 2004). These genes were selected for analysis because their transcript levels showed pronounced changes induced by the nutritional shift. The data set under consideration consists of a table with ~1,000 rows (each labeled with the name of the gene encoding the transcript involved) and six columns representing the time points of measurements, i.e., 0, 5, 120, 360, 450, and 850 min after the nutritional shift. Thus, one gene is associated with a set of six numbers, each representing the average of the triplicate measurements of the transcript level of the gene measured at one of the six time points. *We can represent these data points in an abstract six-dimensional mathematical space* (to be called *the RNA concentration space*), each axis representing one of the six time points of measurements. In this six-dimensional space, one point is equivalent to six numbers, which can be represented as a vector emanating from the origin of the six-dimensional concentration space and ending at the point whose coordinate is specified by the six numbers. The position of a point in the concentration space represents an RNA trajectory in the concentration-time graph (see Fig. 12.1 as an example) and hence encodes the *shape information* of such a trajectory. In other words, *differently shaped RNA trajectories will occupy different positions in the RNA concentration space*.

When we inputted our six-dimensional data (typically 10^4 numbers) to the ViDaExpert program, we obtained a table of numbers indicating the frequencies (or probabilities) of individual RNA molecules (their names appearing at the beginning of each row) exhibiting characteristic kinetic behaviors (or node numbers) appearing at the top of each column. This result of the ViDaExpert analysis can be graphically represented in two ways – as a three-dimensional plot (Figs. 12.10, 12.11) or a two-dimensional plot (Fig. 12.12).

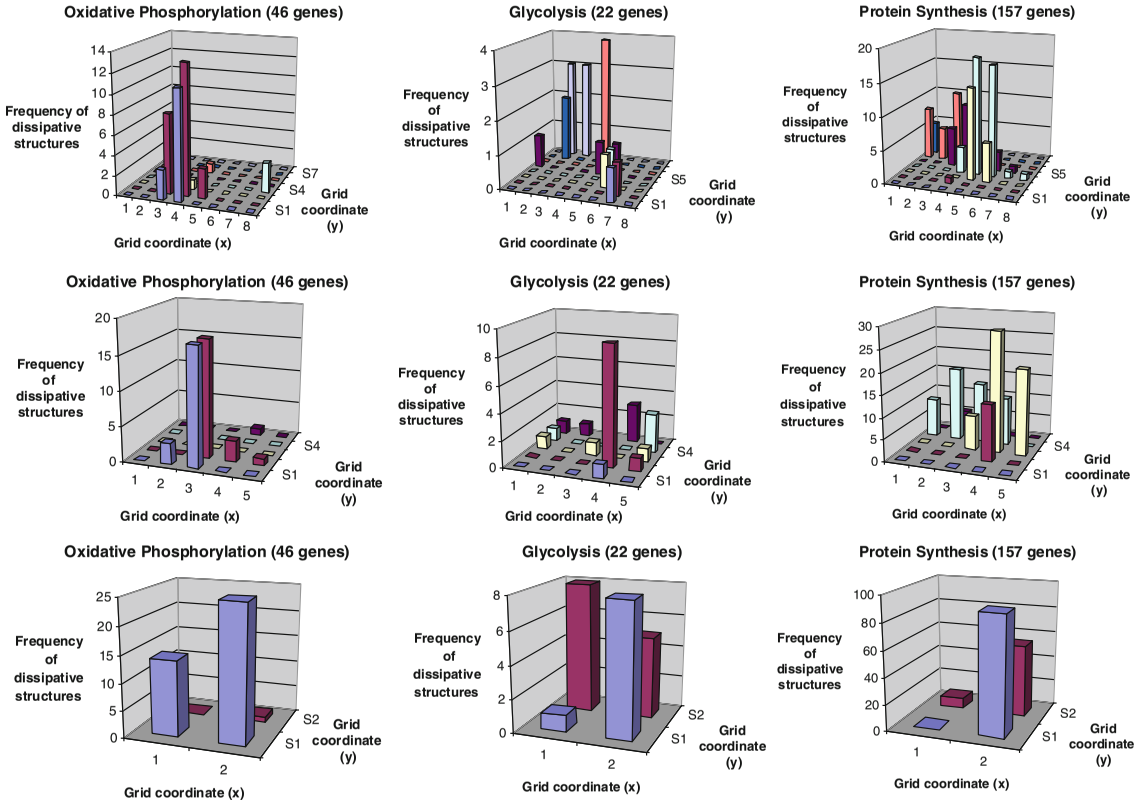


Fig. 12.10 Visualization of the patterns of distributions of RNA *dissipatons* or *ribons* with ViDaExpert with three different grid resolutions. Three functional groups of transcripts were analyzed – the 46 transcripts involved in oxidative phosphorylation (*left column*), the 22 transcripts related to glycolysis (the *middle column*), and the 157 transcripts associated with protein synthesis (*right column*). The grid resolution increases from 4 to 25 to 64 from the *bottom* to the *top* rows

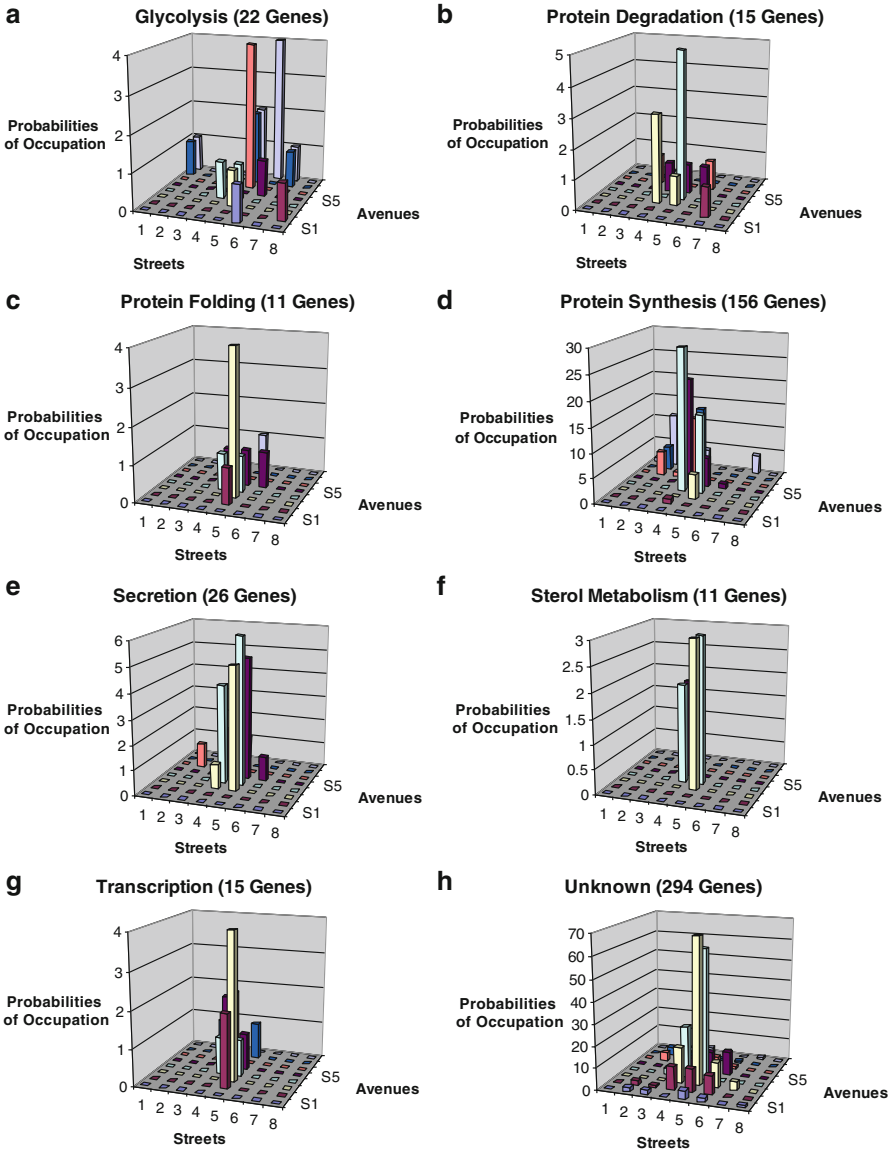


Fig. 12.11 The ViDaExpert-enabled visualization of the RNA trajectories (also called RNA waves, *RNA dissipatons or ribons*) belonging to eight different metabolic pathways of budding yeast undergoing glucose–galactose shift. These patterns of distributions of ribons are functions of at least five parameters as shown in Eq. 12.20

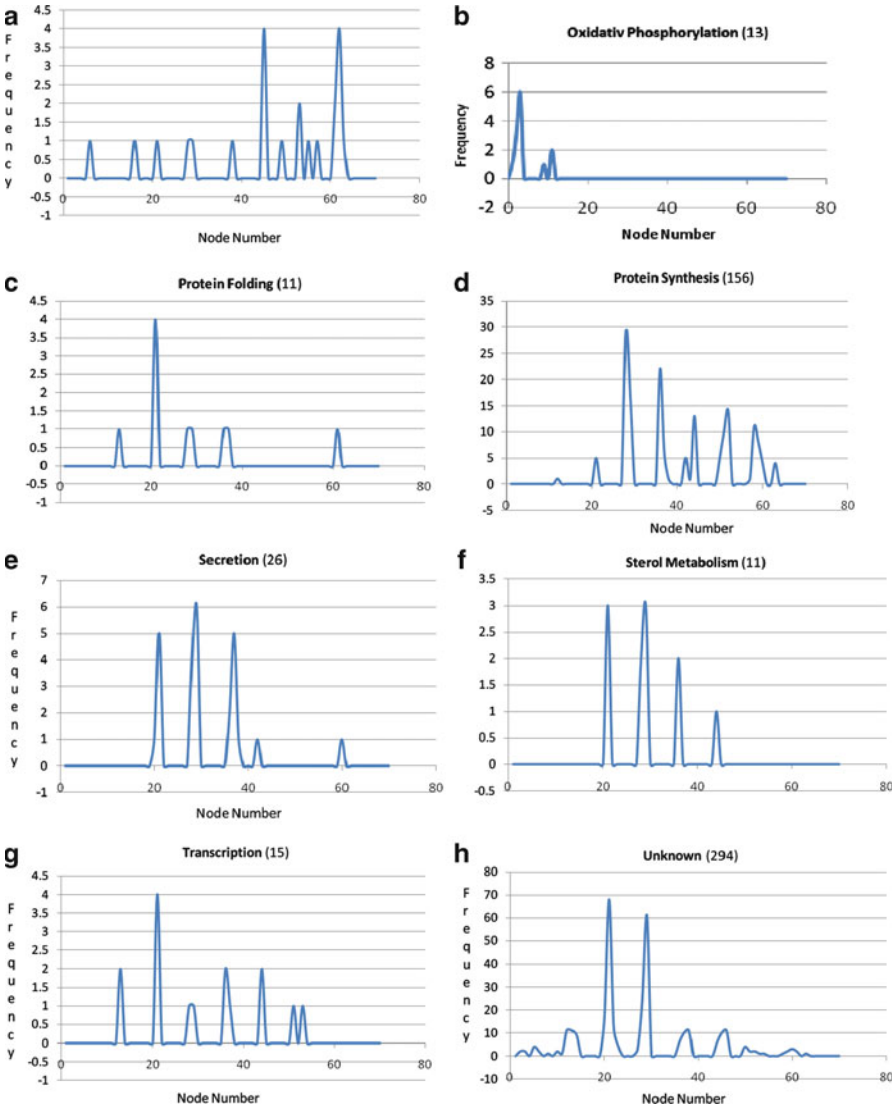


Fig. 12.12 *The RNA spectra (or ribonic spectra)*. The patterns of the distributions of *ribons* such as shown in Fig. 12.1 are represented as what is here referred to as the "RNA spectra"(or "ribonic spectra") which can be obtained by linearizing the two-dimensional (street-avenue) *addresses* of the RNAs on the three-dimensional plots (e.g., Fig. 12.11) as *node numbers* on the *x*-axis and plotting the frequency on the *y*-axis

Focusing on the uppermost row of the three-dimensional plot in Fig. 12.10, what ViDaExpert has done is to project the original data points in the six-dimensional RNA concentration space to the two-dimensional principal grid, i.e., the plane with x and y coordinates. The columns with different heights standing on the xy-plane

indicate the numbers of the transcripts clustering at different nodes. The addresses of the columns on the grid reflect the different shapes of the RNA trajectories (i.e., different kinetic behaviors of individual transcripts observed over the 850-min time period), since the different shapes of the average RNA trajectories of the glycolytic and oxidative phosphorylation genes shown in Fig. 12.2a are transformed by ViDaExpert into different distributions of the columns on the principal grid. (Compare the left and the middle panels on the uppermost row in Fig. 12.10.)

Turning to one of the three columns, say, the left column, in Fig. 12.11, we can see the effects of changing the grid number from 4 to 25 to 64 (or n = 2, 5, and 8) on the pattern of distributions of transcripts on the principal grid. As one increases the grid number, the columns tend to get fragmented into smaller ones but their characteristic pattern of clustering seems to be retained. In general, increasing the grid number (which is equivalent to increasing the number of clusters in K-means clustering) is akin to increasing the *resolution power* of a microscope with which the clusters of the transcript trajectories in the six-dimensional space are viewed.

Figure 12.11 shows the RNA trajectories (i.e., *ribons*) belonging to a set of eight different metabolic pathways or functions – glycolysis (22 genes), protein degradation (15 genes), protein folding (11 genes), protein synthesis (156 genes), secretion (26 genes), sterol metabolism (11 genes), transcription (15 genes), and RNAs with unknown functions (294). The number of nodes in the principal grid (i.e., grid resolution) is fixed at 64. The visual inspection of these plots clearly demonstrates that the RNA trajectories (i.e., *RNA dissipatons* or *ribons*) belonging to different metabolic pathways/functions are distributed in distinct ways on the principal grid. It has been found that these patterns of distribution of ribons are sensitive to small variations (typically from 0.01 to 0.1) of the elastic coefficients, λ and μ. Thus, we can express the *Pattern of the Distribution of Ribons* (PDR) associated with a metabolic function, MF, on the principal grid with node n, stretching coefficient λ, and bending coefficient μ as in Eq. 12.20:

$$\text{PDR} = \text{f}(\text{n}, \lambda, \mu, \text{MF}, \text{EC}) \tag{12.20}$$

where f is a function or a set of rules, and EC stands for the "experimental or environmental conditions" under which observations are made such as the glucose–galactose shift or normal vs. tumor tissues, etc.

Equation 12.20 can be interpreted as the ViDaExert-enabled visualization of the metabolic pathways in cells in terms of ribons under a given observational condition. The PDR defined by Eq. 12.20 may provide a useful method for analyzing microarray data with the goal of identifying *pathway-dependent or pathway-specific biomarkers* that are the focus of intense current attention among workers in the field of DNA array technology, because they possess the potential for facilitating the discovery of drug targets for various diseases and for providing diagnostic and pharmacotherpeutical tools for personalized medicine (Clarke et al. 2004; Burczynski et al. 2005; Watters and Roberts 2006; Boyer et al. 2006; Sears and Armstrong 2007; Dobbe et al. 2008) (see Chaps. 18 and 19).

Examples of the two-dimensional displays of the ViDaExpert results are shown in Fig. 12.12. In general, the kinetic patterns of the RNAs belonging to different metabolic pathways appear more clearly distinguishable in the two-dimensional counterparts (Fig. 12.12) than in the three-dimensional plots (Fig. 12.11). For example, Panels c and d or e and g in Fig. 12.11 are less easily distinguished than their two-dimensional plots in Fig. 12.12. Figure 12.12 clearly demonstrates that each metabolic pathway exhibits a unique RNA spectrum. When the node number is increased to 100 (as compared to 64 in Fig. 12.12), the pathway-specific features have been found to become even more readily distinguishable (data not shown). Also, the shapes of the RNA spectra have been found to change dramatically when RNA trajectories are measured in budding yeast with microarrays under different experimental conditions, for example, under nitrogen-deficient condition during alcoholic fermentation (Mendes-Ferreira et al. 2007) (data not shown). In other words, the RNA spectra (or *ribonic spectra*) described in this book for the first time (Fig. 12.12) are both *pathway-specific* and *cell state-specific*, thus suggesting the possibility that RNA spectroscopy (or *ribonoscopy*) may be employed as a sensitive experimental tool for characterizing living cells in normal and diseased states (see Chaps. 18 and 19 for further discussions).

The two-dimensional plots in Fig. 12.12 are strikingly similar to *molecular spectra*, an example of which is given in Panel a in Fig. 12.13 along with a ribonic spectrum in Panel b. The molecular spectrum in Panel a (Roldán et al. 2004) depicts the probability of exciting certain vibrational motions in the inorganic molecule, tetrachlorophsophonium oxotetrachlorovanadate, as a function of excitation energy expressed in wavenumbers. This similarity motivated invoking the term "RNA spectra" introduced in Fig. 12.12.

The concept of "RNA spectra" (or "*ribonic spectra*") is compared with that of molecular spectra in Table 12.5. One interesting difference between them is that molecular spectroscopy studies the *equilibrium structure* of molecules whereas "RNA spectroscopy" or ("ribonoscopy") studies the *dissipative structures* comprised of the time-dependent RNA concentrations or RNA waves (i.e., ribons) participating in a common metabolic function (or pathway) (see Row 2, Table 12.5). Molecular spectroscopy allows investigators to probe the internal *energy levels* of a molecule available for *electronic, vibrational,* and *rotational excitations*. Analogously, it is here postulated that *ribonoscopy* allows cell biologists to investigate the *internal structures of the cell consisting of the functional connections* (encoded in the genome) among individual *RNA molecules* (1), *RNA pairs* (2), and *systems of RNA molecules* (>2) participating in various metabolic pathways. By "functional connections among individual RNA molecules," I mean, for example, the connection between an identical RNA molecule at two time points, i.e., a temporal autocorrelation.

It is interesting to note that the *x*-axis of molecular spectra encodes *energy* levels expressed in terms of *wavenumbers*, whereas the *x*-axis of ribonic spectra encodes *information* specifying the shape of RNA trajectories, waves, or ribons expressed in terms of *node numbers*: Just as *wavenumbers* imply the *energy* of molecular motions, so *node numbers* carry the *information* about RNA trajectories (see Row 4, Table 12.5). The *y*-axis of molecular spectrum measures the probability of

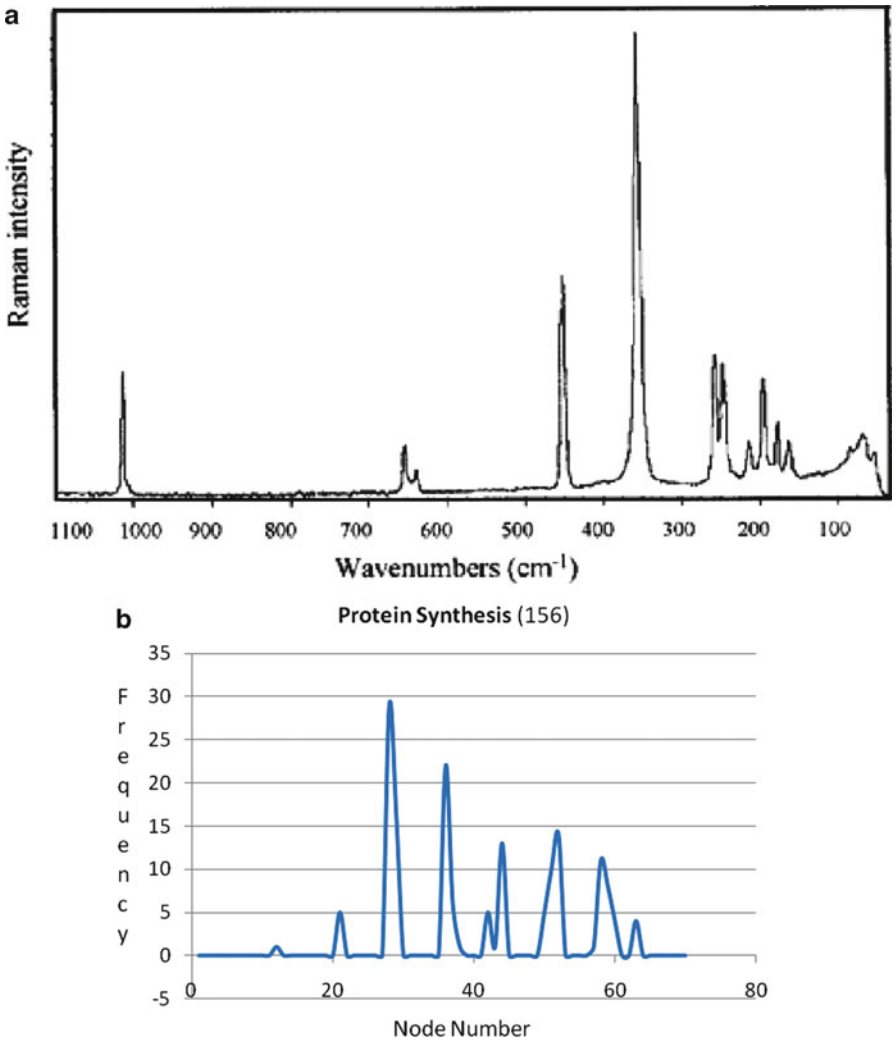


Fig. 12.13 A comparison between a *molecular spectrum* and an "RNA spectrum" (or "ribonic spectrum"). (**a**) The Raman spectrum of PCl_4VOCl_4 (tetrachlorophosphonium oxotetrachlorovanadate) indicates the probability of the vibrational transitions within the molecule as a function of the vibrational energies expressed in the units of *wavenumbers* (Reproduced from Roldán et al. 2004). (**b**) An example of the "ribonic spectrum" indicating the probability of observing various RNA trajectories (ribons) represented by node *numbers*

the transitions among the electronic, vibrational, and/or rotational levels within molecules. In contrast, the *y*-axis of RNA spectrum measures the number of RNA molecules whose trajectories have similar shapes, *regardless of the underlying causes*. In other words, molecular spectroscopy deals with *dynamics*, and RNA spectroscopy (or "ribonoscopy") is concerned with *kinematics* (see Row 8, Table 12.5), the two

Table 12.5 A comparison between *molecular spectra* and *ribonic spectra*

		Molecular spectra	Ribonic spectra
1.	Objects under study	Subatomic structural transitions of a group of identical molecules	Kinetic trajectories (or ribons) of a group of heterogeneous RNA molecules catalyzing a common metabolic function
2.	Stability of the object	Equilibrium structures (*equilibrons*)	Dissipative structures (*dissipatons*)
3.	Internal organization	Electronic energy levels	Pathway-forming RNA molecules
		Vibrational energy levels	Distances between RNA pairs[a]
		Rotational energy levels	Individual RNAs
4.	*X*-axis	Wavelengths of light absorbed (*energy*)	Node numbers encoding the shapes of RNA trajectories (*Information*)
5.	*Y*-axis	Absorbance (or amount of light absorbed by a given number of molecules)	Number of RNA molecules possessing a given shape of their trajectories or waves
6.	Experimental method	Spectrophotometers	DNA microarrays + PCA[b]
7.	Measured	Molecular spectra	RNA spectra, or "ribonic spectra"
8.	Mechanics	Dynamics	Kinematics
9.	Field of study (*Alternative names*)	Molecular spectroscopy	"Ribonoscopy" (or "RNA spectroscopy", "ribonics", transcriptomics, "RNA interactomics")
10.	Theory	Quantum mechanics (1900–1925)	Molecular theory of the living cell (1985–2010)

[a]The dissimilarity between two RNA trajectories or wave forms

[b]Principal component analysis, a mathematical procedure by which high-dimensional data can be projected onto a lower-dimensional space with a minimal loss of information. For example, this can be accomplished by using the ViDaExpert program developed by Zinovyev (2001) (see Sect. 12.8.1)

subfields of mechanics that are complementary to each other (Sect. 2.3.5) (Murdoch 1987; Plotnitsky 2006).

The methodology of *molecular spectroscopy* is based on spectrophotometers that can produce molecular spectra in most cases without having to rely on computers or mathematical analysis (Row 6, Table 12.5). The methodology of *ribonoscopy*, however, depends not only on DNA microarrays invented in the mid-1990s (Sect. 12.1) but also on computer-based visualization techniques that reduce high-dimensional microarray data (e.g., six in the case of the data displayed in Figs. 12.1, 12.11) to low dimensions (e.g., to three in Fig. 12.11 and two in Fig. 12.12) utilizing the mathematical procedure of principal component analysis (Gorban and Zinovyev 2004). Therefore, just as the invention of spectrophotomers (i.e., the device measuring the absorption or emission of photons by molecules as functions of wavenumbers or wavelengths) in the nineteenth century led to the emergence of a vast field of "molecular spectroscopy," so I am here predicting that the combination of DNA microarrays and computer software implementing the

Table 12.6 The "ribonic matrix" for characterizing cell state. P_i = the ith *pathway*, where i runs from 1 to n, where n is ~200 in budding yeast; R_j = the jth *RNA molecule*, where j runs from 1 to m, where m is ~6,300 in budding yeast; N_i = the ith *node number* defined in Fig. 12.12, where i runs from 1 to r^2 where r is the linear size of the principal grid; α/m = the average number of RNA molecules participating in a metabolic pathway, where α is the sum of the numbers in the last row and m is the number of the RNA molecules with known functions, and β is the sum of the numbers appearing in last column, and β/m is the average number of the metabolic functions carried out by an RNA molecule in budding yeast

Cell type X, perturbation Y						
	Metabolic pathways (n)					
RNA molecules with known functions (m)	P_1	P_2	P_3	...	P_n	Number of metabolic roles played by an RNA (μ)
R_1	N_1	–	–		N_7	2
R_2	N_5	N_7	–		–	2
R_3	–	N_{99}			–	1
R_4	N_7	–	N_{25}		–	2
R_5	N_3	–	–			N_{100}
2						
.						
.						
.						
R_m	N_7	–	N_{55}	...	N_6	3
Number of RNAs encoding a pathway (ε)	5	2	2		2	β
						α

mathematics of principal component analysis such as ViDaExpert (Sect. 12.8.1) will give rise to what is here called "RNA spectroscopy" or more briefly "ribonoscopy" as indicated in Eq. 12.21 and exemplified in Fig. 12.12. Finally, just as the interpretation of molecular spectra requires applying the concepts, laws, and principles of *quantum mechanics*, so the correct interpretation of ribonic spectra is predicted to require applying a *comprehensive molecular theory of the living cell*, such as the one developed in this book:

$$\textbf{Ribonoscopy} = \textbf{DNAMicroarrays} + \underset{(\text{implemented by, e.g., } \textit{ViDaExpert})}{\textbf{PrincipalComponentAnalysis}} \quad (12.21)$$

The practical applications of *ribonoscopy* in pharmaceutical science and medicine are discussed in Chaps. 18 and 19.

12.8.3 Ribonics*: The Study of Ribons with Ribonoscopy*

The *ribonic spectra* of metabolic pathways, some examples of which are being shown in Fig. 12.12, can be analyzed in a tabular form, to be referred to as the "ribonic matrix" (see Table 12.6). The rows in the table represent *m* different RNA

molecules encoded by genes, less than *m* in number due to alternative splicing (Myer and Vilardell 2009; Will and Lűhrmann 2006), and the columns represent *n* metabolic pathways (*n* numbering around 200 in the budding yeast cell). The interior of the matrix contains the node numbers, N_i, where an RNA molecule is located in a given ribonic spectrum, where N_i is the ith node in the r × r principal grid (see Sect. 12.8.1) with *r* ranging from 5 to 20. In Table 12.6, r = 10 and N = 100.

The following features of the "ribonic matrix" are noteworthy:

1. If a given RNA molecule participates in more than one metabolic pathway, the number appearing in the last column of the *ribonic table* will be greater than 1.
2. The number of different RNA molecules (i.e., with different ORF's) participating in a given metabolic pathway appears in the last row of the table.
3. Of the total of more than 6,000 RNA molecules, about 4,000 RNA molecules have known functions which number about 200. Hence the average number of RNA molecules supporting one function or one pathway is $\alpha = 4{,}000/200 = 20$.
4. Although the entities on the horizontal and the vertical margins of the table are independent of experimental perturbations Y, the *node numbers* in the interior (yellow shading) of the table are sensitively dependent on Y, which would make the *ribonic matrix* a useful tool for characterizing cell states, both normal and diseased (Chaps. 18, 19).
5. Based on the frequency of occurrence of each node in the interior of the ribonic matrix, a histogram can be generated by plotting the frequency of a node occurrence (which is equal to the number of RNA molecules occupying that node) as a function of node numbers. Such a histogram will be referred to as the "total ribonic spectrum" (TRS) of known RNAs. The "total ribonic spectrum" of unknown RNAs is given in Panel h in Fig. 12.12. By comparing these two kinds of "total" ribonic spectra generated with a variety of different ViDaExpert parameters (e.g., different stretching and bending coefficients and principal grid sizes), it may be possible to identify the biological functions of unknown RNAs (see Chaps. 18 and 19).

12.9 Structural Genes as Regulators of Their Own Transcripts

Completing the sequencing of the human genome in 2003 was not the end (as many might have thought) but only the beginning of our long journey toward understanding the functioning of the genome and hence the living cell on the molecular level. From a nonequilibrium thermodynamics perspective (Prigogine 1977, 1980; Kondepudi and Prigogine 1998; Kondepudi 2008), we can readily identify the nucleotide sequences of the human genome as equilibrium structures or *equilibrons* and their biological functions as dissipative structures or *dissipatons* (see Sect. 3.1). Functions are dissipatons because functions imply processes and processes entail the

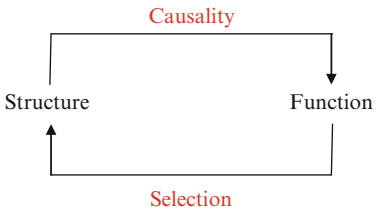


Fig. 12.14 The duality of the structure–function relation in biology or the cyclic relation between structure and function

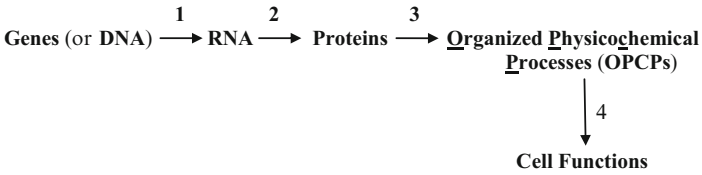


Fig. 12.15 Molecular mechanisms underlying genotype–phenotype coupling. **1** = transcription; **2** = translation; **3** = enzymic catalysis; **4** = Output mechanisms (e.g., secretion, chemotaxis, cell shape changes). OPCPs are synonymous with *dissipatons* (Sect. 3.1), *hyperstructures* (Sect. 2.4.4), and *SOWAWN machines* (Sect. 2.4)

dissipation of free energy (see Sect. 6.2.11). So to completely understand how the human genome functions, it is necessary to elucidate how *free energy* derived from chemical reactions (e.g., oxidation of glucose to CO_2 and water, ATP hydrolysis) is combined with *information* encoded in DNA to effectuate various biological functions of the cell. In this view, the next major step in the Human Genome Project must include a complete elucidation of the molecular mechanisms underlying *genotype–phenotype coupling*.

It is a truism to state that *structures determine functions* over the ontogenetic time scale (seconds to years), but *functions select structures* over the phylogenetic time scale (decades to billions of years). We may refer to this fact as *the duality of structure–function relations in biology, or the cyclic relation between structure and function in biology* which may be represented schematically as shown in Fig. 12.14:

How functions select structures seems well understood in terms of the current evolutionary theories rooted in the environment-initiated selection of the fittest reproducing systems among varieties of organisms made available by mutations and other novelty-generating mechanisms. However, the molecular mechanisms underlying the causal relation between structure and function on the molecular level, i.e., the problem of *genotype–phenotype coupling*, or the question as to how genes control cell functions, are as yet poorly understood.

During the past century, we have learned a great deal about how genes control cell functions, which may be summarized as shown in Fig. 12.15:

The overall processes of the genotype–phenotype coupling can be divided into four distinct subprocesses (Fig. 12.15). Of these four, the first three processes

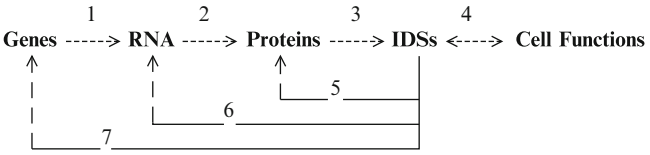


Fig. 12.16 A molecular model of the genotype–phenotype coupling based on the concepts of *dissipative structures* and *conformons,* the key elements of the *Bhopalator model of the cell* (Ji 1985, 2002b) (see Fig. 2.11). This scheme is consistent with the multilevel representation of the cell depicted in Fig. 9.2

(*transcription*, *translation*, and *enzymic catalysis*) are relatively well understood, but the fourth process connecting *OPCPs* to cell functions is not yet well known, because it is difficult to study OPCPs due to the paucity of appropriate experimental techniques. That OPCPs do occur inside the living cell is now beyond doubt. One of the first clear demonstrations of OPCPs was published by D. Sawyer et al. in 1985 as already mentioned in Sect. 3.1.2. Unlike the intracellular calcium ion gradients in human neutrophils measured by Sawyer et al. (1985), which are chemical concentration gradients in the three-dimensional Euclidean space (requiring x, y, and z coordinates for specification), the time-dependent intracellular RNA levels such as those measured by Garcia-Martinez et al. (2004) in budding yeast undergoing glucose–galactose shift exemplify a chemical concentration gradient in the *time dimension*. That is, the intracellular concentrations of RNA molecules can change with time – rising or falling within minutes to hours, depending on the functions of RNA molecules involved. What was most significant was that these time or temporal gradients of RNA levels are associated with activation or inhibition of select cell functions (e.g., glycolysis and oxidative phosphorylation, see Panel a in Fig. 12.2), thereby linking OPCPs to cell functions. This observation has led to the formulation of the *IDS-Cell Function Identity Hypothesis* given in Statement 12.1.

So we have two examples – one involving "spatial gradients" of chemical concentrations and the other "temporal gradients" – that demonstrate the causal relation between OPCPs and cell functions. These observations provide the empirical basis for the postulate that what drives the cell functions are OPCPs. It is important to keep in mind that OPCPs in Fig. 12.15 cannot exist without continuous dissipation of free energy and hence are examples of *dissipative structures* or *dissipatons*. Thus, we can replace the operationally defined OPCPs in Fig. 12.15 with the thermodynamics-based concept of "intracellular dissipative structures" or IDSs (Sect. 3.1) as shown in Fig. 12.16.

Processes 1, 2, and 3 are catalyzed by enzymes and Process 4 is suggested to be an identity relation (see Statement 12.1 in Sect. 12.5). Since functions of enzymes are postulated to be driven by internal mechanical stresses localized in sequence-specific sites referred to as *conformons* (Chap. 8 and Sect. 11.4), it can be concluded that Processes 1–3 and 5–7 are all driven by conformons generated within enzymes catalyzing exergonic chemical reactions. Thus, it may be concluded that the *Bhopalator model of the cell provides molecularly realistic mechanisms for effectuating the genotype–phenotype coupling*.

The RNA trajectories measured by Garcia-Martinez et al. (2004) provide indirect experimental evidence that structural genes can contribute to regulating the intracellular levels of their own transcripts. This novel idea is presented below.

Each of the intracellular RNA trajectories (i.e., *ribons*) such as shown in Fig. 11.6 carries two kinds of information – (1) the name of the gene (or the open reading frame, ORF) encoding the RNA molecule whose concentration is being measured, and (2) the time-dependent change in the intracellular concentration of the RNA (i.e., the ribons). The former can be represented in the N-dimensional sequence (or *genotype*) space, where a point represents an N nucleotide-long RNA molecule, and the latter in the six-dimensional concentration (*phenotype*) space, wherein a point denotes the ribon or the kinetic trajectory of an RNA molecule measured over the six time points. Thus, for any pair of RNA molecules, it is possible to calculate (1) the *genotypic similarity* as the degree of the overlap between the pair of nucleotide sequences (using the ClustalW2 program on line (Chenna et al. 2003)), and (2) the *phenotypic distance* as the Euclidean distance between the corresponding two points in the six-dimensional concentration space. When the phenotypic distances of a set of all possible RNA pairs (numbering $n(n-1)/2$ where n is the number of RNA molecules belonging to a given metabolic pathway such as glycolysis and oxidative phosphorylation) were plotted against the associated genotypic similarities, the results shown in Fig. 12.17 were obtained. To facilitate comparisons, several functional groups of RNA molecules are plotted in one graph in Fig. 12.18.

One of the most unexpected observations to be made in these plots is that most, if not all, of the points belonging to a given function or metabolic pathway lie below a line with a characteristic negative slope (see Table 12.7). We will refer to this phenomenon as the "*triangular distribution of the genotype similarity* vs. *phenotype distance (GSvPD) plots*." This triangular distribution indicates that structural genes have an effect on the intracellular levels of their own transcripts (but it is impossible to predict the phenotype based on genotype, see below), because, if *structural genes had no effect at all on their transcript levels inside the cell (as currently widely believed by most molecular biologists), the distribution of the points on the GSvPD plot should be random and hence cannot account for the triangular distributions observed. On the other hand, if structural genes had a complete control over their intracellular transcript levels, all the points should lie along the diagonal line,* but only a very small fraction of the points actually lie close to it. More than 95% of the points in Figs. 12.17 and 12.18 are contained in the region below the diagonal line. So the relation between genotype and phenotype as revealed in the GSvPD plots contains some regularities but these regularities are unpredictable, leading to the conclusion that the genotype–phenotype relation is *stochastic* or *quasi-deterministic* (see *Glossary*) (Ji et al. 2009b).

A greater absolute slope in the GSvPD plot indicates a greater variation in (or smaller control on) phenotypes for a given genotypic variation (see Figs. 12.17, 12.18). Thus, a greater absolute slope of a GSvPD plot can be interpreted as an indication of a smaller effect of structural genes on the intracellular concentrations of their transcripts, leading to the suggestion that the inverse of the absolute value

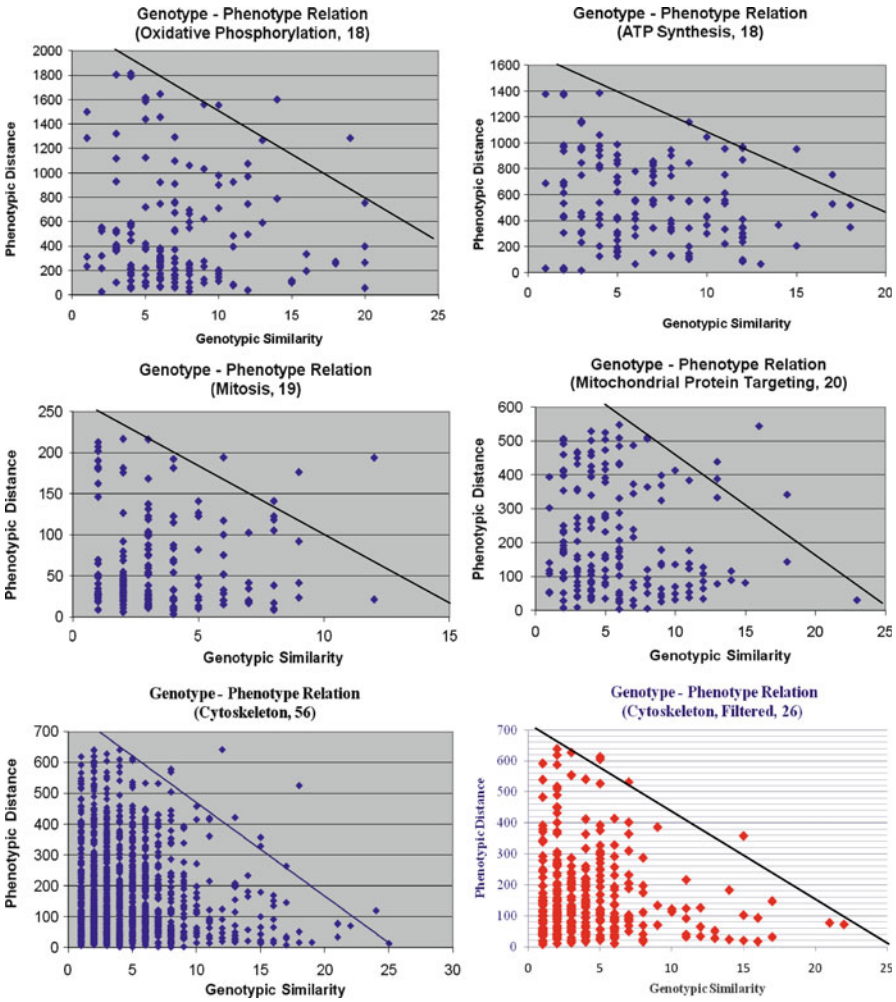


Fig. 12.17 The genotypic similarity vs. phenotypic distance (GSvPD) plots of various metabolic pathways**.** The *bottom two panels* involves the cytoskeleton RNAs. The 56 RNA molecules in the *left bottom panel* were unfiltered original data. The 26 RNA molecules in the *right bottom panel* were selected because their *coefficient of variations*, defined as (standard deviation/mean) $\times$ 100, are less than 50%. Evidently the filtering had little effect on the distribution pattern. *To find the diagonal line objectively, five points with the greatest phenotypic distances (*i.e.*, y coordinates) and five points with the greatest genotypic similarity values (*i.e.*, x coordinates) were selected. From these two sets of points, 25 (= 5 $\times$ 5) candidate diagonal lines were generated by connecting all possible pairs of x and y coordinates. Then the rest of the points were run through a distance formula to find their distance from each of the 25 diagonals. The 10–15% of the points that are closest to each diagonal are selected and a line of regression through these points is found. The median of the resulting lines of regression is chosen as the "true" candidate diagonal that contains 80–90% of the points below it (I thank Mr. Kenneth So for developing this algorithm)*

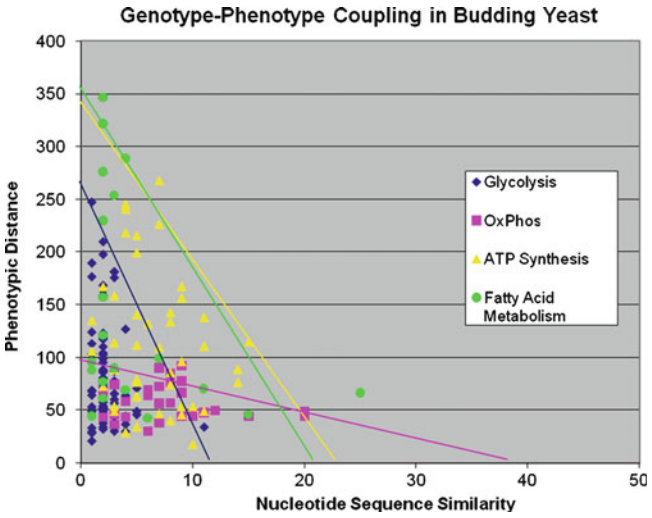


Fig. 12.18 The plot of the phenotypic distances between pairs of RNA against the genotypic similarities between the corresponding RNA pairs. These RNA pairs belong to four metabolic pathways as indicated in the box (The RNA level data from Garcia-Martinez et al. 2004)

Table 12.7 The varying degrees of the efficiency of self-regulation by structural genes. n = the number of RNA molecules or ORFs

Functions of RNA (n)	Slope	*y*-intercept
1. Glycolysis (16)	−24.1	11
2. Oxidative phosphorylation (18)	−2.6	38
3. ATP synthesis (18)	−18.1	21
4. Fatty acid synthesis (14)	−23.5	17

of the slope of a GSvPD plot may be employed as a quantitative measure of the *self-regulatory power of structural genes* (SRPSG):

$$\text{SRPSG} = \left|\text{Slope of GSvPD plot}\right|^{-1} \tag{12.22}$$

On the basis of Eq. 12.22 and the data given in Fig. 12.17 and Table 12.18, it may be concluded that the structural genes of the glycolytic pathway have a lesser *self-regulatory power* than those of the oxidative phosphorylation pathway. Alternatively, it may be stated that glycolytic genes are more "other-regulated" than oxphos genes, "other-regulated" meaning the opposite of "self-regulated," i.e., regulation by DNA regions other than structural genes such as promoters, enhancers, and silencers.

It is important to keep in mind that the points in the GSvPD plot such as Figs. 12.17 and 12.18 represent differences between two sets of numbers, ΔG_{AB} and ΔP_{AB}, where ΔG_{AB} is the genotypic difference between RNA molecules A and

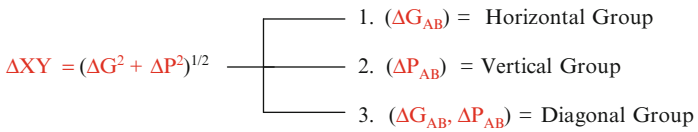


Fig. 12.19 The three possible mechanisms giving rise to the difference between two points, X and Y in the GSvPD plot. Mechanism 1 = the distance, $\Delta XY = ((G_2 - G_1)^2 + (P_2 - P_1)^2)^{1/2}$, is determined by the *genotypic* difference only between RNA pair, A and B. Mechanism 2 = the distance is determined by the *phenotypic* difference only between the RNA pair. Mechanism 3 = The distance is determined by both the *genotypic* and the *phenotypic* differences between the RNA pair

B, and ΔP_{AB} is the phenotypic difference between the same RNA pair. So when we compute the distance, ΔXY, between two points, X (G_1, P_1) and Y (G_2, P_2), in the GSvPD plot using the Pythagorean formula, there are three distinct mechanisms by which the difference can arise as explained in Fig. 12.19.

However, in order to simplify the argument, it will be assumed in this book (e.g., Fig. 12.17) that the mechanism underlying the metric (i.e., distance measurement) in the GSvPD plot is due to Mechanism 3 only. If the three mechanisms defined in Fig. 12.19 all have an equal probability of being realized, any conclusion made on the basis of the simplifying assumption would have approximately 33% of being correct. When more information about the mechanism of interactions among RNA pairs is available and taken into account, this probability could be increased toward unity.

12.10 Rule-Governed Creativity (RGC) in Transcriptomics: Microarray Evidence

The points in the GSvPD plots, e.g., Figs. 12.17 and 12.18, can be divided into four groups as explained in Fig. 12.20. More than 95% of the RNA pairs belong to the self-regulatory group, and only less than 5% belong to the "other-regulatory" group. In other words, during the glucose–galactose shift, most of the structural genes of the budding yeast cells contribute to regulating their own transcript levels, and this *self-regulatory fraction* of structural genes may vary depending on the environmental conditions under which RNA levels are measured.

Group *A* comprises the RNA pairs whose coordinates lie above the diagonal line, and thus their intracellular concentrations are controlled by factors other than their structural genes. These RNA pairs belong to the group of what will be referred to as the "other-regulatory" or "other-regulated" genes, meaning that these genes are regulated by other genes or regulatory DNA regions including promoters, enhancers, and silencers (see Fig. 12.17). Group *B* represents the RNA pairs whose coordinates lie below the diagonal line. The intracellular concentrations of

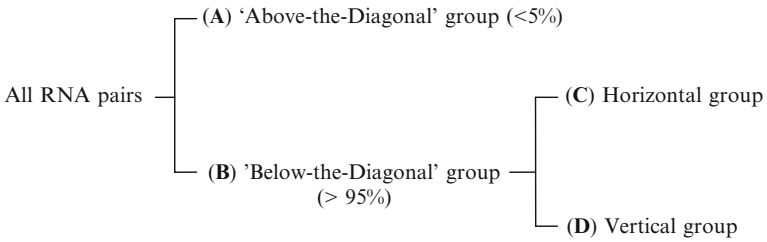


Fig. 12.20 A classification of the points on the genotypic similarity vs. phenotypic distance (GSvPD) plot

these RNA molecules are under the control of their structural genes so that none of their differences lie above the diagonal. These RNA pairs belong to the group of "self-regulatory" or "self-regulated" genes. Group *C* consists of the RNA pairs whose coordinates lie along horizontal lines, indicating that their intracellular concentrations are similar despite the fact that their structural genes are different. We will refer to this behavior as the *genotypic freedom with phenotypic constraint,* which may be viewed as the molecular counterpart of (or as ultimately responsible for) the phenomenon of *convergent evolution* (see Glossary) on the macroscopic scale. Group *D* contains the RNA pairs whose coordinates lie along vertical lines, indicating that their intracellular concentrations can vary over a wide range despite the fact that their structural genes are similar. This behavior may be referred to as the *phenotypic freedom with genotypic constraints*, which may be analogous to (or ultimately responsible for) the phenomenon of *divergent evolution* (see Glossary) on the macroscopic scale.

Group *B* RNA pairs may seem paradoxical in the sense that they contain both Groups *C* and *D* that exhibit no correlation between genotypes and phenotypes, thus embodying the phenomena of the genotypic freedom with phenotypic constraints and the phenotypic freedom with genotypic constraints, respectively. One possible explanation for these seemingly paradoxical observations is that the intracellular levels of Group *B* RNA pairs are controlled not only by their own structural genes but also by other genes such as those encoding transcription factors, enhancers, and silencers. To the extent that intracellular RNA levels are controlled by genes other than their own structural genes, to that extent the points in the *genotypic similarity* vs. *phenotypic distance* (GSvPD) plots would deviate from the associated diagonal lines.

The triangular distribution of points in the GSvPD plots (Figs. 12.17, 12.18) embodies both *determinism* and *nondeterminism*, reminiscent of *deterministic chaos* in dynamical systems theories (Scott 2005). The *determinism* is reflected in the fact that almost all the points in the GSvPD plot lie below the diagonal line, whereas the nondeterminism is exhibited by the fact that Group D RNA pairs (Fig. 12.20) show unpredictable phenotypic behaviors despite their genotypic similarities. The term *nondeterminism* is interpreted here as synonymous with "unpredictability" in physics and *creativity* in linguistics. Therefore, it appears reasonable to conclude that the triangular distribution of the points in the GSvPD plot is an experimental evidence

for the operation of the principle of "rule-governed creativity (RGC)" in the genome-wide metabolism of RNAs, i.e., transcriptomics. (The principle of RGC is discussed in detail in Sect. 6.1.4.) This conclusion is consistent with the postulate that living cells use language, *cellese*, which is isomorphic with the human language, *humanese* characterized by RGC (see Sects. 6.1.2 and 6.1.3).

12.11 Genes as Molecular Machines

The experimental data presented Sect. 12.9 indicate that most structural genes of budding yeast co-regulate their own transcript levels in the cell in cooperation with other genes under the experimental condition of glucose–galactose shift. The extent of such co-regulation may vary from one experimental condition to another. This goes against the commonly held views that structural genes simply act as passive templates for transcription and replication with their rates controlled by other regions of DNA such as promoters, enhancers, and silencers (Fig. 12.22). The idea that structural genes possess the capacity to regulate the intracellular concentration of their own transcripts (as proposed in Sect. 12.9) is novel to the best of my knowledge (Ji et al. 2009c).

If structural genes are to regulate their own transcript levels (through mechanisms discussed in Table 12.8), they must dissipate free energy, since no control of any kind is possible without dissipating free energy (Hess 1975). This means that structural genes must be able to *store* energy as well as control *information*. Structural genes, being DNA segments, can store mechanical energy in the form of conformational strains as exemplified by DNA supercoils (Benham 1996a), which are examples of conformons (Sect. 8.3). Since any material entity possessing both the control

Table 12.8 The energy-dependent self-regulatory powers of structural genes of budding yeast observed during glucose–galactose shift. The slopes were read off from the diagonal lines of the first six plots in Fig. 12.21. The self-regulatory powers were calculated from the slopes using Eq. 12.22

Function of RNA		Slope	Self-regulatory power (×100)	
1. Drug resistance	Early	−5.53	18.1	90% ↑
	Late	−2.91	34.4	
2. Endocytosis	Early	−3.96	25.3	162% ↑
	Late	−1.51	66.2	
3. Lysine biosynthesis	Early	−16.18	6.2	53% ↑
	Late	−10.49	9.5	
4. Autophagy	Early	−12.47	8.0	128% ↑
	Late	−5.48	18.2	
5. Glucose repression	Early	−40.20	2.5	92% ↑
	Late	−20.91	4.8	
6. Heme biosynthesis	Early	−13.88	7.2	28% ↓
	Late	−19.29	5.2	

information and the *energy* to execute such information can be defined as a machine (Ji 1991), and since structural genes possess (1) genetic information encoded in their nucleotide sequences and (2) mechanical energy stored in their conformational strains, structural genes satisfy the necessary and sufficient condition for being *molecular machines*. Extending this argument further, it is here suggested that:

> Not only structural genes but also any DNA segment or the DNA molecule itself can be viewed as molecular machines since they all participate in *controlling* one or more phenotypes. (12.23)

Statement 12.23 will be referred to as the "Genes as Molecular Machines Postulate" (GAMMP).

One indirect evidence for the GAMM Postulate is provided by the energy-dependency of the self-regulatory powers of structural genes that can be estimated from the GSvPD plots such as shown in Fig. 12.21. As summarized in Table 12.8, the slopes of the GSvPD plots of most metabolic pathways decrease (except for the heme biosynthesis and oxphos pathways) as the budding yeast cell undergoes cell-state transition from the energy-poor early to the energy-rich late phases. The corresponding self-regulatory powers of structural genes increase by 53–162% (see the last column in Table 12.8), indicating that the regulatory activity of structural genes are generally enhanced by the availability of metabolic energy.

A structural gene can regulate its transcript level inside the cell as summarized in Table 12.8.

Mechanisms *A, C, E*, and *G* are *trans-mechanisms,* i.e., genes exert their control power through other molecules such as RNA, whereas Mechanisms *B, D, F,* and *H* represent both *trans-* and *cis-mechanisms*, the *cis*-mechanisms implicating genes regulating other genes directly (e.g., via transmitting mechanical or conformational strains), without being mediated by other molecules such as RNAs or proteins. The *cis*-regulatory mechanisms of structural genes postulated here appear to be new but are consistent with the ideas already discussed earlier – (1) the *Bianchini cone* in Fig. 9.2 which represents the set of the mechanisms by which DNA itself regulate transcription without being mediated by RNA or proteins, and (2) the concept of *d-genes* (see Fig. 11.8), i.e., the notion that the DNA molecule as a whole acts as a gene, for example, in self-replication where DNA acts as its own template.

One way to characterize the mechanism underlying the *self-regulatory power of a structural gene* is to represent it as a vector in an eight-dimensional "mechanisms space" defined by eight orthogonal axes, each encoding the extent (with numerical values ranging from 0 to 1) of the contribution of one of the eight mechanisms, A through H, shown in Table 12.9, to the overall mechanism of self-regulation, $\mathbf{M_i}$:

$$\overrightarrow{\mathbf{M_i}} = \mathrm{M_i}\ (\mathrm{c_{i1}}, \mathrm{c_{i2}}, \mathrm{c_{i3}}, \ldots, \mathrm{c_{i8}}) \tag{12.24}$$

where the subscript, i, refers to the ith RNA under consideration, and $\mathrm{c_{i1}}$, $\mathrm{c_{i2}}$, $\mathrm{ci_3}$, . . ., $\mathrm{c_{i8}}$ are the coordinates of the head of the vector , $\overrightarrow{\mathrm{M_i}}$ **,** whose base is located at the origin of the eight-dimensional mechanisms space.

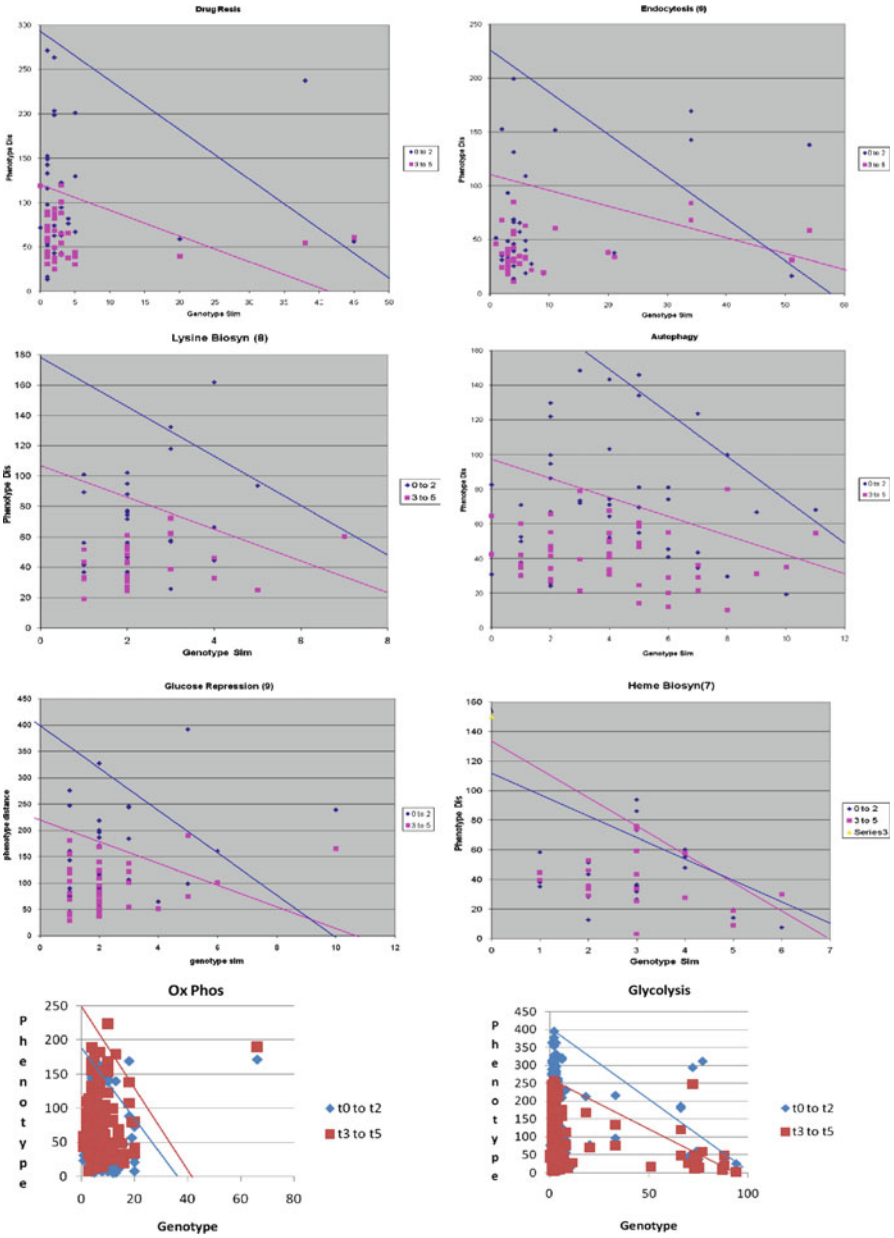


Fig. 12.21 The genotypic similarity vs. phenotypic distance plots (GSvPD) of the RNA pairs belonging to different metabolic groups in the budding yeast were divided into the energy-poor early phase (*blue*) and the energy-rich late phases (*red*). The energy-poor phase obtains during the first 120 min after switching glucose to galactose when the energy source glucose is absent and the energy-rich phase obtains between 360 and 850 min when galactose is metabolized to provide energy. The slopes decrease as the budding yeast cells undergo the cell-state transitions from the energy-poor early phase to the energy-rich late phase, except for the heme biosynthesis and oxphos pathways where the slopes either increase or unchanged within experimental error

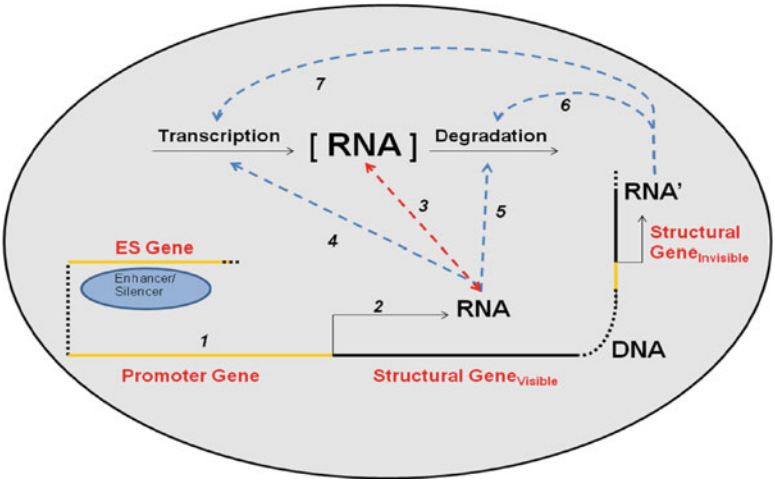


Fig. 12.22 The hypothesis that a DNA molecule itself is a gene consisting of two subtypes – (1) the RNA-coding *structural genes* (see 2) and (2) the *regulatory genes* including promoters, enhancers and silencers (see 1). *Structural genes* act as templates for transcription (Step 4) catalyzed by RNA polymerase or for replication catalyzed by DNA polymerase (not shown). Regulatory genes, in conjunction with various transcription factors and ATP-driven molecular motors (including DNA gyrase and topoisomerases), are postulated to control the *timing* of the turning on or off of the expression of structural genes (Ji 1991), thereby contributing to the control of the observed intracellular levels of RNA (indicated by the square brackets) (Step 3) which result from the balance between *transcription* (4) and *transcript degradation* (5). It is convenient to distinguish between "visible" genes encoding the "visible" RNA being measured or observed and "invisible" or "hidden" genes encoding the "invisible" RNA molecules that affect the levels of "visible" RNA molecules via regulating the *transcription* (see Step 7) and the *degradation* (Step 6) of visible RNAs. It should be noted that visible RNAs can also regulate the levels of invisible RNAs (not shown) thereby indirectly regulating themselves via feedback (not shown) (The figure was drawn with the assistance of my undergraduate student Julie Bianchini in 2009)

In order for a d-gene (i.e., a gene acting as template for DNA replication) to be able to regulate the activities of other genes through *cis*-mechanisms, it is necessary for the d-gene to exert a mech7anical force on its target gene(s) in order to meet the energy requirement for control (Hess 1975) and not to violate the laws of thermodynamics. One possible source of the energy needed to generate such forces is the *conformational energy* stored in DNA duplexes introduced by ATP-dependent enzymes such as DNA gyrases, variously called SIDDs (Benham 1992, 1996a, b) and conformons (Ji 1974b, 2000) (see also Sect. 8.4). Unlike protein molecular machines that can transduce chemical energy into the mechanical energy or conformons by their catalytic actions, d-genes cannot directly utilize chemical energy to generate their mechanical forces due to lack of enzymic activity and hence must rely on energy transfer from force-generating or conformon-generating

Table 12.9 Possible mechanisms of structural genes self-regulating the intracellular levels of their own transcripts. An arrow can be read as "regulates." The structural genes correspond to "visible genes" in Fig. 12.22, i.e., those genes whose transcripts are being measured, and those genes whose transcripts are not measured directly but are assumed to affect the "visible genes" in one way or another are referred to as "invisible genes" in Fig. 12.22

Mechanisms		Details
1	A	Structural genes → RNA → Transcription
2	B	Structural genes ↓ Other structural genes → RNA → Transcription
3	C	Structural genes → RNA → Transcript degradation
4	D	Structural genes ↓ Other structural genes → RNA → Transcription degradation
5	E	Structural genes → RNA → Protein → Transcription
6	F	Structural genes ↓ Other structural genes → RNA → Protein →Transcript ion
7	G	Structural genes → RNA → Protein → Transcript degradation
8	H	Structural genes ↓ Other structural genes → RNA → Protein →Transcript degradation
9	I	$c_1A + c_2B + c_3C + c_4D + c_5E + c_6F + c_7G + c_8H$ where c_1–$\mathbf{c_8}$ are positive fractions adding up to 1

protein machines as exemplified by supercoiled DNA. This leads me to suggest that molecular machines be divided into three groups as shown in Fig. 12.23, in analogy to the division of transport processes into a similar scheme.

Utilizing the machine classification scheme shown in Fig. 12.23, the following generalization may be proposed:

> d-Genes cannot act as *primary active molecular machines* but can act only as secondary *active molecular machines* (SAMM) or *passive molecular machines* (PMM). (12.25)

Statement 12.25 may be referred to as the "d-Gene as Molecular Machines (DGAMM)" hypothesis. Since structural genes are members of the drp-gene family (Sect. 11.2.4), *the hypothesis that structural genes are molecular machines* would follow as a corollary from the DGAMM hypothesis.

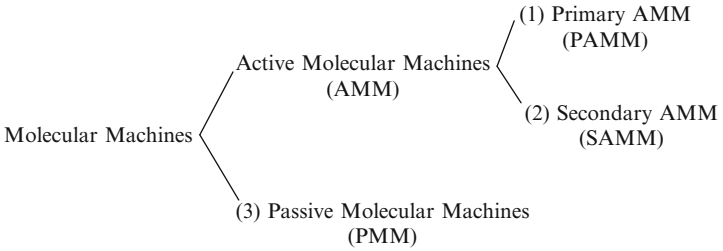
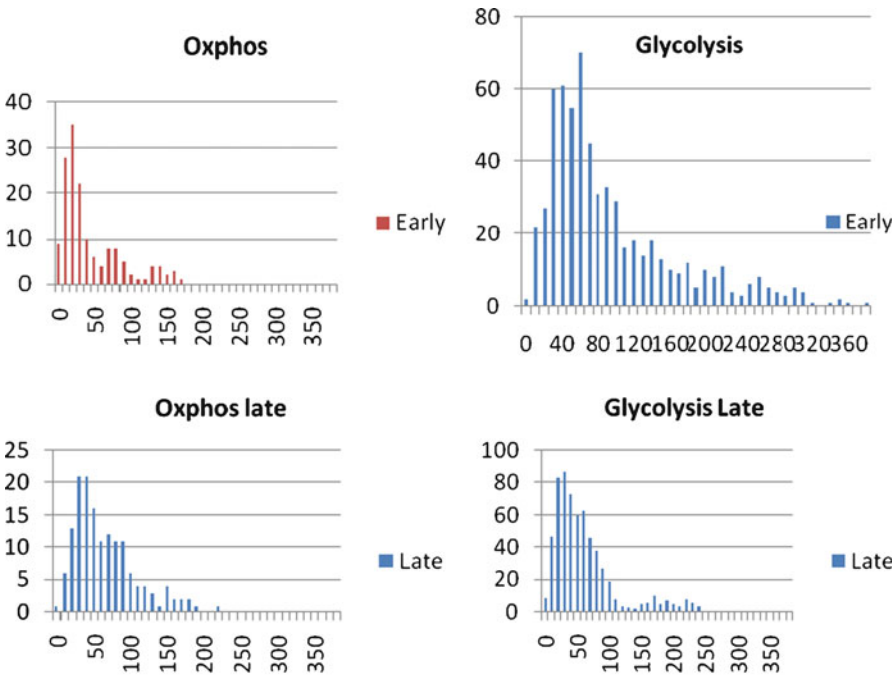


Fig. 12.23 Three kinds of molecular machines. *Active molecular machines* (e.g., ATP-dependent ion pumps) are autonomous in that they can generate mechanical forces directly from exergonic chemical reactions that they catalyze. *Passive molecular machines* (e.g., passive ion channels) cannot perform any active processes such as ion movements against their concentration gradients. Active molecular machines divide into two groups – the *primary* and the *secondary*. The *primary active molecular machines* (PAMM) can generate mechanical forces or conformons directly from the chemical reactions catalyzed by them (e.g., myosin). The *secondary active machines* (e.g., Ca^{+} $^{+}$-ion driven Na^{+} -ion channel, DNA supercoils) cannot generate mechanical forces or conformons from any chemical reactions but depend on the energy or conformon transfer from primary active molecular machines

12.12 The Isomorphism Between Blackbody Radiation and Whole-Cell Metabolism: The Universal Law of Thermal Excitations (ULTE)

The genotypic similarity vs. phenotypic distance (GSvsPD) plots such as shown in Fig. 12.17 were useful in gauging the overall behaviors of the kinetic differences between all possible RNA pairs within a metabolic pathway but did not reveal any clear patterns of distribution of the points within the main body of the plots. However, when the data points in a GSvsPD plot are graphed in the form of what is called the phenotypic distance vs. frequency (PDvsF) plot by displaying the number of points found within an arbitrary interval (or a bin) of the phenotypic distance against the phenotypic distance class, unexpected patterns or regularities in frequency distribution emerged as shown in Fig. 12.24. This contrasts with the seemingly random distributions found in the corresponding GSvsPD plots shown in the bottom two panels in Fig. 12.21. The following observations can be made:

1. The PDvsF plots are energy-dependent. When budding yeast cells undergo a state transition from the energy-poor early phase to the energy-rich late phase, the mean and the variance of the PDvsF plot of the oxphos pathway remain unchanged and increase, respectively (see the table in the bottom panel of Fig. 12.24). In contrast, the mean and the variance of the glycolytic pathway both decreased during the same cell-state transition. These changes are most likely the results of the metabolic transitions from the respiratory to the glycolytic mode induced by the glucose–galactose shift (Ronne 1995; Winderickx et al. 2002).
2. A decrease in the variance of a pathway-specific PDvsF plot indicates a more coherent behaviors of RNA trajectories in the yeast cell secondary to the activation



	Early	Late	Early	Late
Mean	42	43	101	51
Variance	2397	5005	5716	4454
% Change in Variance	+ 109		-22	

Fig. 12.24 Phenotypic distance vs. frequency (PDvF) plots of *oxphos* and *glycolytic* pathways in the energy-poor early phase and the energy-rich late phase. The *x*-axis represents the phenotypic distance divided into bins of 50 units and the *y*-axis records the number of points located within each bin

of the pathway involved (Ji et al. 2009, unpublished observation). An increase in the variance would indicate the opposite, namely, the deactivation of the metabolic pathway. This interpretation is consistent with the fact that upon removal of glucose, yeast cells (1) activate the oxphos pathway in order to generate ATP from respiration converting ethanol (presumably left over from the glycolysis before glucose was removed) to carbon dioxide and water and (2) subsequently deactivate oxphos and activate glycolysis when the LeLoir enzymes are induced (see Fig. 12.3) which convert galactose to glucose-1-phosphate, the substrate for the glycolytic pathway (Winderickx et al. 2002).

3. The shapes of the frequency distributions in PDvsF plots are not random nor normal but resemble surprisingly the *blackbody spectrum* (see the upper right-hand panel of Fig. 11.24). As evident in Fig. 12.25, this visual impression is validated by the quantitative agreement found between the experimental data points of PDvsF plots and the theoretical predictions based on the following equation (referred to as *the blackbody radiation-like equation*, or BRE) that has the same form as the Planck's radiation law (see Eq. 11.26 in Sect. 11.3.3):

$$y = a(Ax + B)^{-5}/(e^{b/(Ax+B)} - 1) \tag{12.26}$$

where y is frequency, x is the phenotypic distance, and a, b, A, and B are constants (Ji and So 2009d).

4. The Plank radiation law, Eq. 11.26, which successfully explained the blackbody radiation data in 1900 (Nave 2009; Kragh 2000) is of the form:

$$y = (a/x^5)/(e^{b/x} - 1) \tag{12.27}$$

where a and b have the numerical values given in Table 12.10. The concept of the *quantum of action* introduced by this equation gave birth to quantum mechanics which revolutionized physics in the first three decades of the twentieth century. In the last decade of the same century, two experimental techniques known as the *single-molecule enzymological method* (Sect. 11.3) and *DNA microarrays* (Sects. 12.1 and 12.2) were invented that have been revolutionizing experimental biology ever since. Equation 12.27 generalized as Eq. 12.26 (by replacing x with Ax + B) has been found to fit not only the single-molecule enzymological data of cholesterol oxidase (as shown in Sect. 11.3.3) but also the whole-cell RNA metabolic transitions as shown in Fig. 12.25. In addition, Fig. 12.25 includes protein stability data (see Panel f), because they are found to obey the Universal Principle of Thermal Excitations (UPTE), i.e., Eq. 12.26, as indicated by the solid line. The x-coordinates of the experimental points (open circles) were the negatives of the ΔG values read off from Fig. 12.26, which was reproduced from Zeldovich et al. (2007b). The solid curve is predicted by the equation:

$$P(\Delta G) = A exp\left(hE/\left(h^2 + D\right)\right) \sin\left(\pi(E - E_{min})/(E_{max} - E_{min})\right) \tag{12.28}$$

derived in Zeldovich et al. (2007b), where h and D are, respectively, the mean and the mean square change of protein stability induced by point mutation. E is the energy of the native state of a protein, and E_{max} and E_{min} are the maximum and minimum energies that a protein store upon folding. It is assumed that E can be replaced by G, which is tantamount to assuming that the volume and entropy changes accompanying protein folding are relatively insignificant.

The fact that protein stability data fit Eq. 12.26 indicates that *thermal excitations* or *transitions* are implicated in protein stability as well. One possible

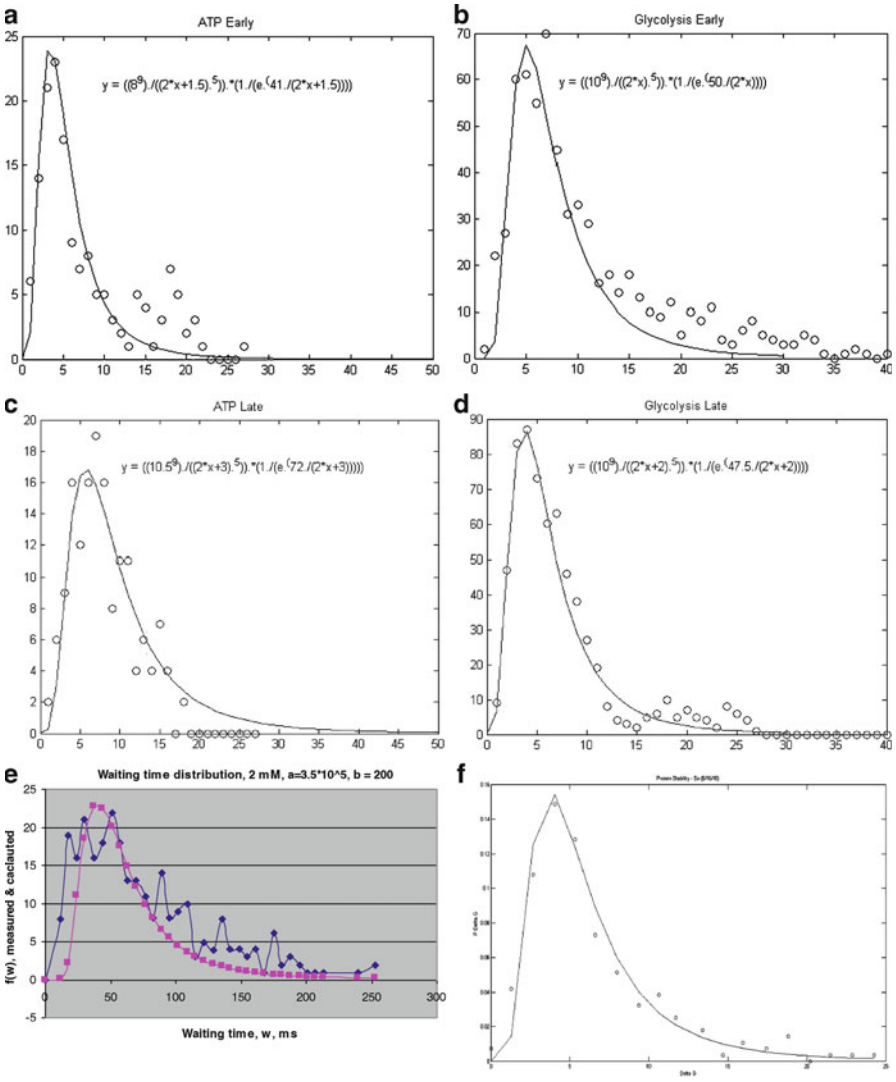


Fig. 12.25 The blackbody radiation law-like equation, Eq. 12.26, also referred to as the universal principle of thermal excitations, has been found to be obeyed by single-molecule enzymology (Panel **e**), whole-cell metabolism (Panels **a**–**d**), and protein stability (Panel **f**) with the following numerical values for the parameters, a, b, A and B: (**a**) $a = 1.3 \times 10^8$, $b = 41$, $A = 2$, $B = 1.5$; (**b**) $a = 10^9$, $b = 50$, $A = 2$, $B = 0$; (**c**) $a = 1.6 \times 10^9$, $b = 72$, $A = 2$, $B = 3$; (**d**) $a = 10^9$, $b = 47.5$, $A = 2$, $B = 2$; (**e**) $a = 3.5 \times 10^5$, $b = 200$, $A = 1$, $B = 0$; (**f**) $a = 1.8 \times 10^{10}$, $b = 300$, $A = 14$, $B = 18$

Table 12.10 The Universal law of Thermal Transitions, $y = (a/(Ax + B)^5)/(e^{b/(Ax + B)} - 1)$, as applied to black-body radiation, single-molecule enzymology, and whole-cell metabolism

		Black-body radiation	Single-molecule enzymology	Whole-cell metabolism
1.	y	Light intensity	Frequency	Frequency
2.	x	Wavelengths	Waiting times	Phenotypic distances
3.	a	5.00×10^{-15} ($8\pi hc$)	3.5×10^5	10^7–10^9
4.	b	4.816×10^{-3} (hc/kT)	200	40–70
5.	A	1	0.33	2
6.	B	0	0	0–3
7.	System of	*Electrons* in atoms[a]	*Atoms* forming proteins[b]	Proteins forming protein complexes[c] (?)
8.	Size of components (m)	10^{-15}	~10^{-9}	~10^{-7}
9.	Thermal excitation of	Electronic states[d]	Vibrational, rotational and bending states[e]	Translational and rotational states[e] (?)
10.	Resulting in	Emission[f]	Catalysis (by a single enzyme)[g]	Control (i.e., catalysis by a system of enzymes)[h]
11.	New concept	Photons[i]	Conformons[j]	Dissipatons[k] (?)
12.	New principle	Quantization of action[l]	Quantization of conformational energy levels within biopolymers[m]	Quantization of the Gibbs free energy levels of biopolymer complexes inside the cell[n]
13.	Energy due to	Electromagnetic field in atoms[o]	Mechanical stress field in biopolymers[p]	Concentration field inside the cell[q] (?)
14.	New theory	Quantum mechanics[r]	Local dissipaton (LD) theory of molecular machines[s]	Global dissipaton (GD) theory of the regulation of cell metabolism[t] (?)

rationale for this inference is that protein stability data are *quantitatively identical with the activation free energies of protein denaturation*. If this interpretation is correct, the same mechanism of single-molecule enzymic catalysis proposed in Fig. 11.28 would apply to protein denaturation, except that the common transition state, $C^{\ddagger}$, now replace the denatured (or unfolded) state of a protein. Based on these findings, it is here suggested that Eq. 12.26 can be viewed as a *universal law* applicable to *blackbody radiation, single-molecule enzymology*, protein stability, and *whole-cell metabolism,* three of which are summarized in Table 12.10 with extensive commentaries and footnotes. The common mechanisms underlying all of the three phenomena listed in Table 12.10 are postulated to be the *thermal excitations* or *activations of molecular motions* (or *Brownian motions*), including bond vibrations, rotations, and translational motions of molecules (see Row 9, Table 12.10). It is for these reasons that

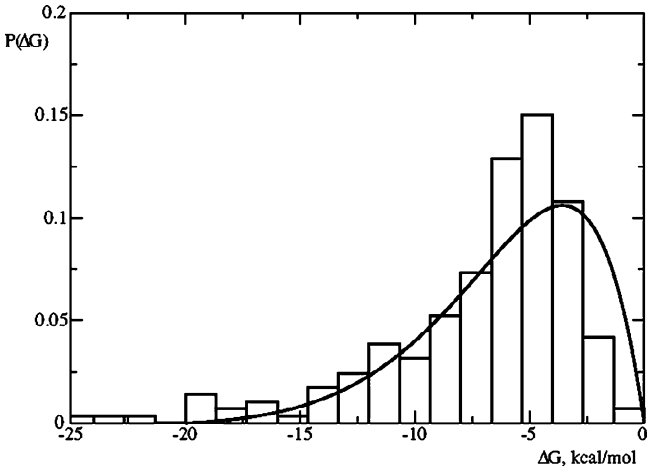


Fig. 12.26 The distribution of single-domain proteins reproduced from Zeldovich et al. 2007b. The *x*-axis records the Gibbs free energy change, ΔG, accompanying protein folding processes, and the *y*-axis registers the probability, P(ΔG), of observing free energies of protein folding

Eq. 12.26 is thought to deserve to be referred to as the *Universal Law of Thermal Excitations (ULTE)*.

5. To the best of my knowledge, Eq. 12.26 represents the only mathematical equation known so far that applies to thermal motions of material objects, from atoms to molecules to metabolic pathways and to living cells, having volumes that differ maximally by a factor of about 10^{15}. Thus, Eq. 12.26 provides the experimental evidence for the hypothesis that thermal motions are one of the necessary conditions of life, leading to the following generalization:

   No thermal motions, no life. (12.29)

   We may refer to Statement 12.28 as the *Heat Principle of Life* (HPL) or the *Principle of the Thermal Requirement of Life* (PTRL). HPL is consistent with many mechanisms of the origin of life that invoke *thermal cycling*, including the conformon model of the origin of life (Sect. 13.2) (Ji 1991) and the RNA-based model of the origin of life proposed by Anderson (1983, 1987) (Sect. 13.1).
6. The first six rows of Table 12.10 demonstrate the quantitative fitting of the experimental data to the Universal Law of Thermal Excitations (ULTE), Eq. 12.26, that have been obtained from the experiments performed on very different kinds of phenomena, namely, black-body radiation, single-molecule enzymology, and whole-cell metabolism. Rows 7–10 (with extensive footnotes) attempt to provide possible mechanistic rationale for the universal application of ULTE to these three phenomena. Finally Rows 11–13 suggest the new concepts, principles, and theories that have been suggested by the mathematical fitting of the experimental data from single-molecule enzymology and whole-cell metabolism to the same type of equation that fits the black-body radiation data.

7. It is interesting to note that the last two columns of Table 12.10 summarize the key results of my theoretical research in molecular and cell biology that spans a period of almost four decades – from 1972 through 2010.

[a]When matter is heated above some threshold temperature, electrons in their ground states are excited and promoted to higher energy levels (see Fig. 11.28). When these electrons return to their ground states, light is emitted with varying frequencies (or colors), giving rise to the so-called blackbody spectrum (see the upper right-hand panel in Fig. 11.24).

[b]When biopolymers are heated to physiological temperatures, all the degrees of freedom of motions of atoms and groups of atoms constituting them are excited to higher energy levels, including vibration, rotation, and bending motions and rarely electronic motions as in blackbody radiation which usually requires heating beyond the physiological temperature range.

[c]The cell is densely packed (or "crowded") with m different types of biopolymers, each type being represented by n copies, where m can be maximally 6,300 in budding yeast, the size of the yeast genome, and n can range from 1 to over 10^3. Out of the almost an infinite number, mn, of the systems of biopolymers that can form inside a single cell through various combinations of the biopolymers in different combining ratios, only a small fraction of them is thought to be metabolically active at any given time to meet the metabolic demand of the cell under a given environmental condition. It is assumed here that these metabolically active *biopolymeric complexes* (acting as a SOAWAN machine; Sect. 2.4) constitute a set of cell states, analogous to the electronic states in atoms or quantum dots (see Sect. 4.15). Therefore, just as heating matter leads to alterations in the electronic configurations of atoms, so it is postulated that heating causes rearrangements of component biopolymers leading to alterations in the number and kinds of *metabolically active biopolymeric complexes* (MABCs, or SOWAWN machines) formed, each catalyzing a specific metabolic pathway or its component processes during their lifetime. Ribons discussed earlier can be thought to represent the activities of MABCs.

[d]Blackbody radiation implicates heating at high temperatures, typically from 3,500 to 5,500 K. At these temperatures, electrons can undergo transitions from one energy level to another.

[e]Heating biopolymers to physiological temperatures (280–320 K) usually does not affect electronic energy levels of atoms (except at active sites) but cause transitions between vibrational, rotational, and bending energy levels of groups of atoms within biopolymers as well as alterations in the translational (or diffusional) motions (speeds) of biopolymer molecules as motional units.

[f]Most, if not all, of the energy absorbed by matter during heating is re-emitted as light during blackbody radiation.

[g]The heat absorbed by an enzyme from its environment is re-emitted as heat after the residence time τ', where τ' is much shorter than the turnover time, τ, of an enzyme, the time required for an enzyme to catalyze one cycle of a chemical reaction: $\tau' < \tau$. But what is measured in a single-molecule enzymological

experiment (see Sect. 11.3) is not the heat re-emitted by an enzyme (as in blackbody radiation) but the consequence of heating, i.e., the catalysis (e.g., the disappearance of the fluorescence of FAD, the coenzyme of cholesterol oxidase, due to reduction) proceeding in times shorter than τ'.

[h]During whole-cell metabolism two or more metabolic pathways (or SOWAWN machines) are coupled (e.g., transcription and transcript degradation pathways; see Fig. 12.22) to maintain a certain cell state (e.g., RNA levels) and meet the metabolic demand of the cell. It is postulated here that thermal (also called Brownian) motions of biopolymers are essential for the cell to explore and access the right biopolymeric complexes among a large repertoire of the biopolymeric complexes available to it. In this view, what is measured in whole-cell metabolic experiments (e.g., the genome-wide RNA measurements in budding yeast undergoing glucose–galactose shift) is not the activities of individual enzymes but the balance of all the activities of the coupled metabolic pathways, i.e., the system properties of a group of dozens or more enzymes and other biopolymers.

[i]The discrete units of light, a member of the family of *quantum objects* (Plotnitsky 2006) that include all microscopic entities such as electrons, protons, and neutrons. According to quantum mechanics (Morrison 1990; Plotnitsky 2006), light can be viewed as streams of particles (i.e., photons) or as waves.

[j]The discrete units of mechanical energy stored as sequence-specific conformational strains of biopolymers (see Chap. 8).

[k]The dynamic and transient systems of biopolymers (e.g., SOWAWN machines; Sect. 2.4) and associated small molecules that are coupled together to perform elementary metabolic functions inside the cell such as glycolysis, transcription, and RNA degradation. There are many different kinds of *dissipatons* just as there are many different kinds of *molecules*.

[l]The fitting of the blackbody radiation data into Planck's radiation law (see Eq. 11.27) established the concept that the physical quantity known as action, defined as the product of energy and time, is not continuous but quantized, ushering in the era of quantum revolution in physics beginning in 1900 (Nave 2009). One consequence of the quantization of action is the establishment of the energy levels in an atom between which electrons are constrained to undergo transitions. Thus, *quantization of action* and the *electronic energy levels* within an atom are the two sides of the same coin.

[m]The idea that the conformational energy of biopolymers plays essential roles in catalysis (Lumry 1974, 2009), gene expression (Benham 1992) and molecular motions (Ji 1974b; Astumian 2001) is gaining general acceptance among biologists (Frauenfelder 1987; Frauenfelder et al. 2001; Ji 2000). But the idea that conformational energy levels of biopolymers may be *quantized* just as the electronic energy levels are in atoms is novel and suggested here (see Sect. 11.3.3) for the first time on the basis of the finding that the single-molecule enzymic data of Lu et al. (1998) fit the Planck radiation law-like equation, Eq. 11.26, which, when applied to atoms, leads to the "quantization" of the electronic energy levels in atoms. The term

"quantization" here means that the energy levels are not continuous but are separated into discrete states.

[n]Just as electrons have their energy levels within an atom (which can be depicted diagrammatically as shown in the left panel in Fig. 11.28), it is postulated here that biopolymers or SOWAWN machines (Sect. 2.4) possess their unique Gibbs free energy levels (or more accurately "partial molar free energies," also known as "chemical potentials" [Wall 1958, p. 192]) within a living cell. The partial molar free energy of the ith chemical, μ_i, including biopolymers, can be calculated as:

$$\mu_i = (\partial G/\partial n_i)_{T,P,n1,n2,\ldots} \tag{12.30}$$

which states that the chemical potential of the ith chemical in a system consisting of components labeled as 1, 2, 3, ..., is equal to the partial derivative of Gibbs free energy of the system with the temperature, pressure, and the concentrations of all the components held constant except the ith component.

If the ith chemical, say, A, interacts with at least one another chemical, B, to produce two products, C and D, i.e., A + B $\leftrightarrow$ C + D, the Gibbs free energy change, ΔG, experienced by the system under consideration is given by:

$$\Delta G = G_{Final} - G_{Initial} = \Delta G^\circ + RT \ln ([C][D]/[A][B]) \tag{12.31}$$

where G_{Final} and $G_{Initial}$ are the Gibbs free energy content of the system in the final (or product) and initial (or reactant) state, respectively, R is the universal gas constant, ln is the natural logarithm, and ΔG° is the change in the standard Gibbs free energy of the system, namely, the Gibbs free energy change per mole of the system at the standard state characterized by the standard T and P, and the unit concentrations (or more accurately activities) of all the chemicals in the system. At equilibrium nothing can change and hence $\Delta G = 0$, and the quotient, ([C][D]/[A][B]) assumes a unique numerical value known as the *equilibrium constant* denoted as K, leading to the following equation:

$$\Delta G^\circ = -RT \ln K \tag{12.32}$$

$$K = e^{-\Delta G^\circ/RT} \tag{12.33}$$

As Eqs. 12.31 and 12.32 indicate, the standard Gibbs free energy change, ΔG°, can be determined by measuring the equilibrium constant, K, of the chemical reaction system under the standard condition.

Gibbs free energy has the interesting property that it *minimizes* when spontaneous processes occur under the environmental conditions of constant temperature (T) and pressure (P) (Callen 1985; Kondepudi and Prigogine 1998; Kondepudi 2008). In other words, Gibbs free energy is a quantitative measure of the tendency of a physical system to change spontaneously, for whatever reasons, given the right environmental conditions to overcome kinetic barriers. Under constant T and P, all spontaneous processes occur with a net decrease in Gibbs free energy, indicating

the special relevance of Gibbs free energy (among many other forms of energy including the Helmholtz free energy, enthalpy, etc.) to the biochemical reactions proceeding in homeothermic organisms. Thus, for all spontaneous processes occurring under homeothermic and constant pressure conditions, the accompanying Gibbs free energy change must be negative:

$$\Delta G = \Delta E + P\Delta V - T\Delta S < 0 \tag{12.34}$$

where E is the internal energy of the thermodynamic system under consideration, V is its volume, and S is its entropy content (see Eq. 2.1).

Just as *photons* are related to the *electronic energy levels* in atoms and *conformons* are associated with the *mechanical energy levels* in biopolymers, so it is here postulated that *dissipatons* are related to the *Gibbs free energy levels* or chemical potentials (Wall 1958, pp. 193–195; Moore 1963, p. 98) of biopolymers inside the cell that associate themselves transiently to form a functional unit (i.e., a SOWAWN machine) for the purpose of catalyzing a specific metabolic process or pathway. In other words, just as atoms contain a set of electronic energy levels (see the left panel of Fig. 11.28) and enzymes contain a set of mechanical energy levels (see the right panel of Fig. 11.28), so it is hypothesized that:

> Cells contain a set of Gibbs free energy levels, some of which being associated with or occupied by biopolymers constituting a dissipation (also called a SOWAWN machine or hyperstructure) that catalyzes a metabolic function. (12.35)

For convenience, Statement 12.34 will be referred to as the Postulate of the *Quantization of Intracellular Gibbs Free Energy Levels (QIGFEL) postulate*. The QIGFEL postulate may be viewed as addressing the energetic aspect of cell metabolism, whereas the theories of SOWAWN machines (Sect. 2.4.3) and hyperstructures (Sect. 2.4.4) focus on the structural and informational aspect of cell metabolism. In other words, the QIGFEL postulate and the theories of SOWAWN machines and hyperstructures may be viewed as complementary aspects of the phenomenon of cell metabolism driven by gnergy (Sect. 4.11).

[o]In physics, the term "field" is defined as a *region of space at every point of which a physical property, such as gravitational or electromagnetic force or fluid pressure, has a characteristic value*. Electrons in an atom can be said to exist in an electromagnetic field at every point of which electrons possess unique values for their potential and kinetic energies.

[p]The interior of a biopolymer may be viewed as a field at every point of which a mechanical stress can be defined that arises from physical properties such as electrical, mechanical, and van der Waals interactions among the monomeric units of biopolymers.

[q]Unlike the mechanical stress field confined within a biopolymer described in Footnote 16 which is "intramolecular"and "node-dependent," the concentration field postulated to exist inside the cell is an "extramolecular," "intermolecular," and "network-dependent" property. Consequently, Eqs. 12.26 and 2.27 or their equivalents may apply to the concentrating field inside the cell but not to the mechanical stress field within a biopolymer.

[r]The discovery of the *quantization of action* by Planck in 1900 (Kuhn 1978) led to the development of quantum mechanics by the mid-1920s which has revolutionized physics and the philosophy of science (Murdoch 1987; Plotnitsky 2006; Bacciagaluppi and Valenti 2009).

[s]Prigogine's dissipative structures (also called dissipatons in this book) can be divided into *local* and *global* dissipatons based on the dichotomization of kinematics into *local* and *global* branches (see Sect. 3.1.6). The conformon theory of molecular machines developed between 1972 and 1991 (Ji 2000) represents a theory of *local dissipatons (LDs)*, whereas the theories of SOWAWN machines (Sect. 2.4.3), hyperstructures (Sect. 2.4.4), and metabolic spacetime (Welch and Smith 1990; Smith and Welch 1991; Welch and Keleti 1981) belong to the family of the theories of *global dissipatons* (*GDs*).

The cell can be viewed as a dynamic system of molecules (biochemicals, proteins, nucleic acids, etc.) that is organized in space and time to form LDs (e.g., enzyme turnovers driven by conformons) as well as GDs (e.g., cell migration powered by conformons, cell cycle coordinated by dissipatons). Since all organizations in the cell are ultimately driven by the Gibbs free energy supplied by chemical reactions catalyzed by enzymes which in turn are driven by *conformons* (Chap. 8), it follows that all GDs in the cell are ultimately driven by LDs or that LDs are the necessary condition for GDs . This is reminiscent of the replacement of the Newtonian action-at-a-distance (i.e., the "gravitational force") with the *local* curvature of spacetime induced by mass at the location (Wheeler 1990, pp. 12.15). That is, it appears that:

Both in physics and biology, there is no action-at-a-distance but only local actions. (12.36)

We may refer to Statement 12.35 as the "Universal Principle of Local Actions (UPLA)."

[t]According to the UPLA formulated in Footnotes, all global dissipatons (GDs) must derive from local dissipatons (LDs). What is the possible mechanism by which a GD can be produced from a set of LDs? In other words, how can a set of LDs give rise to a GD? The *pre-fit hypothesis* which was formulated on the basis of the *Principle of Slow and Fast Processes* or the *Generalized Franck–Condon Principle* described in Sect. 7.1.3 suggests the following plausible mechanism for coupling the formation of a GD from a set of LDs (or as set of two LDs as a simplest case):

1. $LD_1 + \sim + LD_2 \leftrightarrow LD_1 \sim LD_2$
2. $LD_1 \sim LD_2 \leftrightarrow (LD_1 \text{ —— } LD_2)$
3. $(LD_1 \text{ —— } LD_2) \rightarrow LD_1' \text{ —— } LD_2'$ or GD

In Step 1, two LDs, i.e., LD_1 and LD_2, and a structural element denoted as ~ such as a microtubule spanning the cytosolic space between the nucleus and the cell membrane are thermally fluctuating, occasionally forming a tripartite complex shown on the right-hand side of the double-headed arrow. In Step 2, the loose complex, $LD_1 \sim LD_2$, is in equilibrium with its tight but transient complex denoted as (LD_1 — LD_2). Finally, in Step 3, the unstable, transient complex (LD_1 — LD_2) is stabilized to form LD_1' — LD_2' through a *synchronized* dissipation of a part of the free energies of LD_1 and LD_2 which form their lower free energy states, LD_1' and LD_2', that are now coupled by a rigid connector symbolized by — which is equivalent to a GD.

As evident in Steps 1–3 above, the coupling between LD_1 and LD_2 across an arbitrary distance symbolized by the bar, — does not depend on any action at a distance but only on (1) local actions of thermal fluctuations of LD_1 and LD_2 and (2) the synchrony of the relaxations of LD_1 and LD_2 to LD_1' and LD_2' and the process of the rigidification of the connector, namely, $\sim \rightarrow —$. If this mechanism proves to be correct, the main principles underlying the *theory of global dissipations* as applied to cell metabolism may turn out to be the *Principle of Slow and Fast Processes* or the *generalized Franck–Condon principle* (Sect. 2.3.3) (Ji 1991) and the *Principle of Enzymic Catalysis* based on enzymes acting as coincidence detectors (Sect. 7.2.2).

Based on the fact that both the single-molecule enzymic data (reflecting the activities of conformons, a member of LDs) and the genome-wide RNA trajectories of budding yeast undergoing glucose–galactose shift (reflecting GDs) obey the blackbody radiation law-like equation, Eq. 12.26, it may be asserted that (see Row 11, Table 12.10):

> Conformons and intracellular dissipatons are to biology what photons and quantum objects are to physics. (12.37)

Statement (12.37) is consistent with the atom-cell isomorphism postulate (ACIP) described in Fig. 10.4.

12.13 The *Cell Force*: Microarray Evidence

The concept of the *cell force* was invoked in Ji (1991, pp. 8, 95–118) to account for the *functional* stability of the living cell, just as physicists were led to invoke the concept of the *strong force* to account for the *structural* stability of the nucleus of the atom:

> . . .'Cell force' is a hypothetical force thought to act within the living cell to hold together biopolymers in functional states. The cell force is postulated to be mediated by a combination of conformons and IDSs called 'cytons' . . . , just as the strong force is mediated by gluons.. . . (Ji 1991, p. 8; see also Appendix K) (12.37a)

> . . .It is postulated that there exists a new kind of force in nature called the *cell force* that 'holds' together h-particles (i.e., biopolymers; h = heavy, my addition) and l-particles (i.e., small-molecular weight chemicals; l = light, my addition) of the cell together in the living state against environmental perturbations, just as the *strong force* holds nucleons together in atomic nuclei against electrostatic repulsions. (12.37b)

The purpose of this section is to present the first experimental evidence supporting the cell force concept. The evidence was derived from the observation that the whole-cell RNA metabolic data measured with microarrays from budding yeast (Garcia-Martinez et al. 2004) fit the blackbody radiation–like equation (BRE) discussed in Sect. 12.12. When I formulated the cell force concept over two decades ago (Ji 1991 and Appendix K), I did not know then that one day I might be analyzing experimental data shedding light on the existence of the *cell force* in

living cell. In retrospect, it is not surprising that it took over two decades for the cell force concept to be tested against experimental data, because the relevant whole-cell metabolic kinetic data did not become available until 2004 when Garcia-Martinez et al. (2004) measured the time-dependent changes in the genome-wide RNA levels and transcription rates in budding yeast (Sect. 12.2), and it was not until 2009 when the fitting of the whole-cell RNA kinetic data to BRE was discovered (Ji and So 2009). Realizing the connection between the fitting of the genome-wide RNA kinetic data to BRE and the *cell force* concept invoked two decades earlier was not immediately obvious and took another couple of years to occur as a result of writing this book. The recognition of the cell force-BRE connection was made possible by a qualitative application to cell biology of the renormalization group theory described in Huang (2007) (see below).

In addition to the yeast RNA kinetic data, BRE was found to fit (after renormalizing the four parameters, a, b, A, and B) the data from single-molecule enzymic catalysis, and protein folding as summarized in Table 12.10A.

It is interesting to note that the numerical values of the four parameters of BRE, i.e., a, b, A, and B, increase in the following order as indicated by the a/b ratios:

$$\text{Blackbody radiation} < \text{Single-molecule enzymology} < \text{Transcription} < \text{RNA level control} < \text{Protein stability} \tag{12.37a}$$

The order revealed in Inequality (12.37a) appears to coincide with the *energy scales* (and hence *distance scales*) characterizing each process, since the interaction energies are expected to decrease in the same order, i.e., from electronic energy levels involved in blackbody radiation (i.e., covalent bond energies of ~100 kcal/mole) to non-covalent energies involved in protein folding (1–5 kcal/mole).

When the logarithms of the a and b values of the five processes are plotted in what may be called the "BRE parameter space," a continuous nonlinear trajectory is obtained that passes through Processes 1, 2, and 5, with Processes 3 and 4 deviating from it (Fig. 12.26a).

The nonlinear trajectory shown in Fig. 12.26a is reminiscent of the *renormalization group (RG) trajectory* discussed in physics, i.e., in quantum electrodynamics (QED) and quantum chromodynamics (QCD) (Huang 2007). The concept of renormalization was discussed in Sect. 2.4 in connection with bionetworks (e.g., metabolic pathways) viewed as *renormalizable networks*. A more detailed characterization of the concept of renormalization is given by Huang (2007, pp. 217–225):

> . . .Renormalizability is not just a property of QED, but of all successful theories in physics. The important point is that a renormalizable theory describes phenomena at a particular length scale (*e.g., nuclear, atomic, molecular, cellular, etc.; my addition*), in terms of parameters that can be measured at that scale. . . . .For example, we can explain the everyday world using thermodynamics, without invoking atoms. Properties such as specific heat and thermal conductivity, which really originate from atomic structure, can be treated as empirical parameters. At a smaller length scale atoms appear, and they can be described by treating the nucleus as a point. Similarly, at the scale of nuclear structure we do not need quarks (*i.e., protons and neutrons are sufficient; my addition*). Renormalizability is a closure property that makes physics possible. We would not be able to understand the world, if we had to understand every minute detail all at once. (12.37b)

Table 12.10A Planck's radiation law–like equation (BRE) is obeyed by (1) blackbody radiation; (2) single-molecule enzymic activity of cholesterol oxidase, whole-cell RAN metabolism measured as (3) distances between transcription rate trajectories[a] and (4) distances between transcript level trajectories[b]; and (5) protein stability data. The numerical values of the BRE parameters for Processes 3 and 4 are the averages of 17–18 metabolic pathways (listed in the legend to Fig. 12.26a) with standard deviations as indicated

	$y = a(Ax + B)^{-5}/(e^{b/(Ax + B)} - 1)$						
Process	a	b	A	B	a/b	y	x
1. Blackbody radiation	5×10^{-15}	4.8×10^{-13}	1	0	1.04×10^{-2}	Spectral intensity	Wavelength
2. Single-molecule enzymic turnover times	3.5×10^{5}	2.0×10^{2}	1	0	1.75×10^{3}	Frequency of occurrences	Waiting time[c]
3. Distances between transcription rate trajectories in budding yeast[e] (n = 17)	$(3.2 \pm 2.3) \times 10^{8}$	51 ± 9.5	1.41 ± 0.26	2.41 ± 0.36	6.27×10^{6}		
4. Distances between RNA trajectories in budding yeast[e] (n = 18)	$(8.8 \pm 8.9) \times 10^{8}$	50 ± 11.6	2.23 ± 1.45	3.21 ± 1.67	1.7×10^{7}	Frequency of occurrences	Phenotypic similarity classes[d]
5. Protein stability	1.8×10^{10}	300	14	18	6.0×10^{7}	Frequency of the occurrence of ΔG	Δ G, i.e., the Gibbs free changes accompanying protein denaturation

[a] Transcription rates (TRs) were measured at six time points from budding yeast after glucose-galactose shift and plotted against time to generate one TR trajectory for each gene. The similarity between a pair of TR trajectories was quantified as the Euclidean distance between the two trajectories

[b] Transcript levels (TLs) were measured at the same time points as TRs producing one TL trajectory for each gene. The distances between pairs of TL trajectories were calculated as described in Footnote a

[c] The time it takes for an enzyme to be thermally activated to perform simple catalysis

[d] Different classes of the similarities between all possible pairs of RNA trajectories belonging to a pathway

[e] Undergoing glucose-galactose shift

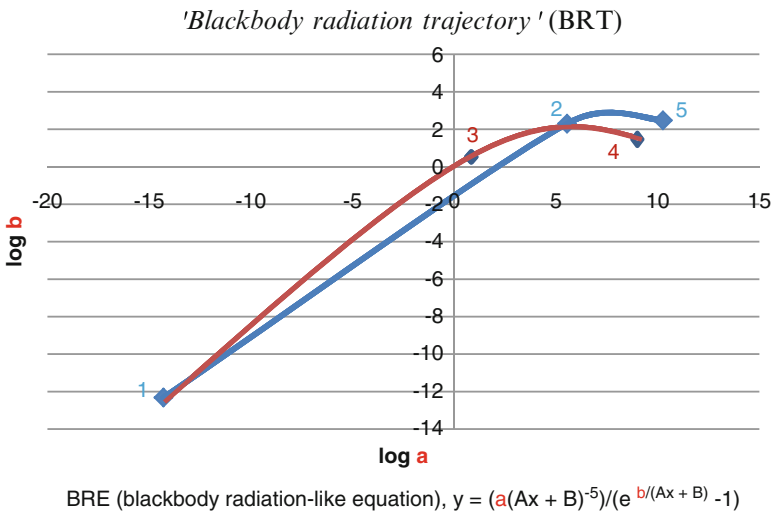


Fig. 12.26a The double logarithmic plot of the average values of a and b of the BREs that best fit the distance data of the TL (RNA level) and TR (transcription rate) trajectories (see Table 12.10A) of 17–18 metabolic pathways in budding yeast undergoing glucose-galactose shift, including (1) ATP synthesis, (2) fatty acid synthesis, (3) glycolysis, (4) oxidative phosphorylation, (5) respiration, (6) cell cycle, (7) cell wall biogenesis, (8) DNA repair, (9) DNA replication, (10) meiosis, (11) mitosis, (12) mRNA splicing, (13) nuclear protein targeting, (14) protein degradation, (15) protein folding, (16) protein glycosylation, (17) protein processing, (18) signaling, (19) cytoskeleton, (20) protein folding, (21) protein synthesis, (22) secretion, (23) transcription, and (24) transport. The means and standard deviations of a and b are given in Table 12.10A. 1 = *blackbody radiation;* 2 = *single-molecule enzyme kinetics*; 3 = *distances between transcription rate trajectories*, 4 = *distances between transcript level trajectories*, and 5 = *protein stability*

> . . .In general a renormalizable theory is characterized by an RG trajectory in a space spanned by a definite and fixed number of parameters (i.e., in the 'parameter space'; my addition). (12.37c)

On pages 223 and 224 of his book cited above, Huang discusses RG (renormalization group) trajectories representing QCD (quantum chromodynamics, the theory of the strong force) and QED (quatum electrodynamic theory, the theory of the electromagnetic force). The trajectory shown in Fig. 12.26a more closely resembles the *RG trajectory* of QED than that of QCD. This is most likely because the predominant force operating in the systems listed in Table 12.10A is the *electromagnetic force*, which is manifested in two extreme forms – the covalent interactions (i.e., those processes involving electronic transitions; see Fig. 11.28) and the non-covalent interactions (see Sect. 3.2), located graphically at the beginning and the end, respectively, of the trajectory shown in Fig. 12.26a.

As already indicated, Points 3 and 4 deviate from the trajectory that passes through Points 1, 2, and 5. If these deviations are not due to experimental error or noise but reflect reality as I assume here, this may indicate that Points 3 and 4

represent processes that implicate not only the *electromagnetic force* but also a new force that is intrinsic to these processes which happen to occur inside the living cell in contrast to those processes represented by Points 1, 2, and 5 that occur outside of living cells. It may be justified to refer to this new force as the *cell force*, since its action is postulated to be confined to the interior of the living cell just as the strong force is confined within the atomic nuclei (Han 1999; Huang 2007). If the proposed explanation for the trajectory in Fig. 12.26a turns out to be true, we may have here the first experimental evidence supporting the concept of the *cell force* that was invoked in Ji (1991; see Appendix K) based on a qualitative application of the Yang-Mills gauge field theory to cell biology in part inspired by the *field theory of cell metabolism* described in Smith and Welch (1991).

Therefore, it may be reasonable to refer to the trajectory in Fig. 12.26a as the "blackbody radiation trajectory (BRTs)" or, more speculatively, as the "blackbody radiation RG trajectory" suggesting that the so-called bare theory (Huang 2007, pp. 219–225) behind BRTs is QED and the single-molecule enzymology (Point 2) and the theory of protein folding (Point 5) represent the renormalized version of QED.

12.14 The Quantization of the Gibbs Free Energy Levels of Enzymes and the Living Cell

The finding that the rate constant (or waiting time) data of a single-molecule of cholesterol oxidase fit the blackbody radiation-like equation (BRE) (see Fig. 11.24) led me to postulate that the Gibbs free energy of the cholesterol oxidase molecule is quantized (or associated with discrete Gibbs free energy levels) as visualized in Fig. 11.28.

This postulate is supported by the fact that the Gibbs free energy changes accompanying protein denaturation also fit BRE (see Panel f in Fig. 12.25), suggesting that both enzymic catalysis and protein denaturation require *thermal excitations of proteins* from their ground-state free energy levels (depicted as C_1 through C_n in Fig. 11.28) to their excited/activated states (depicted as $C^{\ddagger}$ in the same figure) leading to *catalysis* or *denaturation*.

Based on these observations, *I postulate that the Gibbs free energy levels of enzyme molecules in the living cell are quantized*. The biochemical and cell biological consequences of this cannot be fully gauged without taking into account the molecular environment of the cell in which enzymes function. Figure 12.27 depicts simplified biochemical pathways involved in determining the intracellular concentrations of mRNA molecules. The cross-hatched lines in Fig. 12.27 symbolize the cytoskeleton to which most biopolymers (including *transcriptosomes* and *degradosomes*) are probably bound most of the time, exhibiting the phenomenon of

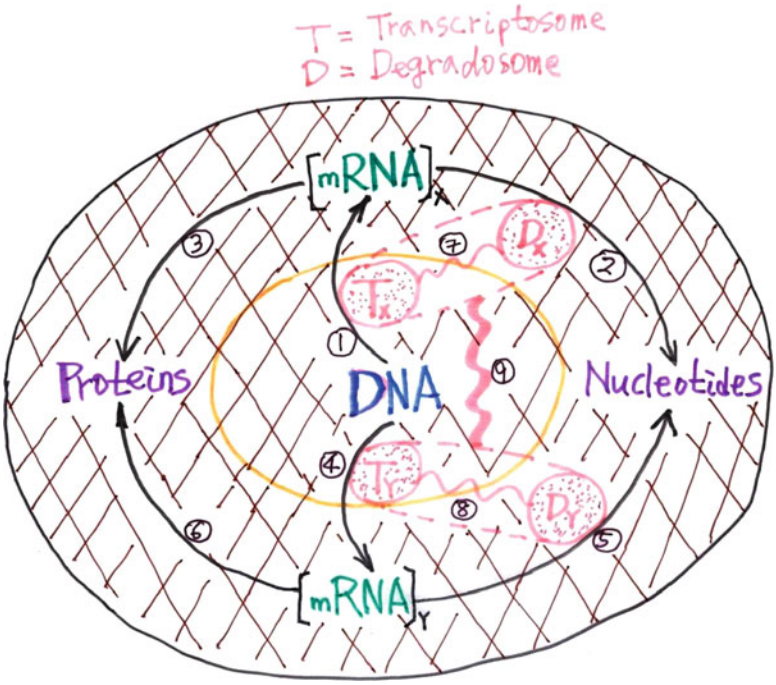


Fig. 12.27 A simplified diagram indicating the interactions between *transcriptosome* (T) and *degradosome* (D) that together determine the trajectory of an RNA molecules, X or Y. Steps 1 and 4 = transcription; Steps 2 and 5 = transcript degradation; Steps 3 and 6 = translation; Steps 7 and 8 = functional coupling between the transcriptosome and degradosome associated with $mRNA_X$ and $mRNA_Y$; Steps 9 = the functional coupling between the two transcriptosome/degradosome complexes, (T_XD_X) and (T_YD_Y), that determine the trajectories of the difference ($[mRNA]_X - [mRNA]_Y$). $[RNA]_X$ and $[RNA]_Y$ refer to the intracellular concentrations of $mRNA_X$ and $mRNA_Y$, respectively

intracellular "crowding" (Goodsell 1991; Minton 2001; McGuffee and Elcock 2010). A more realistic model of the cytoplasm of the living cell is shown in Fig. 12.28 which was computationally constructed by McGuffee and Elcock (2010) utilizing quantitative proteomic data (Link et al. 1997) and atomic-level structural data of protein molecules ranging in size from 7,000 to 1,350,000 Daltons (Berman et al. 2000). The McGuffee and Elcock model of the cytoplasm shown in Fig. 12.28 incorporates steric (i.e., molecular shape), electrostatic and short-range attractive hydrophobic interactions but does not yet include water, hydrodynamic interactions, and protein flexibility (and hence the role of conformons; Chap. 8). The maximum average distances moved by each molecule type during 15 μs of simulation decreases nonlinearly with molecular weights, ranging from 12 molecular diameters for 5,000 Da molecules to 1 molecular dimension for 1,000,000 Da molecules. The average number of neighbors possessed by a molecular type increases nonlinearly with molecular weights. Thus, the immediate neighborhood of a GFP molecule

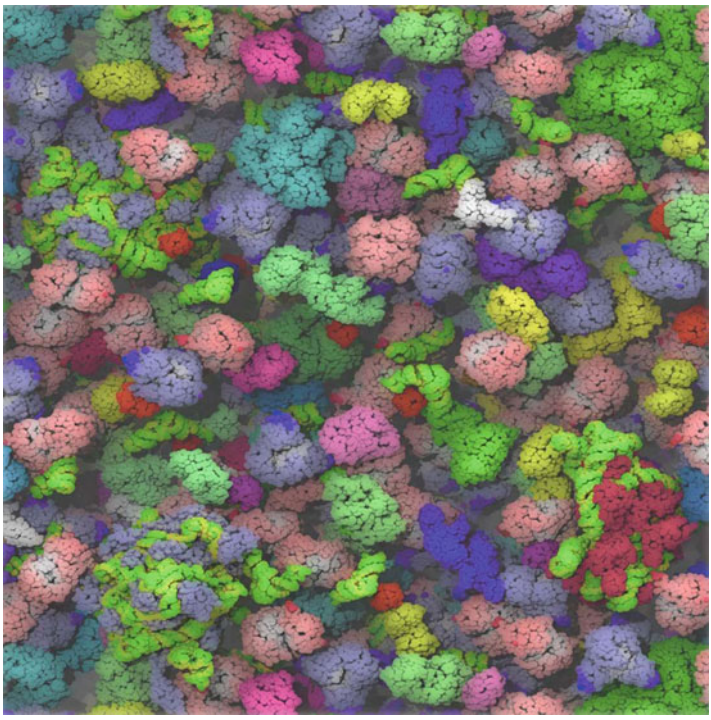


Fig. 12.28 The computer model of the cytoplasm of *E. coli* that contains over 80% of the 50 different types of the most abundant proteins in the organism (McGuffee and Elcock 2010). RNA molecular are colored *green* and *yellow* (Reproduced by permission of Adrian Elcock)

(26,000 Da), for example, is only five, at any instance, while, for the 50 S ribosomal subunit (1,355 KDa), it is more than 25. It is clear that the Gibbs free energy levels of enzymes will critically depend on their microenvironment inside the cell.

The kinetic trajectories of mRNA molecules of budding yeast undergoing glucose–galactose shift are not random but exhibit regularities as amply demonstrated by Figs. 9.1, 12.2a and 12.3, especially the mRNA trajectories shown in the last two figures that are function-related. This indicates that the *transcriptosome* (T) and the *degradosome* (D) responsible for the nonrandom behavior of an mRNA trajectory must be *coupled* (see Steps 7 and 8 in Fig. 12.27, where the wiggly lines indicate the functional coupling between T and D), although the molecular mechanisms underlying such a coupling are not obvious. If these two enzyme systems are not coupled, the associated mRNA trajectory is expected to behave randomly and unpredictably, contrary to our observations.

Since the rate constant of an enzyme is the exponential function of its ground-state Gibbs free energy level (see the right panel of Fig. 11.28 and Eq. 12.42), it would follow that the rate of the synthesis of an mRNA molecule depends on the ground-state Gibbs free energy level of the associated transcriptosome (see Steps 1 and 2 in Fig. 12.27),

Table 12.11 The relative rate constants of the transcriptosome–degradosome (TD) complexes predicted on the basis of the conformational (or quantum) states (1, 2, 3, 4, and 5) of their T and D components. These numbers can also be viewed as the "quantum numbers" of transcriptosome ($\mathbf{n}_T$) and degradosome ($\mathbf{n}_D$). The following symbols are used: n = no change; d = down regulation or decrease; u = up regulation or increase in the rate of change in the level of RNA molecules x and y. The subscripts indicate the relative magnitudes of the rates of changes in TL, i.e., $u_1 < u_2 < u_3 < u_4$, and $d_1 < d_2 < d_3 < d_4$. The numbers above these symbols are the difference between the quantum numbers of the transcriptosome and degradosome, i.e., $\mathbf{\Delta n} = \mathbf{n}_T - \mathbf{n}_D$, that are associated with the changes in TL levels, i.e., dTL/dt, indicated in parentheses

	1	2	3	4	5
1	0	−1	−2	−3	−4
	(n)	(d_1)	(d_2)	(d_3)	(d_4)
2	1	0	−1	2	−3
	(u_1)	(n)	(d_1)	(d_2)	(d_3)
3	2	1	0	−1	2
	(u_2)	(u_1)	(n)	(d_1)	(d_2)
4	3	2	1	0	−1
	(u_3)	(u_2)	(u_1)	(n)	(d_1)
5	4	3	2	1	0
	(u_4)	(u_3)	(u_2)	(u_1)	(n)

and the rate of its degradation depends on the Gibbs free energy level of the associated degradosome (see Steps 2 and 5 in Fig. 12.27). Thus, the kinetics of the Xth RNA trajectory "catalyzed" by T_X and D_X, either acting as separate entities or as components of a functional unit (to be denoted as (T_XD_X); see Step 7 in Fig. 12.27), is determined by the Gibbs free energy levels (or the quantum states) of T_X and D_X.

The analysis of the TL vs. TR plots such as Fig. 12.6 indicates that transcriptosomes and degradosomes can exhibit at least five distinct turnover rates, i.e., (1) slow decrease, (2) rapid decrease, (3) no change, (4) slow increase, and (5) rapid increase. For example, in (a), Fig. 12.6, during the first phase (i.e., 0–5 min), TL decreases despite the fact that TR increases. This can be accounted for only if we can assume that, during this phase, the rate of transcript degradation (TD) decreases more than TR does. If each enzyme system has five conformational (or quantum) states with free energy levels arbitrarily labeled as 1–5 as in Fig. 12.29, there are 25 possible conformational (or quantum) states for the (T_X + D_X) system, each associated with a rate of change in TL given in parenthesis as described in Table 12.11. These 25 different entries group into 9 classes (to be denoted as 1, 2, 3, 4, 5, 6, 7, 8, and 9) as indicated by the dotted lines, and these dotted lines are associated with the relative frequencies of 1, 2, 3, 4 , 5, 4, 3, 2, and 1 for the classes 1–9, respectively. For example, the relative frequencies of the occurrence of the (dTL/dt) classes, n, d_1, d_2, d_3, and d_4 (or n, u_1, u_2, u_3, and u_4) are 5, 4, 3, 2, and 1 (counting the number of cells along the dotted lines). Thus, if all the possible couplings between the quantum states of T and D have an equal probability of occurrence (as assumed in Table 12.11), RNA trajectories are five times more likely to remain unchanged, i.e., dTL/dt = 0 (or n), than to decrease (or increase) rapidly with dTL/dt = $d4$ (or $u4$). However, the experimentally observed data (see Series 9 in Fig. 12.30a) deviate from the theoretically predicted

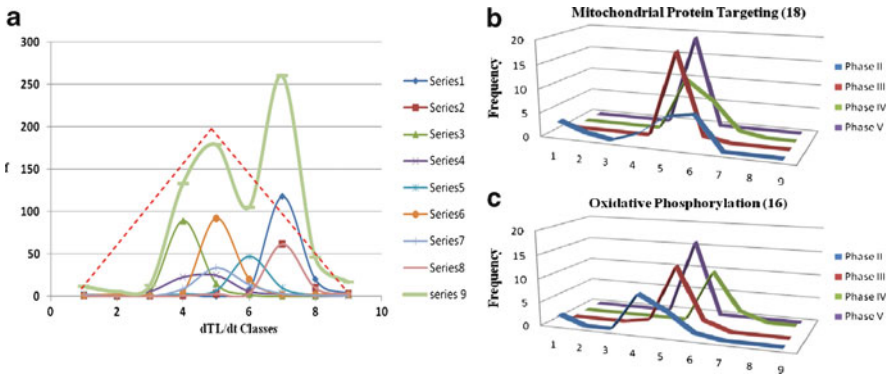
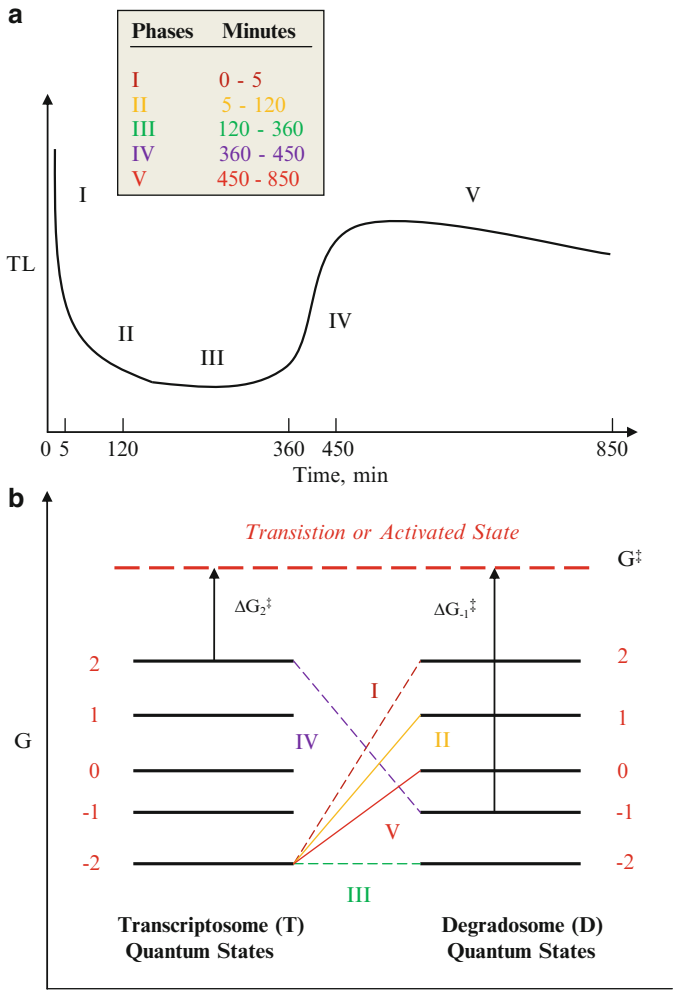


Fig. 12.29 The distributions of the slopes (i.e., dTL/dt) of RNA trajectories of budding yeast undergoing glucose–galactose shift. The *y*-axis represents the frequency (f) and the *x*-axis the rate (or slope) classes divided into nine based on Table 12.12. (**a**) Series 1 = chromatin structure (38 RNAs); Series 2 = DNA repair (21); Series 3 = glycolysis (30); Series 4 = meiosis (17); Series 5 = mitochondrial protein targeting (19); Series 6 = nuclear protein targeting (32); Series 7 = oxidative phosphorylation (16); Series 8 = protein folding (28); Series 9 = sum of series (201 RNAs). The red dotted lines indicate the slope distribution predicted by in Table 12.12. (**b**) The phase-dependent slope distributions of the 18 RNA trajectories belonging to the mitochondrial protein targeting metabolic pathway. In Phase II and IV, the fifth slope or rate class is dominant with no contributions from the fourth and sixth slopes or rate classes. In contrast, the fourth and sixth classes dominate during Phases III and V, respectively. (**c**) The phase-dependent slope distributions of the 16 RNA trajectories belonging to the oxidative phosphorylation metabolic pathway. Again, in Phase II and IV, the fifth slope or rate class is dominant with no or little contributions from the fifth and sixth slopes or rate classes. In contrast, the sixth and fourth classes dominate during Phases III and V, an opposite pattern to what was observed in (**b**). Phase I slopes are not included because they are likely to contain large errors due to the short time of observation, 5 min. For the definition of the phases, see Fig. 12.30

behavior depicted as a red triangle. However, two interesting features emerge. (1) Different metabolic pathways tend to show peak frequencies located at different rate classes (see a in Fig. 12.29), and (2) different phases within a given metabolic pathway tend to show peak frequencies at different rate classes (see b and c in Fig. 12.29). Thus, the possibility suggests itself that two metabolic pathways that overlap in a two-dimensional frequency-rate class (FR) plot such as Fig. 12.28a may be distinguishable in three-dimensional frequency-phase-rate class (FPR) plots such as Fig. 12.29b, c and this may make the FPR plots a sensitive tool for monitoring cell states in drug discovery research and personalized medicine (see Chaps. 18 and 19).

As indicated above and according to Eq. 12.42 and Statement 12.43, the rate constant of an enzyme or an enzyme complex is an exponential function of the Gibbs free energy level of the enzyme. Hence it should be possible to infer the changes in the Gibbs free energy levels of transcriptosomes (T) and degradosome (D) from the kinetic patterns of TL or the RNA trajectories which reflect the enzymic activities of T and D (see Steps 1 and 2, and 4 and 5 in Fig. 12.27). A prototypical RNA trajectory of budding yeast undergoing glucose–galactose shift is schematically depicted in Panel a in Fig. 12.30. During each of the five phases, TL exhibits one of the nine



c

The quantum states of the TD complexes and their effect ts on dTL/dt						
	Degradosome					
Transcriptosome		-2	-1	0	1	2
	-2	0	-1	-2	-3	-4
	-1	1	0	-1	-2	-3
	0	2	1	0	-1	-2
	1	3	2	1	0	-1
	2	4	3	2	1	0

Fig. 12.30 The interpretation of the RNA trajectories in terms of the quantum states of the underlying transcriptosomes and degradosomes. (**a**) The five phases of the typical RNA trajectory (or the kinetics of TL, transcript level) of budding yeast after replacing glucose with galactose at $t = 0$. (**b**) The five quantum states each postulated for the transcriptosome (T) and degradosome (D) constituting a TD complex that determines the shape of an RNA trajectory. (**c**) all possible quantum states for a TD complex and their effects on the shape of an RNA trajectory, i.e., on dTL/dt

Table 12.12 The fraction of the RNA pairs showing linear or nonlinear correlations among intra-pathway and inter-pathway RNA Pairs. Both members of an *intra-pathway RNA pair* belong to one metabolic pathway, whereas an *inter-pathway RNA pair* involves two pathways, each contributing one of the two members of a pair. The extent (or fraction) of the linear correlations (numbers in bold) were determined by counting the RNA pairs whose Pearson correlation coefficients were greater than 0.7 or less than −0.7, and the fraction of the nonlinear correlations (numbers in italics) were determined by counting the RNA pairs whose phenotypic distances fit the *blackbody radiation-like equation* (BRE), Eq. 12.26. The number of RNA molecules per pathway ranged from 12 to 50. P1 = *protein folding*, P2 = *cytoskeleton*, P3 = *protein glycosylation*, P4 = *oxidative phosphorylation*, P5 = *respiration*, P6 = *glycolysis*, P7 = *nuclear protein targeting*, P8 = *DNA repair*, P9 = *protein degradation*, P10 = *meiosis*

	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
P1	**0.88**					**0.70**	**0.99**			
P2		**0.54** (*0.13*)							**0.57**	
P3			**0.74**				**0.99**			
P4				**0.72**		**0.20**				
P5					**0.44** (*0.17*)					
P6						**0.47** (*0.91*)				
P7							**0.98**			**0.76**
P8								**0.59**		
P9									**0.609** (*0.43*)	
P10										

rate behaviors, i.e., dTL/dt classes (denoted as −4, −3, −2, −1, 0, 1, 2, 3, 4, and 5) (see the interior of the table in Panel c, Fig. 12.30), that result from the interactions between T and D, each of which is postulated to exist in one of the five quantum states (denoted as −2, −1, 0, 1, and 2 in Panel b, Fig. 12.30). If we identify the value of dTL/dt during Phase I in Fig. 12.30 with the most rapid decrease, i.e., −4, the quantum states of the underlying T and D would be predicted to be −2 and +2, respectively (see the dotted line labeled I in Panel b, Fig. 12.30). During Phases II and V, TL is not decreasing as rapidly as during Phase I, so we may infer the quantum states of T and D during these phases to be −2 and 1 for Phase II and −2 and 0 for Phase V as indicated by the dotted lines in Panel b, Fig. 12.30. Phase IV is characterized by a relatively rapid increase in TL and hence the quantum states of T and D may be inferred to be 2 and −2. During Phase III, TL remains more or less unchanged and hence the quantum states (and the Gibbs free energy levels) of T and D are likely to be the same, leading to the equality of their rate constants, according to Eq. 12.42.

The *quantization of the Gibbs free energy levels of enzymes* in cells provides a possible explanation for the pathway-dependent correlations found among some of the RNA trajectories in budding yeast during glucose–galactose shift (see Table 12.12). This conclusion is based on the following reasoning.

1. RNA trajectories can be correlated in two ways – (1) linearly and (2) nonlinearly. The former indicates that, when the concentration of the ith RNA molecule is increased by a factor of x and that of the jth is increased or decreased also by the same factor, the ith and jth RNA concentrations are said to exhibit a positive and a negative linear correlation, respectively. However, when the concentration of the ith RNA is increased (or decreased) by two different factor, say, x and x^n, respectively, where the absolute value of n is greater than or less than 1, we are dealing with nonlinear correlations.
2. It is evident that the correlated changes in the intracellular concentrations of any pair of RNA molecules are impossible if the two enzyme systems, each supporting its associated RNA trajectory, are not coupled. That is, a linear correlation between [mRNA]x and [mRNA]y in Fig. 12.27 would be impossible without the functional coupling between the (TXDX) complex and the (TYDY) complex, where T is transcriptosome and D is degradosome, and X and Y are the two different RNA molecules, the correlation between whose trajectories are under consideration (see Steps 9 in Fig. 12.27). We can represent this idea symbolically as follows:

$$\underset{a}{(T_XD_X)} + \underset{b}{(T_YD_Y)} \rightleftarrows \underset{c}{(T_XD_X)(T_YD_Y)} \qquad \Delta G \qquad (12.38)$$

3. In principle, there are two distinct mechanisms for coupling two enzymes or enzyme complexes – (1) the *cis-mechanism* whereby two enzyme systems form a higher-order structure or complex through direct physical binding interactions and (2) the *trans-mechanism* whereby two enzyme systems are coupled indirectly by sharing diffusible substrates (e.g., mRNA) or regulators (e.g., ATP, ADP, glucose). Similar *cis-* and *trans-mechanisms* operate in the control of gene expression mechanisms. Since no spontaneous interaction can occur without the associated Gibbs free energy decrease (under the conditions of constant temperature and pressure), Eq. 12.39 holds, where G is Gibbs free energy and the subscripts indicate the reactants and the products appearing in Reaction (12.38):

$$\Delta G = G_c - (G_a + G_b) < 0 \qquad (12.39)$$

4. The Gibbs free energy levels of (T_XD_X), (T_YD_Y) and $(T_XD_X)(T_YD_Y)$ in Reaction (12.38) are represented diagrammatically as G_i, G_j, and G_{ij} in Fig. 12.31. It is assumed that the transition state of all these enzyme systems is common as indicated by the red dotted line labeled $G^{\ddagger}$. Once the higher-order complex $(T_XD_X)(T_YD_Y)$ is formed spontaneously, it may act as a functional unit (or better as a SOWAWN machine; see Sect. 2.4.4), catalyzing the net formation of $mRNA_X$ and $mRNA_Y$ in a *coordinated manner* so that their trajectories are correlated either linearly or nonlinearly as shown in Table 12.12. Just as the function-related behavior of an mRNA trajectory (or ribon) signals the underlying coupling between its transcriptosome and degradosome (see Steps 7 and 8 in Fig. 12.27), the nonrandom correlations found between two mRNA trajectories

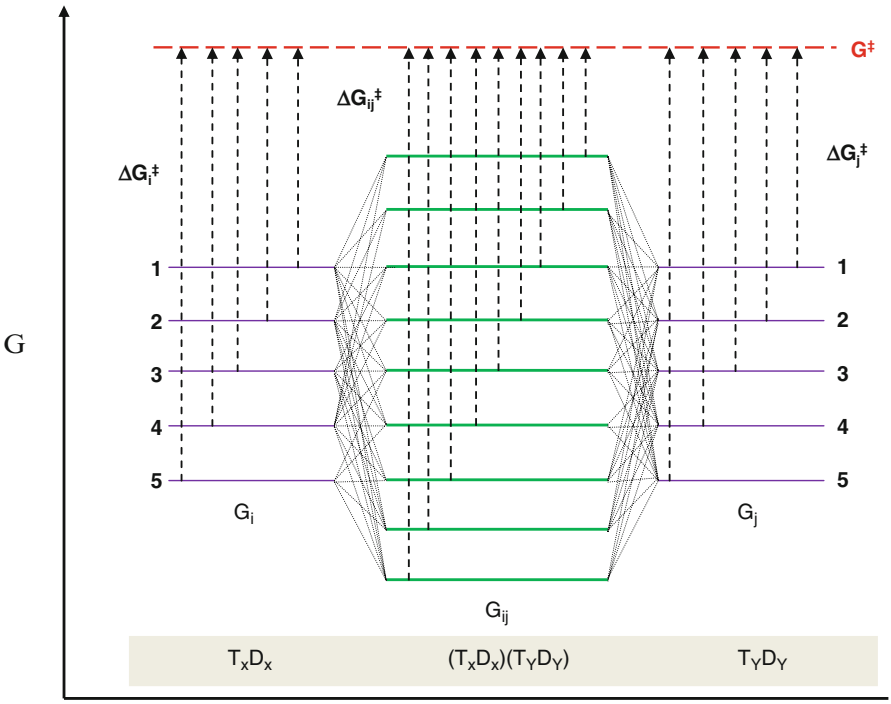


Fig. 12.31 A diagrammatic representation of the Gibbs free energy levels of T_XD_X and T_YD_Y complexes (see G_i and G_j) and their higher-order complex $(T_XD_X)(T_YD_Y)$ enzyme complexes (see G_{ij}). The Gibbs free energy level of the common excited state is denoted by $G^{\ddagger}$. ΔG_i is the Gibbs free energy difference between the excited and ground states of the ith enzyme system, i.e., $\Delta G_i = G^{\ddagger} - G_i$. It is assumed that T_XD_X and T_YD_Y complexes have five energy levels and the $(T_XD_X)(T_YD_Y)$ complex has nine free energy levels (see Fig. 12.29 for related discussions). T = tra*nscriptosome*, D = *degradosome*, and X and Y are two different RNA trajectories

(or ribons) (see $[mRNA]_X$ and $[mRNA]_Y$ in Fig. 12.27) signal the underlying *control mechanism* that is thermally activated and functions during the observational period of 850 min (see Step 9 in Fig. 12.27). Therefore, it seems logical to invoke at least two levels of metabolic control in budding yeast – the first-order control catalyzed by the individual (TD) complexes and the second-order control exerted by the pathway-wide $(T_XD_X)(T_YD_Y)$ complexes. By "pathway-wide," I mean the system of transcriptosomes and degradosomes belonging to a given metabolic pathway. Since each metabolic pathway usually involves 10–30 enzymes, the number of all possible pairs of enzymes, X and Y, that belong to a pathway would range from about 50 to 500 (based on the equation $n(n-1)/2$, where n is the number of different enzymes belonging to a pathway). If all these possible pairs of enzymes function coherently, as evidenced by the correlations found among the intra-pathway mRNA trajectory pairs shown in Table 12.12,

it may be reasonable to assume that any *pathway-wide enzyme complexes* such as $(T_XD_X)(T_YD_Y)$ complexes work, at least transiently, as a functional unit (i.e., as a SOWAN machine). Furthermore, it seems possible that the biochemical and control behaviors of pathway-wide enzyme complexes $(T_XD_X)(T_YD_Y)$ differ from the behaviors of individual enzymes, T and D, just as quantum dots behave quite differently from their constituent atoms (see Table 4.7). If this is true, the Gibbs free energy levels of the $(T_XD_X)(T_YD_Y)$ complex may contain the elements not predictable from the Gibbs free energy levels of its component enzymes alone.

5. The $(T_XD_X)(T_YD_Y)$ complex in Fig. 12.31 can coordinately catalyze the formation of $mRNA_X$ and $mRNA_Y$ (1) if it possesses a set of different conformational states (or different Gibbs free energy levels or quantum states) and (2) if it can be thermally excited from any one of these *ground states* with free energy level G_{ij} to the common excited state with free energy level $G_{ij}^{\ddagger}$, during the life time of which the complex can catalyze the coordinated enzymic process (through Step 9 in Fig. 12.27) with the rate constants determined by $\Delta G_{ij}^{\ddagger}$ (see also Row 8 in Table 11.9):

$$k_{ij} = Ae^{-(\Delta G\_ij\wedge\ddagger)/RT} \tag{12.40}$$

$$\text{where } \Delta G_{ij}^{\ddagger} = G^{\ddagger} - G_{ij} \tag{12.41}$$

and k_{ij} is the rate constant with which two RNA trajectories i and j change in coordination, and R is the gas constant (which is equal to Nk, where N is the Avogadro' number and k is the Boltzmann constant), and T is the absolute temperature. Inserting Eq. 12.41 into 12.40 and dropping the subscript for brevity leads to:

$$k = Ae^{-(G^{\ddagger}-G)/RT} = A'e^{G/RT} \tag{12.42}$$

where $A' = Ae^{-G^{\ddagger}}$ which is a constant, since $G^{\ddagger}$ is assumed to be constant for all enzymes and enzyme complexes as indicated by the red dotted line in Fig. 12.31. Equation 12.42 is identical with the equation derived in Table 11.9 (see Row 8). The significance of Eq. 12.42 is that:

The rate constant of an enzyme is the exponential function of its ground-state Gibbs free energy level, G, and not the Gibbs free energy level of the activated states, $G^{\ddagger}$. (12.43)

The justification of Statement 12.43 derives from the fitting of the single-molecule enzymic data of cholesterol oxidase to the blackbody radiation-like equation, Eq. 11.27 (see Table 11.9).

6. The interiors of Table 12.11 and Fig. 12.30c deal with the *rates* of changes in RNA levels, denoted as dTL/dt, where TL stands for transcript level, while the margins of these tables and Fig. 12.31 address the *Gibbs free energy levels* of

enzymes and hence *rate constant*, k (see Eq. 12.42). *Rates* (usually denoted as v, from velocity) and *rate constants* (denoted as k) are not the same but are related to each other through Eq. 12.44 under the first-order kinetics conditions, i.e., in the presence of enzymes in excess of their substrates:

$$v = d[S]/dt = k[S] \tag{12.44}$$

where [S] is the concentration of the substrate for an enzyme. As evident in Eq. 12.44, k can be defined as the v measured under condition where [S] is kept at the unit concentration, i.e., [S] = 1. The key idea behind Eq. 12.44 is that *v depends on substrate concentration but k does not or that, under a constant substrate concentration, v and k are quantitatively equivalent*.

7. The kinetics of the X^{th} RNA trajectory catalyzed by the (T_XD_X) complex is determined by the Gibbs free energy levels (or the quantum states) of T_X and D_X. The analysis of the TL vs. TR plots such as Fig. 12.6 indicates that *transcriptosomes* and *degradosomes* can exhibit at least five distinct turnover rates, i.e., (1) slow decrease, (2) rapid decrease, (3) no change, (4) slow increase, and (5) rapid increase. For example, in (a), Fig. 12.6, during the first phase (i.e., 0–5 min), TL decreases despite the fact that TR increases. This can be accounted for only if we can assume that, during this phase, the rate of transcript degradation (TD) decreases more than TR does. If each enzyme system has five conformational (or quantum) states with free energy levels labeled as −2, −1, 0, 1, and 2 as in Fig. 12.30b, there are 25 possible conformational (or quantum) states for the (T_XD_X) complex, each associated with a rate of change in TL given in parenthesis as described in Table 12.11. These 25 difference entries group into nine classes as indicated by the nine dotted diagonal lines, and these lines are associated with the relative frequencies of 1, 2, 3, 4, 5, 4, 3, 2, and 1. For example, the relative frequencies of the occurrence of the (dTL/dt) classes, n, d_1, d_2, d_3, and d_4 (or n, u_1, u_2, u_3, and u_4) are 5, 4, 3, 2, and 1 (counting the number of cells along the dotted lines). Thus, if all the possible couplings between the quantum states of T and D have an equal probability of occurrence (as assumed in Table 12.11), RNA trajectories are five times more likely to remain unchanged, i.e., dTL/dt = 0 (or n), than to decrease (or increase) rapidly with dTL/dt = *d4* (or *u4*). However, the experimentally observed data (see Series 9 in Fig. 12.29a) deviate from the theoretically predicted behavior depicted as a red triangle. However, two interesting features emerge. (1) Different metabolic pathways tend to show peak frequencies located at different rate classes (see a in Fig. 12.29), and (2) different phases within a given metabolic pathway tend to show peak frequencies at different rate classes (see b and c in Fig. 12.29). Thus, the possibility suggests itself that two metabolic pathways that overlap in a two-dimensional frequency-rate class (FR) plot such as Fig. 12.29a may be distinguishable in three-dimensional frequency-phase-rate class (FPR) plots such as Fig. 12.29b, c and this may make the FPR plots a sensitive tool for monitoring cell states in drug discovery research and personalized medicine (see Chaps. 18 and 19).

12.15 Time-Dependent Gibbs Free Energy Landscape (TGFEL): A Model of Whole-Cell Metabolism

When two RNA trajectories exhibit a linear Pearson correlation coefficient greater than 0.7 or smaller than −0.7, these trajectories are *positively* or *negatively linearly correlated, respectively*. The degree of such linear correlations differs from one metabolic pathway to another, ranging from 39% to 98% (see the bold numbers in Table 12.12). The degree of *nonlinear correlation* among RNA pairs was determined by calculating the percentage of the intra-pathway or inter-pathway RNA pairs, the Euclidean distances between whose trajectories fit the blackbody radiation-like equation (BRE) (see the numbers in parentheses in Table 12.12).

To account for these observations based on the molecular mechanisms postulated to underlie the coupling between transcriptosomes and degradosomes (see Sect. 12.14), I have been led to invoke what is here called the *time-dependent Gibbs free energy landscape* (TGFEL) model of whole-cell metabolism as depicted in Fig. 12.32 and explained below:

1. Just as the atom is associated with a set of atomic orbitals representing the energy levels of electrons, the living cell is thought to be associated with a set of space- and time-dependent *Gibbs free energy levels* of biopolymers to be called the *time-dependent Gibbs free energy landscape (TGFEL)* of the cell.
2. The TGFEL model is formulated in terms of Gibbs free energy (G) and not just energy (E) as in the "energy landscape" concept frequently employed in chemistry and biology (see Eq. 2.1 for the difference between E and G), in order to emphasize the potential role of *entropy* in determining the ground-state of enzymes. Thus two enzymes, both at their lowed energy levels, can still be at two different Gibbs free energy levels, if entropy contributions are different. The five different Gibbs free energy levels of the TD complexes shown in Figs. 12.30 and 12.31 may all be associated with the same internal energy levels due to the same environmental temperature but still can exist at different ground-state Gibbs free energy levels mainly due to different entropy (or negentropy) contents of the complexes (Ji 1974a).
3. The TGFEL model can be represented as a five-dimensional surface since it takes five numbers to specify the position of a biopolymer in it – the three dimensions of the Euclidean space, time, and the Gibbs free energy level of a biopolymer. In Fig. 12.32, the three Euclidean dimensions are collapsed to (or compactified into) one dimension on the x-axis, the Gibbs free energy levels are encoded on the y-axis, and the time dimension is represented by the z-axis.
4. TGFEL is composed of valleys and a set of sub-valleys within a valley (see Valleys 1 and 2, and sub-valleys labeled 1–5 for T and 1′–5′ for D). The transcriptosomes (T) and degradosomes (D) catalyzing the transcription and degradation of a set of RNA molecules belonging to a metabolic pathway

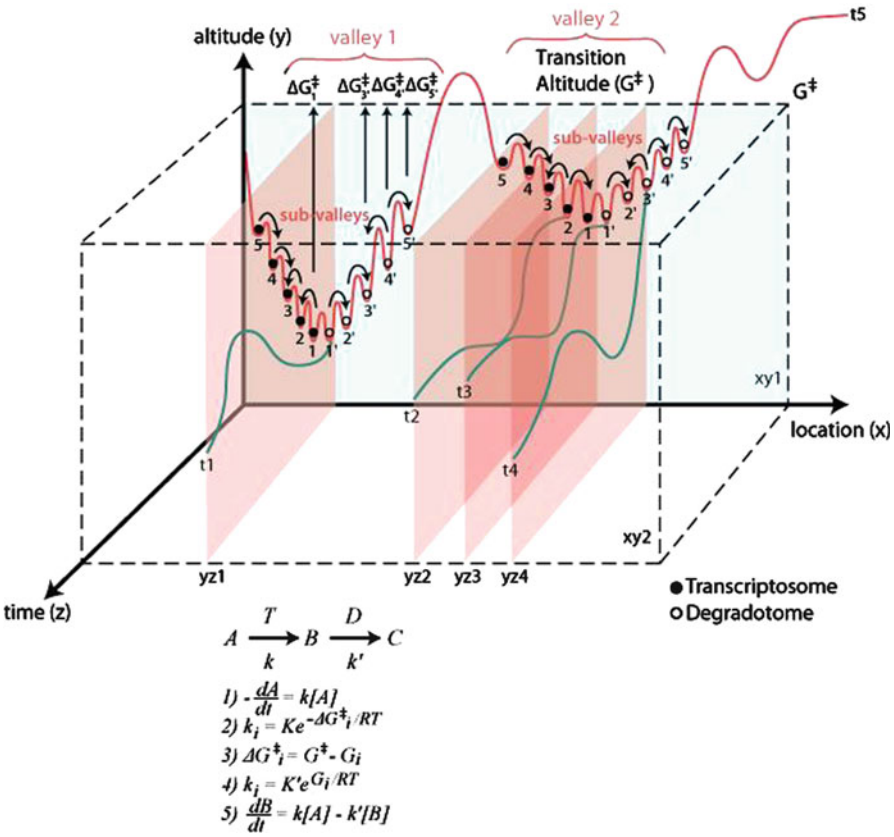


Fig. 12.32 The time-dependent Gibbs free energy landscape (TGFEL) model as applied to the whole-cell metabolism of genome-wide RNA molecules. A = precursor of RNA; B = RNA; C = ribonucleotides. k_i = the rate constant for the ith quantum state of an enzyme, i.e., T or D; $\Delta G_i^{\ddagger}$ = the Gibbs free energy of activation for the ith quantum state of an enzyme; G_i = the ith ground-state Gibbs free energy level of an enzyme; R = gas constant; T = temperature; K, K′ = proportionality constants; *1* the rate law of RNA synthesis; *2* the rate constant as the exponential function of the ith Gibbs free energy of activation; *3* the ith Gibbs free energy of activation as the function of the ith ground-state Gibbs free energy level; *4* the ith rate constant as the exponential function of the ith ground-state Gibbs free energy level, and *5* the rate of change in TL, i.e., dTL/dt, as the balance between the transcription rate and the transcript degradation rate

are postulated to occupy the same valley. Thus, Valley 1 may be occupied mostly by the glycolysis RNA molecules and Valley two mostly by protein glycosylation RNA molecules, for example. RNA molecules appear to be able to "cross over" from one valley to another just as they can cross over from one sub-valley to another within a valley (see the curved arrows).

5. The transcriptosomes and their conjugate degradosomes are thought to be coupled mostly through *trans*-mechanisms, i.e., through sharing common

diffusible molecules (e.g., RNA precursors, ATP, nucleotides) which may accumulate within a valley, in contrast to the *cis*-mechanism of interactions assumed for the (TXDX)(TYDY) complex in Fig. 12.31. In the absence of further evidence, we cannot exclude the possibility that both *trans*- and *cis*-mechanisms operate in budding yeast, the relative contributions of which being determined by environmental factors.

6. The Gibbs free energy levels of transcriptosomes can fluctuate randomly among levels 1–5 and those of degradosomes among levels 1′–5′, and the probability of coupling between them may be different under different micro-environmental conditions as evidenced by the pathway-dependent and phase-dependent distributions of dTL/dt values shown in Fig. 12.29.
7. The rate constants of transcriptosomes and degradosomes are determined by their ground-state Gibbs free energy levels obeying an equation similar to Eq. 12.42, because the Gibbs free energy of activation of a given enzyme is the function of its ground-state Gibbs free energy level (see the upward arrows in Fig. 12.29 and (4) in Fig. 12.32).
8. TGFEL consists of two orthogonal planes denoted as the xy- and the yz-planes in Fig. 12.32. The former will be referred to as the synchronic plane and the latter as the diachronic plane to reflect the assumption that the processes occurring on the synchronic plane (see the arrows connecting the sub-valleys on trajectory 5) are much faster than those occurring on the diachronic plane (see the green trajectories labeled t1–t4) by a factor of at least 102 so that the generalized Franck–Condon principle or the Principle of Slow and Fast Processes (Sect. 2.2.3) applies to TGFEL.
9. The topology of TGFEL is postulated to evolve in time (as indicated by the green trajectories labeled 1–4). The shapes of these trajectories are postulated to be selected by biological evolution and hence record the evolutionary history of living cells (e.g., *S. cerevisiae*).
10. Since the height of the landscape where an enzyme (e.g., T and D) or an enzyme complex (e.g., TD) is located is directly related to the rate constant of the enzyme according to Eq. 12.42, we can quantitatively equate the curves on the yz-plane as RNA trajectories under the first-order kinetics conditions mentioned in connection with Eq. 12.44. In other words:

    Equation 12.42 transforms the curves on the diachronic plane of TGFEL into RNA trajectories under the first-order kinetic conditions. (12.45)

11. Not all the RNA trajectories located in a valley are correlated (e.g., see trajectories t3 and t4), thus accounting for the variable degrees of the linear and nonlinear correlations found in budding yeast undergoing glucose–galactose shift (see Table 12.12).
12. Two RNA trajectories belonging to two different metabolic pathways can be correlated (e.g., see trajectories t1 and t4), thus accounting for the high degrees of linear correlations found between some inter-pathway RNA pairs (see P1-P7 and P3-P7 entries in Table 12.12).

12.16 The Common Regularities (Isomorphisms) Found in Physics, Biology, and Linguistics: The Role of Gnergy

So far I have described two kinds of regularities. The *quantitative regularity* in the form of the blackbody radiation-like equation (BRE), Eq. 11.27 (without the additive term), that has been found to apply to blackbody radiation, single-molecule enzymology (Sect. 11.3.3), protein stability, and whole-cell metabolism (Sect. 12.12) and the *qualitative regularity* in the form of the linguistic rules and concepts found in natural (or human) language and cell language (Sect. 6.1.2). These regularities and their fields of applications are summarized in Rows 2 and 3 in Table 12.13. The first row of this table also exhibits another quantitative regularity, i.e., $y = ax \log x$, which can be viewed as a generalization of both the Shannon entropy equation, Eq. 4.2, and the Boltzmann entropy equation, Eq. 4.23. It may be asserted that BRE and the Boltzmann entropy-like equation (BEE), $y = ax \log x$, represent two of the very few mathematical equations that have been found to apply to both *physics* and *biology*.

It should be pointed out that both BRE and BEE can be viewed as the "nondimensionalized" version of Planck's radiation formula, Eq. 11.26, and Boltzmann equation, Eq. 4.23. A "nondimensionalized" equation is an equation with nondimensional parameters (i.e., numbers without any measuring units) that can be derived from its original physically meaningful equation based on the *Buckingham π theorem*. According to this theorem, if a physically meaningful equation contains a certain number, n, of physical values which can be expressed in terms of k independent fundamental physical quantities (e.g., mass, length, charge, temperature, etc.), the original expression can be converted into an equation involving a set of $p = n - k$ dimensionless parameters constructed from the original variables (http://en.wikipedia.org/wiki/Buckingham_%CF%80_theorem).

The first two rows numbered 1 and 2 exhibit the *quantitative regularities* common to six different fields (see 1a, 1b, and 2a–2d in the second column) and the last row numbered 3 lists the *qualitative regularities* found in two fields (3a and 3b). Thus, the topics analyzed in this table using the "table method" of analysis (Ji 1991, pp. 8–13) cover the widest possible range of sciences, unlike, say, the dimensional analysis (http://en.wikipedia.org/wiki/Dimensional_analysis) which is limited to analyzing *quantitative aspect* of reality (Stahl 1961). As evident in Table 12.13, the objects appearing in the first six categories have either some dimensions or are dimensionless, while the objects in the last two categories represent qualitative entities without any quantitative dimensions.

The regularities appearing in the first column of Table 12.13, whether quantitative or qualitative, can be viewed as *systems*, *machines*, *functions*, or *structure-preserving maps* that convert an input (denoted as x on the top row) into an output (denoted as y). In category theory (defined in Sect. 12.17, Eqs. 12.55 and 12.56), such regularities are referred to as *morphisms*, and x and y are referred to as the *source object* and the *target object*, respectively. A *category* is a very abstract mathematical construction characterized by a set of *objects* that can be transformed

Table 12.13 The regularities common to physics, biology, and linguistics as revealed by the "table analysis" (Ji 1991). Experience is assumed to possess two complementary aspects – *quantitative* and *qualitative*. Only the quantitative aspect of experience is subject to *dimensional analysis* (Stahl 1961) . The following dimensionalities are assumed to be fundamental: M = mass; L = length; T = time; Q = electrical charge; Θ = temperature; and N = number of moles of chemicals. Three universal properties are suggested in this table: Iqt = *quantitative information* (Sect. 4.3); E = *energy*, including free energy (Sect. 2.1.2); and G = *gnergy*, postulated to be the universal driving force for all organizations in the Universe including communication (Sect. 2.3.2)

Regularities (*morphisms*)	Fields	y (Target object)	x (Source object)	Universal properties[a]
1. $y = ax \log x$	(1a) Statistical mechanics	Entropy (S) $[ML^2T^{-2}\theta^{-1}]$	# of microstates [dimensionless}	Selection[b] (counting) I_{qt}
	(1b) Information theory	Information (I_{qt})[c] [dimensionless]	Probability of an event [dimensionless]	
2. $y = a/(Ax + B)^5/(e^{b/(Ax+B)} - 1)$	(2a) Blackbody radiation	Light intensity $[ML^{-1}T^{-2}]$	Wavelength [L]	Quantization of energies[d] E
	(2b) Protein stability	Frequency [dimensionless]	Ground-state free energy levels [dimensionless]	
	(2c) Single-molecule enzymology	Frequency [dimensionless]	Waiting times [T]	
	(2d) Whole-cell metabolism	Frequency [dimensionless]	Pair-wise similarity scores of RNA trajectories $[L^{-3}N]$	
3. Linguistics	(3a) Human language (humanese)	Meaning (quality)	Signs (I) (quality)	Communication (representation) G
	(3b) Cell language (cellese)	Gene-directed processes (quality)	Stimuli to cell (quality)	

[a] The properties or characteristics common to two or more categories

[b] Selection has three aspects: (1) The message source from which something is selected, (2) the selector or the channel that selects, and (3) the selected message carrying information. We may refer to this notion as the "triadic definition of selection." The *biological evolution* can be viewed as a member of the class of *selection*

[c] Information I is postulated to have two complementary aspects – the quantitative (I_{qt}) and qualitative (I_{ql}). See text for a detailed explanation

[d] Including Gibbs free energy of enzymes

into one another according to a set of rules called *morphisms*. Hence each of the eight rows in Table 12.13 numbered 1a–3b can be viewed as a category. The eight categories in Table 12.13 are grouped into three *higher-order categories* numbered 1, 2, and 3 based on the common properties (or universal properties) given in the last column. The *universal property* is here simply defined as the *properties common to two or more categories*. The formal definition of the universal property (http://en.wikipedia.org/wiki/Universal_propeerty) is complex and beyond the scope of this book. The universal properties common to a set of categories may require more than one term to be adequately expressed as evidenced by the appearance of multiple terms in each of the major categories in the last column of Table 12.13.

The universal property common to statistical mechanics and information theory (see Rows 1a and 1b) is suggested to be the quantitative aspect of "information," denoted as I_{qt}. Information (I) is thought to have two complementary aspects – quantitative (I_{ql}) and qualitative (I_{qt}). The Shannon equation applies only to I_{qt} and is blind to I_{ql}. We may represent this idea thus:

$$I = I_{gt}\text{^}I_{ql} \tag{12.46}$$

where the symbol "A = B^C" represents the statement that "A is the complementary union of B and C " or, equivalently, that "B and C are the complementary aspects of A" (Sect. 2.3.1). In addition, it is suggested here that I may be related to Firstness of Peirce (see Sect. 6.2.2) (hence denoted as 1-I), I_{qt} to Secondness (hence denoted as 2-I), and I_{ql} to Thirdness (hence denoted as 3-I), although it is not possible to prove the legitimacy of this assignment.

The universal property spanning the four categories 2a–2d is suggested to be the *quantization* of energies (E), including free energies. It should be recalled that free energies are the functions of both energy (E) and entropy (S) (see Eq. 2.1). The process of *quantization* may be more general than has been thought in quantum mechanics. Quantization occurs not only in blackbody radiation (see Row 2a) but also in protein folding (Row 2b), single-molecule enzymology (Row 2c), and whole-cell RNA metabolism (Row 2d), as evidenced by the fact that some aspects of these processes all obey the same mathematical equation, the blackbody radiation-like equation (BRE) (see the second row and the first column of Table 12.13). Not only energy (or more accurately "action") but entropy (and hence free energy) may be quantized. According to Gilson and McPherson (2011), the Boltzmann constant k is quantized and hence so is entropy (S), since k and S have the same dimensionality as evident in Eq. 4.23. The fact that protein stability, single-molecule enzyme activity, and whole-cell RNA kinetic data fit BRE may be an experimental evidence supporting the postulate of the *quantization of the Gibbs free energy in the living cell*. Just as the fitting of the blackbody radiation data into the Planck's formula indicated the organization of the energy levels of electrons within the atom, so perhaps the fitting of the above biological data into BRE indicates that the Gibbs free energy levels of enzymes are organized inside the living cell. Again:

> Just as the transitions of electrons between the energy levels in atoms are responsible for the absorption or emission of photons, so the transitions of enzymes between their Gibbs free energy levels inside the cell may be responsible for the rise and fall of the concentrations of intracellular biochemicals (including RNA) that determine cell functions. (12.47)

We may refer to Statement 12.47 as the Postulate of the Quantization of the Gibbs Free Energy of the Living Cell, or more briefly the Cell Free Energy Quantization Postulate (CFEQP).

In 1991, I postulated that all the molecular machines inside the cell are driven by *conformons* (i.e., the conformational strains of biopolymers harboring mechanical energy at sequence-specific sites) and that the minimum energy content of the conformon is kT or ~4×10^{-14} ergs, which is about 10 orders of 10 greater than

Planck's quantum, hν (where ν is the wave number) (Ji 1991; Table 1.9). This postulate may be expressed alternatively as:

> The Boltzmann constant k is to biology what the Planck constant h is to quantum mechanics. (12.48)

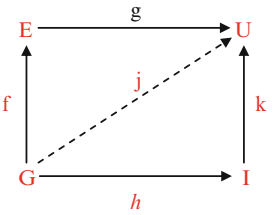
Statement 12.48 may be referred to as the *k-h isomorphism postulate*.

The universal property inherent in the last two categories of Table 12.13 is suggested to be *communication* or *information exchange,* for which both *information* (I) to be transferred and the energy (E) to drive the transfer process are absolutely required according to Shannon's channel capacity equation, Eq. 4.29. Since the complementary union E and I is referred to as gnergy (G) (Sect. 2.3.2), it would follow that communication absolutely requires (or is synonymous with) gnergy.

The selection of I (not I_{gt}), E, and G as the universal properties of the associated categories in Table 12.13 is motivated by the *information-energy complementarity postulate* described in Sect. 2.3.2. In other words, the three universal properties, I, E, and G, are postulated to form a higher-order category, to be designated as C^2 (from "CC" or the "cosmological category"), which is a 9-tuple consisting of four objects (denoted with capital letters) and five morphisms (denoted with lower-case letters) as follows:

$$CC = (E,\ I,\ G,\ U,\ f, g,\ h,\ j,\ k) \tag{12.49}$$

Equation 12.49 can be represented graphically using the "commutative diagram" as shown in Fig. 12.33. A commutative diagram can be viewed as a network



Complementarity (G → E → U)^(G → I → U)

or (g∘f)^(k∘h) = j (12-50)

Supplementarity : (G → E → U) = G → I → U) = (G → U)

or f∘g = h∘k = j (12-51)

Therefore j is both complementary and supplementary!

Fig. 12.33 The *commutative diagram* for the cosmological category (CC or C^2) consisting of four objects, energy/matter (E), information (I), gnergy (G), the universe (U) and five morphisms, tentatively identified as *f* (physical interactions), *g* (quantization), *h* (biological evolution), j (cosmogenesis), and *k* (communication) embodying/reflecting/ organized by two universal principles of *complementarity* and *supplementarity* discussed in Sect. 2.3.1

wherein the vertices are objects and directed edges (or arrows) are morphisms with the characteristics that all directed paths in the network with the same endpoints lead to the same result by the operation called "composition" usually denoted by the symbol ◦. Thus if the diagram in Fig. 12.33 commutes, it follows that g◦f = k◦h. I find it necessary to introduce another kind of composition to be denoted by the symbol ^ such that A^B = C indicates that A and B are the complementary aspects of C. The commutativity diagram in Fig. 12.33 embodies two major principles discussed in this book, namely, *complementarity* and *supplementarity,* first introduced into physics by N. Bohr (1958) and discussed in detail in Sect. 2.3.1. These principles are represented as two different compositions of morphisms as shown in Eqs. 12.50 and 12.51.

Hence we can characterize the commutativity diagram in Fig. 12.33 by the following statement:

The C^2 category is *complementarity/supplementarity dual*. (12.52)

Based on Statement 12.52, we may refer to the C^2 category as the *complementarity/supplimentarity dual category*. The physical interpretations of the five morphisms appearing in the C^2 commutativity diagram are indicated in the legend to Fig. 12.33. These interpretations may be subject to improvements as our knowledge progresses.

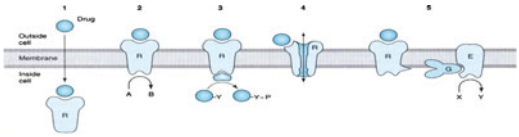
12.17 Signal Transduction

Living cells constantly communicate with their environment using molecules as information carriers. The molecules carrying environmental information are called the *primary messengers,* and most primary messengers cannot enter the cell interior due to the impermeable cell membrane, except steroids that are lipid-soluble and hence can penetrate the hydrophobic barrier provided by the cell membrane. Thus, in order for the extracellular information to be transmitted to the interior of the cell, the information carried by primary messengers must be *transferred to,* or *transduced* into, *secondary messengers* catalyzed by receptors embedded in the cell membrane (see Table 12.14). This is phenomenon is known as *signal transduction*.

Barbieri (2003, p. 108) recognizes three distinct mechanisms of signal transduction across the cell membrane as explained in the legend to Fig. 12.34. What is common to all these mechanisms of transmembrane signal transduction is the role played by *membrane receptors* which act as molecular machines that "translate" *first messengers* to *second messengers* (see Table 12.14). As can be seen in the second and the fifth columns of Table 12.14, there is no structural relation (or similarity) between first and second messengers (compare, for example, acetylcholine and cAMP, the first and second messengers for G-protein coupled receptors). In other words, the relation between first and second messengers are *arbitrary* from the point of view of chemistry and physics but fixed and constant (or *absolute*) from the point of view of semiotics or communications theory in that the information carried by first messengers are reliably

Table 12.14 Five mechanisms of transmembrane signaling in cells. The table was reproduced from Fig. 2.8, p. 18 in Katzung (2001)

Transmembrane signaling mechanisms



Mechanism	Ligand (first messenger)	Receptor	Second messenger
1	NO	Guanyl cyclase	cGMP
	Glucocorticoids	Glucocorticoid receptor/hsp90	Glucocorticoid receptor
2	Insulin, EGF, PDGF, ANF, TGF-β, etc.	Receptor tyrosine kinase Receptor serine kinase Receptro guanyl cyclase	Phosphorylated target proteins
3	Cytokines (interferons, interleukins, TNF-α and -β, CSF, erythropoietin, etc.)	Cytokine receptors	Phosphorylated target proteins (e.g., STATs, or signal transducers and activators of transcription)
4	Acetylcholine, γ-aminobutyric acid (GABA), excitatory amino acids (glycine, aspartate, glutamate, etc.)	Ligand-gated ion channels	Changes in local membrane potential (e.g., depolarization)
5	Acetylcholine, ACTH, angiotensin, catecholamines, FSH, glucagon, histamine, parathyroid hormones, PGE_2, serotonin, dopamine, etc.	G protein-coupled receptors (GPCRs)	cAMP, Ca^{++}, IP_3, diacyglycerol, cGMP

transmitted across the cell membrane to second messengers. This phenomenon is reminiscent of the *arbitrariness of signs* in linguistics (see Sect. 6.1.3), and this principle evidently applies to signal transduction in the cell as postulated by the cell language theory (Ji 1997a, b).

There are five well-established mechanisms effectuating transmembrane signaling in living cells as summarized in Table 12.14. All except Mechanism 1 are mediated by receptors embedded in the cell membrane. Membrane receptors can be viewed as *molecular machines* that perform three major biological functions:

1. The specific *recognition* of the cognate primary messengers
2. The *coupling* between first messengers and their intracellular counterparts, i.e., second messengers and
3. The *amplification* of the second messenger signals either directly by acting as a kinase or an ion channel (see Mechanisms 2 and 4 in Table 12.14) or indirectly via another protein acting as a kinase (see Mechanisms 3 and 5)

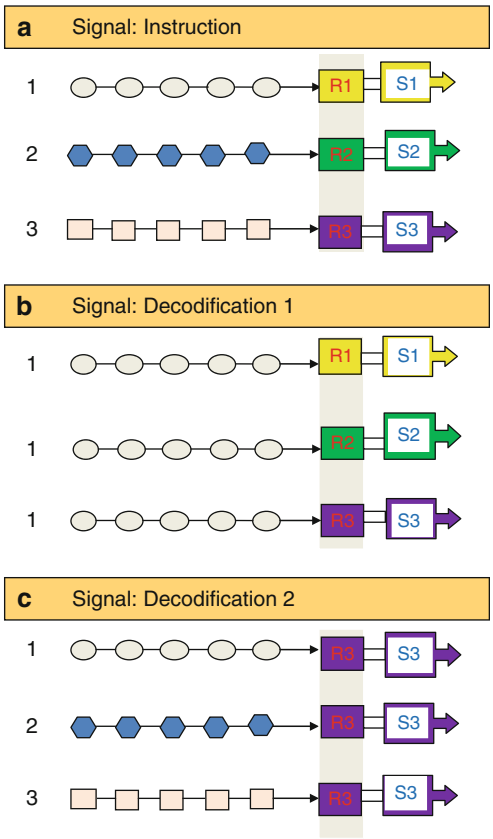


Fig. 12.34 Three mechanisms of transmembrane signal transduction according to Barbieri (2003). (**a**) The one-to-one signal transduction, where one primary messenger produces a corresponding secondary messenger. (**b**) The one-to-many signal transduction, where one primary messenger produces more than one secondary messenger. (**c**) The many-to-one signal transduction, where many different primary messengers produce an identical secondary messenger

We may refer to these functions as the *triadic functions of membrane receptors*. Since all molecular machines must work in more than one cycle in a given direction, their operation cannot be driven by random thermal fluctuations or Brownian motions *alone* but must ultimately be driven by free energy dissipation. There are two free energy sources for membrane receptors – (1) ATP or GTP for Mechanisms 2, 3, and 5 (see Table 12.14), and (2) transmembrane ion gradients for Mechanism 4.

The *signal transduction machinery* (STM) is more complex than membrane receptors and the interactions with their ligands. The STM of the cell may be viewed as composed of at least eight distinct components as depicted in Fig. 12.35. Common examples of the first three components of STM are listed in Table 12.14.

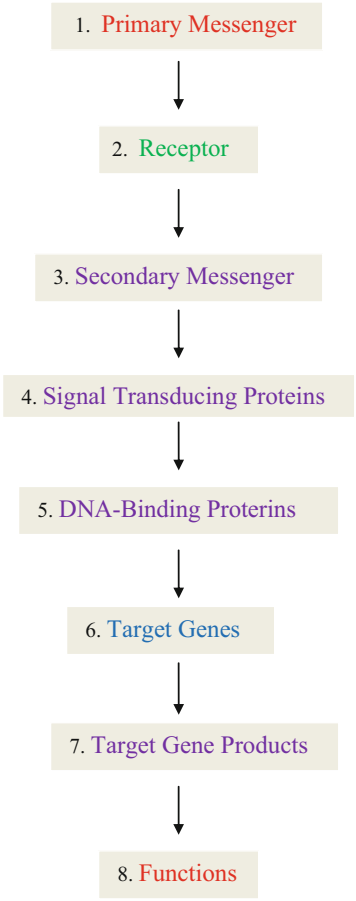


Fig. 12.35 The major components of the *signal transduction pathways* in the living cell. *Red* = extracellular space; *Green* = cell membrane; *Purple* = intracellular space. *Blue* = nucleus. The receptor in this figure can be either membrane embedded or located in the cytosol

Components 4, 5, 6, and 7 in Fig. 12.35 cooperate inside the cell to produce *intracellular dissipative structures* (IDSs or *dissipatons*) that are thought to determine (or are identical with) cell functions. The principle of their operation can be described in two complementary ways, based on either (1) the *energetic/structural perspective* or (2) the *semiotic/linguistic perspective*. The energetic/structural principle underlying the workings of Components 4–7 is generally known as "protein–protein interactions" where *structural complementarity* and *free energy of binding* play fundamental roles. In contrast, the semiotic/linguistic principles underlying the operation of Components 4–7 are rarely discussed in the current literature on signal transduction, one exception being the cell language theory (Ji 1997a, b). According to the cell language theory (Sect. 6.1.2), the linear sequence of Components 4–7 in Fig. 12.34 can be viewed as *molecular sentences* and hence the principles of (1) double (or triple) articulations and (2) syntagmatic and paradigmatic relations should apply to them.

Table 12.15 Triple articulations in cell and human languages

Parameters	Human language	Cell language
1. Key material component	Book	DNA
2. Size of signs	Macroscpic (e.g., words)	Microscopic (e.g., molecules)
3. Reader/effector	The human brain	The cell
4. First articulation	Words → sentences	Noncovalent structures (e.g., protein conformations)
5. Second articulation	Letters → words	Covalent structures (e.g., protein primary structures)
6. Third articulation	Sentences → texts	Gradient structures, (e.g., transmembrane ion gradients, intracellular mechanical stress gradients (Ingber 1998), intracellular ion and metabolite gradients

The triple articulation is defined in the second column and Rows 4, 5, and 6 in Table 12.15, where the arrow symbol can be read as "form" or "produce." I formulated the notion of *third articulation* in 2003. Although linguists apparently have not widely discussed *third articulation*, there is no reason why the number of articulations in human language should stop at two. Hence it was proposed that human language exhibits the phenomenon of "third articulation," defined as a *sequential arrangement of sentences to form texts*. If the isomorphism thesis between cell and human language is valid, there should exist the first, second, and third articulations in cell language as well (see the third column). The third articulation in cell language is suggested to be *space-and time-dependent changes in concentrations or diffusible molecules or mechanical strains (known as conformons) inside the cell*. Such dynamic structures were referred to as IDSs (intracellular dissipative structures or *dissipatons*) in the *Bhopalator model* of the living cell (Fig. 2.11), and IDSs in turn may be viewed as related to the concept of *metabolic spacetime* proposed by Welch and his colleagues (Welch and Smith 1990; Smith and Welch 1991; Welch and Keleti 1981).

The concept of *paradigmatic* and *syntagmatic* relations are useful in understanding the structure of signal transduction pathways in general and the mode of operations of Components 4–7 in Fig. 12.35, in particular. These concepts are explained in Table 12.15 using familiar examples. The *syntagmatic relation* refers to the relation among the components of a sentence such as the subject, verb, and object as shown in the first row of Table 12.16. Thus, in English language, the subject of a sentence precedes the verb which in turn precedes the object: "He" precedes "loves" which precedes "her," etc. This is analogous to Component 4 preceding Component 5 which precedes Component 6 which precedes Component 7 in STM shown in Fig. 12.35 or to MAPKKK preceding MAPKK which precedes MAPK which precedes transcription factors in Fig. 12.36. This figure summarizes the MAP kinase signaling cascade of vertebrates as reviewed by Seger and Krebs in 1995. An analogous signaling pathway was found to operate in the unicellular organism *S. cerevisiae* (Seger and Krebs 1995).

Table 12.16 The syntagmatic (*row*) and paradigmatic (*column*) in human language

Meaning	Subject	Verb	Object
Sentence 1	He	loves	her
Sentence 2	I	saw	a play
Sentence 3	She	adores	him
Sentence 4	The university	fired	him

Table 12.17 The paradigmatic (*row*) and syntagmatic relations (*column*) in cell language. The question mark indicates the protein predicted to exist in vertebrate cells in analogy to the protein found in *S. cerevisiae* (Seger and Krebs 1995). See Fig. 12.36 for a more complete description of the MAPK signaling cascade

MAPKKK (or MAP3K)	MAPKK (or MAP2K)	MAPK	Meaning (i.e., A, B, C or D in Fig. 12.36)
MEKK	MEK 1/2	ERK 1/2	Growth, proliferation, etc.
Raf-1	MEK 1/2	ERK 1/2	Growth, proliferation, etc.
MOS	MEK 1/2	ERK 1/2	Growth, proliferation, etc.
??	RKK	RK	Growth, proliferation, etc.

Table 12.18 Structural and functional comparison of protein language (p*roteinese*) and human language (*humanese*)

Level of organization	Proteinese (A)	Humanese (B)	Function (C)
1. Primary	Amino acids	Phonemes	Units of communication
2. Secondary	Functional domains	Morphemes	Units of meaning
3. Tertiary	Folded polypeptides	Words	Units of denotation
4. Quaternary	Protein complexes	Sentences	Units of judgment
5. Quintic	Protein networks	Texts	Units of reasoning or computing

The paradigmatic relation is obtained between two or more words that can occupy the same syntagmatic position in a sentence. Thus all the words appearing within a column in Table 12.16 are related *paradigmatically*. Some examples of the paradigmatic relation as applied to the MAP kinase signal transduction pathway are given in the columns in Table 12.17, along with examples showing the syntagmatic relations given in the rows of the same table.

It is possible that, depending on the environmental conditions, an extracellular signal (or a first messenger) can trigger more than one series of protein–protein interactions (or molecular sentences) thereby activating a molecular text, which is an example of a third articulation. The postulated biological functions of the first, second, and third articulations are discussed in Table 12.18 in terms of the protein molecular language.

Although proposed more than a decade before the cell language theory (Ji 1997a), which has proven to provide a sound theoretical foundation for *signal transduction*, the Bhopalator model of the cell (Ji 1985a, b, 2002b) appears to be capable of acting as the signal transduction machinery described in Fig. 12.36. The 20 steps constituting the Bhopalator can be roughly grouped into 6 steps of the signal transduction machinery as shown in the lower right-hand corner of Fig. 12.37.

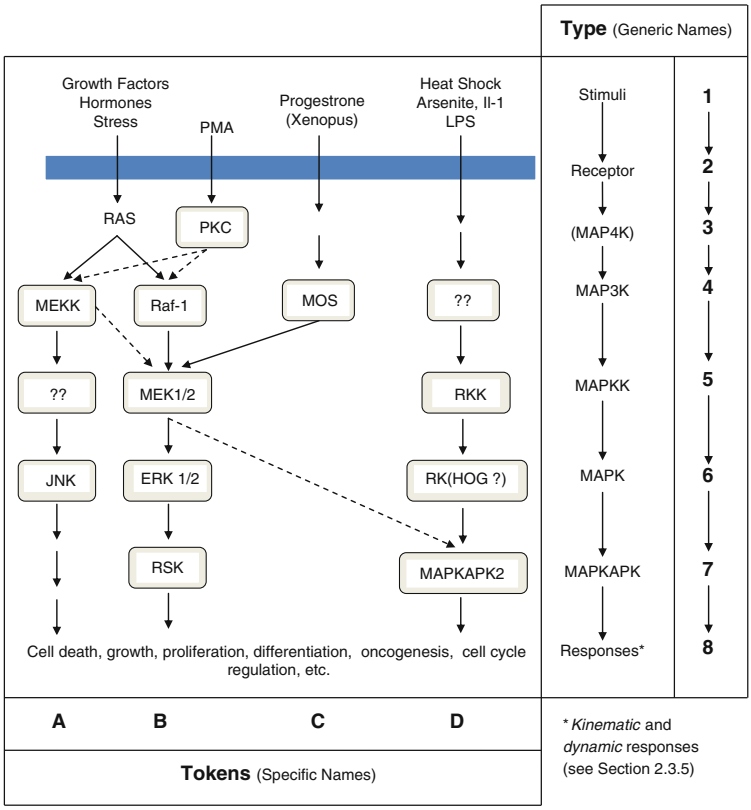
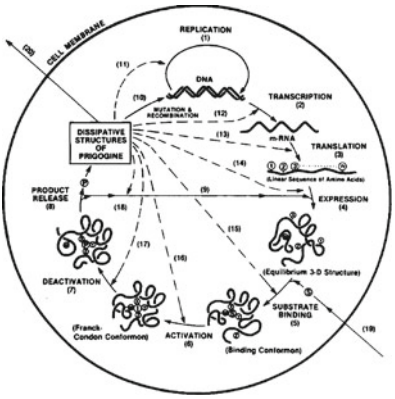
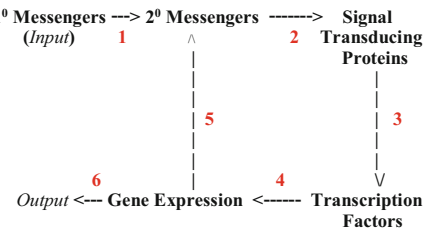


Fig. 12.36 The MAPK Signal Transduction Pathways (Cascades), adopted from Seger and Krebs (1995). Three distinct signal transduction pathways are shown. All of these pathways are composed of six functional elements (numbered 2–7), which, when activated by primary messengers or stimuli (numbered 1), lead to specific functions or responses (numbered 8). The kinematics (concerned with the question as to which of the possible pathways are actually activated under a given environmental condition) and the dynamics (concerned with the question about for how long and how fast a given pathway is activated) are determined by the primary messenger (or primary perturbation) and the state of the cell involved. To completely describe a signal transduction event, it is necessary to elucidate not only the *kinematics* but also *dynamics* of signal transduction since these are the complementary aspects of signal transduction (Sect. 2.3.5). *MAPK* mitogen-activated protein kinase, *MAPKK or MAP2K* MAPK kinase, *MAPKKK or MAP3K* MAPKK kinase, *MAP4K* MAP3K kinase, *RAS* rat sarcoma, *PKC* protein kinase C, *MEKK* MEK kinase, *MEK* mitogen-activated, ERK-activating kinase, *MEK ½* MEK 1 and 2, *ERK ½* ERK 1 and 2, *ERK* extracellular regulated kinase, *RSK* ribosomal S6 protein kinase, *MAPKAPK2*, MAP kinase-activated protein kinase 2. This table exemplifies the distinction between types and tokens discussed in Sect. 6.3.9. Seger and Krebs refer to *types* and *tokens* as *generic* and *specific* names, respectively

It is a truism to state that *no communication is possible without a language*. Since communication is essential for cells to survive and function, cells must possess languages of their own, and such a *hypothetical language* was referred to as the cell language in (Ji 1997a, b) (see Sect. 6.1.2). Just as the computer language

The Cell as a *Signal Processor* (Recognizer/Receiver, Transducer, and Effector/Constructor)





Approximate correspondence between the two figures:

1 = (19)
2 = (5) + (6) + (7) + (8) + (9)
3 = (8)
4 = (10) + (1) / (2) + (3) + (4)
5 = (12) + (13) + (14) + (15) + (16) + (17) + (18) +(19)
6 = (11) + (20)

Fig. 12.37 The living cell as a signal-transducing machinery. The overall signal transduction process carried out by the cell can be decomposed into six major steps. Step 1 = transmembrane signaling; Step 2 = intracellular signal processing (also called molecular computing); Step 3 = activation or inhibition of protein factors that bind to DNA; Step 4 = interaction between processed transcription factors and target DNA regions, including promoters, enhancers and silencers; Step 5 = feedback interactions between the genome and membrane receptors; and Step 6 = cell outputs, including secreted proteins and small molecules, and mechanical processes such as cell shape changes and cell migration

has many layers (i.e., digital logic, microarchitecture, instruction set architecture, operating system machine, assembly, and problem-oriented languages (Tanenbaum 2003)), so the cell language appears to have multiple layers:

1. DNA language = *DNese*
2. RNA language = *RNese*
3. Protein language = *proteinese*
4. Metabolite language = *metabolese* (e.g., ATP, ADP, glucose, H+, metal ions)
5. Intercellular language = *intercellese* (e.g., hormones, cytokines, PGs, ion gradients)

Of these cell sub-languages, *proteinese* is unique because it is the only *autonomous (or active) language* in the sense that only proteins acting as enzymes (except for some RNAs acting as ribozymes) can utilize the chemical free energy locked up in small molecules such as glucose, NADH, and ATP. Therefore, we can state that *proteinese* is the primary engine of the cell language and the other sub-languages are *secondary* and *passive*. So, to understand how the *cell language* works, it would be essential to understand how *proteinese* is constructed and works.

Proteinese and the human language (or briefly *humanese*) are compared at five structural levels in Table 12.18.

1. B = C (from Linguistics)
2. A = B (from Cell Language Theory)
3. A = C (leads to Semantic Biology)

Fig. 12.38 Predicting the biological functions of the components of proteinese based on the cell language theory (Ji 1997a, b). 1 = Major premise; 2 = minor premise; 3 = conclusion. A, B and C refer to the columns so labeled in Table 12.18

The relation between Columns *B* and *C* are well established in linguistics (Hockett 1960; Culler 1991). The relation between Columns *A* and *B* is suggested by the cell language theory. Therefore, Column *A* and *C* must be related, as the following syllogism demonstrates:

Based on the inference presented in Fig. 12.38, it appears reasonable to suggest that *semantic biology* of Barbieri (2003, 2008a, b) emerges logically from the combination of *linguistics* and *molecular biology,* i.e., the *cell language theory* (Ji 1997a, b).

12.18 Computing with Numbers, Words, and Molecules

The concept of *computing* is widely discussed not only in computer science and engineering but also in mathematics (Wolfram 2002), physics (Lloyd 2006), brain/mind research, and biology (Adleman 1994; Ji 1999a). This is most likely because computing is a general concept that can be defined as follows:

> Computing is a series of the input-induced state transitions of a material system, artificial or natural, obeying a set of axioms, rules, and/or laws, leading to observable outputs. (12.53)

Thus defined, the concept of computing can be applied even to the Universe (Lloyd 2006, 2009). In Table 12.18 in Sect. 12.16, it was suggested that protein networks of the cell are the units of reasoning or computing. That is, *the cell computes*. In this section, the following items are discussed:

1. Three classes of computing
2. Computing as a category
3. The "conformon-P machine" as a formal model of the living cell
4. The "Turing/Zadeh complementarity" model of computing
5. The Bhopalator, a molecular model of the living cell, and its implications for computational theories of mind

(**1**) We can recognize three classes of computing– *numerical*, *lexical*, and *molecular*. They are distinguished by the nature of signs being manipulated to accomplish computing. The first class of computing is too well known to be

Table 12.19 Three classes of computing

	Computing		
	Numerical	Lexical	Molecular
1. Signs	Numbers	Words	Molecules
2. Manipulated by	Computer	Computer	Living cell
3. Logic	Crisp	Fuzzy	Crisp and fuzzy
4. Energy source	Electricity	Electricity	Chemical reactions
5. Model	Turing machine	"Zadeh" machine	Bhopalator

commented on. The concept of "computing with words (CW)" was developed by Lotfi Zadeh in the mid-1990s by "fuzzifying" traditional crisp numerical variables into what he called "linguistic variables" (1996a, b, 2002). In Adleman (1994) an instance of the directed Hamiltonian path was solved by manipulating DNA fragments in test tubes. Living cells can be considered to be the smallest molecular computers in nature, since cells have evolved to manipulate molecular signals or messages based on genetic instructions or rules encoded in DNA, leading to desired outputs (Ji 1999a). In 1997, I reviewed some of the vast amount of experimental data available in the literature concerning the phenomenon of "apoptosis" (also called "programmed cell death") and was led to conclude that cells have evolved to obey the following type of instructions (Ji 1997b):

If you are in cell state X and receive signal Y, then do Z. (12.54)

The conditional instruction, Statement 12.54, is very similar to (or is an example of) the "if-then" rule in fuzzy computing or computing with words. In this sense, the living cell and its molecular model, the Bhopalator (Ji 1985a, b), can be viewed as the natural "fuzzy computer." The Turing machine is not a fuzzy computer in that its hardware is constructed on the basis of crisp binary logic, not fuzzy logic. But the Turing machine can be made to perform computations using fuzzy logic. The salient features of the above three classes of computing are summarized in Table 12.19.

(**2**) Each of the three classes of computing shown in Table 12.19 may be viewed as a *category* in the mathematical sense. According to (Herrlich and Strecker 1973):

A category is a triple:

$$C = (O, U, \text{hom}) \tag{12.55}$$

where C is category; O is a class (or a collection) whose members are called C-objects; U: $O \rightarrow u$ is a set-valued function, where for each C-object A, U(A) is called the underlying set of A; and hom: $O \times O \rightarrow u$ is a set-valued function, where for each pair (A, B) of C-objects, hom(A, B) is called the set of all C-morphisms with domain A and codomain B.

It should be noted that u is the class of all sets. Classes differ from sets in that they are immune to the logical contradiction known as Russell's paradox: Let R be the set of all sets that are not members of themselves. If R is a member of itself, then

by definition, it must not be a member of itself. If *R* is not a member of itself, again by definition, it must be a member of itself. Thus *R* is both X and not–X at the same time, violating the principle of crisp logic, the law of excluded middle.

Baez (http://math.ucr.edu/home/baez/week73.html) provides another useful definition:

> A category is something just as abstract as a set, but a bit more structured. It is not a mere collection of objects; there are also morphisms between objects, in this case the functions between sets. . . . A category consists of a collection of "objects" and a collection of "morphisms." Every morphism f has a "source" object and a "target" object. If the source of f is X and its target is Y, we write f: X → Y. In addition, we have:
>
> (a) Given a morphism f: X → Y and a morphism g: Y → Z, there is a morphism fg: X → Y, which we call the "composition" of f and g
> (b) Composition is associative: (fg)h = f(gh)
> (c) For each object X there is a morphism 1_X: X → X, called the "identity" of X. For any f: X → Y we have $1_X f = f\ 1_X = f$. (12.56)

The first two three rows of Table 12.19 may correspond to the O (i.e., objects) and hom (i.e., morphism) components of a category defined in Statement 12.56.

(**3**) In analogy to the Turing machine, it may be convenient to refer to computing machines based on words or "linguistic variables" as "Zadeh machine." A linguistic variable consists of a "linguistic term" and a positive real "number," between 0 and 1, indicating a degree of membership to a fuzzy set (for a definition of fuzzy set, see Sect. 5.2.5) (Kosko 1993; Zadeh 1996c). Frisco and Ji (2002, 2003) applied the biological concepts of the conformon (Ji 1974b, 2000) and the cell membrane to modeling computability. It is shown that this so-called conformons-P system belongs to the universality class of the Turing machine. The suffix P stands for the P-system, a biological membrane-inspired computational model developed by G. Paun and his school in the 1990s (Paun 2002; Paun et al. 2002). The conformons-P system can be viewed as a formal model of the *computing aspect* of the living cell in contrast to the Bhopalator (Ji 1985a, b) which is its molecular model of the *living cell as a whole*. We can alternatively refer to the *conformons-P system* as the *conformon-P machine*, whenever convenient.

The *conformon* of the conformons-P system is a pair, [X, x], where X is the "name" and x the "value" of the conformon. X and x thus defined are the abstractions of their biological counterparts, *information* and *energy*, that constitute the complementary pair of the original *conformon*. *Conformon* [X, x] is formally identical with Zadeh's *linguistic variable*, if X and x are equated with the *linguistic term* and the *degree of membership to a fuzzy set*, respectively. Consequently, the conformon-P machine can be reduced to the Zadeh machine, as it can be reduced (or related) to the Turing machine (Fig. 12.39).

(**4**) As pointed out by fuzzy theorists (Zadeh 1996a, b, c; Kosko 1993; Yen and Langari 1999), the Turing machine is based on *crisp sets*, while Zadeh machine is rooted in *fuzzy sets*. I here postulate that the set of molecules underlying the conformon-P machine is both *crisp* (e.g., nucleotide sequences of DNA) and *fuzzy* (e.g., ensemble of conformations belonging to a given amino acid sequence of a protein) (Ji 2004a). Because of its "A AND not-A" nature (Kosko 1993), it may be asserted that the Bhopalator can act as the ultimate source or ground for both the

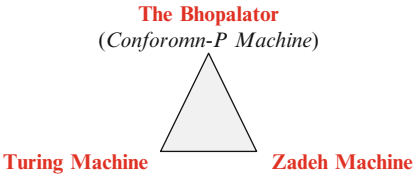


Fig. 12.39 The *Turing* and the *Zadeh* machines as the complementary aspects of the *conformon-P machine*, or the formal model of the Bhopalator

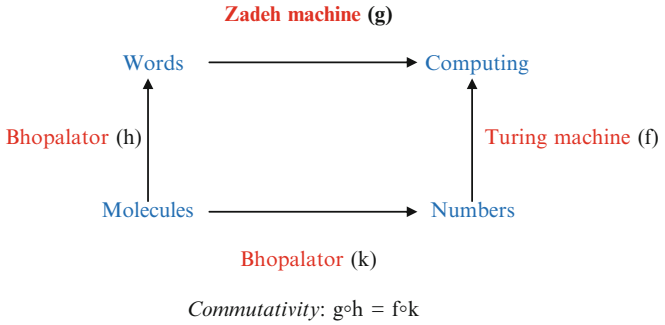


Fig. 12.40 The commutative diagram relating the molecular model of the cell, the Bhopalator, to the computer models of Turing and Zadeh. This diagram is consistent with Fig. 12.38 wherein the Turing and Zadeh machines are viewed as the complementary aspects of the Bhopalator

Turing and Zadeh machines. According to Zadeh, probability theory (which is based on crisp sets) and fuzzy logic are complementary rather than competitive (Zadeh 1995). Therefore, it may be reasonable to suggest that the *Turing machine* and *Zadeh machines* are complementary. If so, there must exist a third term or entity, of which these two machines represent its complementary aspects, and it seems logical to conclude that the Bhopalator (and its formal model, the conformon-P machine) can qualify as the third entity.

(**5**) If the Turing/Zadeh complementarity model of computing turns out to be true in principle, it may have important applications in cognitive sciences. The computational theories of mind described in Putnam (1961) and Fodor (1975) appear to assume that the Turing machine is the best theoretical framework now available to model computing (Ji 1991, pp. 205–209). If the content of Figs. 12.39 and 12.40 is correct, the Turing machine may at best capture the crisp aspect of human mind, and misses out on its fuzzy aspect. In addition, the Turing machine, being formal and macroscopic, may completely miss out on the molecular energetic grounds for the working mechanisms of the human mind. Hence, it may be reasonable to suggest that the Bhopalator provides a sound starting point for modeling the human mind (Ji 2003a). This suggestion may gain support from the cell language theory, according to which living cells use a molecular language that shares with human language a common set of semiotic principles (Ji 1997a, b) (see Sect. 6.1.2).

Chapter 13
Mechanisms of the Origin of Life

13.1 The Anderson Model of the Origin of Biological Information

Any theory purporting to account for life cannot avoid facing the fundamental question about how life originated on this planet. One of the most physically realistic models of the origin of biological information (and hence of life) that I know of was proposed by P. W. Anderson and his coworkers (1983, 1987) (see Fig. 13.1). The model was based on thermal cycling (i.e., the cyclical changes of the temperature on the surface of the earth due to its daily rotation around its axis) of an RNA "soup" presumed to be present somewhere on the primordial earth surface some 3.5 billion years ago. The following quotation from Anderson (1987) describes the key ideas behind his model:

> . . . The autocatalytic mechanism which must be at the core of any prebiotic evolution scheme is the complementary conjugation of polymeric molecules, nominally RNA. It is assumed that the thermal cycle periodically breaks up the weak conjugation bonds between RNA polymers, and at a later stage allows them to reconjugate randomly. Once two polymers have simultaneously conjugated with the same 'template', matching adjoining sequences (see the RNA double strands located on the bottom of Fig. 13.1; my addition), they are permitted with some probability to bond completely together, thus elongating the chain and reproducing a longer sequence of the 'template'. This is the basic autocatalytic process, while the basic energy source is a constant supply of energy rich monomers (or short sequences of 2 or 3 monomers) which are added at each cycle and can be joined to the sequences already present by the conjugation-thermal cycling process. To achieve realism and a reasonably steady state, we must also postulate an error probability and a probability of chain death and/or breaking.

Anderson based his model of the origin of biological information on the concept of "frustrations" imported from spin glass physics (van Hemmen 1983). *Frustrations* are observed in physical systems with three or more components, each being able to exist in at least two energy (or spin) states (conveniently designated as + and –, or up and down, with opposite signs attracting and identical ones repelling each other) but, no matter how their spins are arranged, there exists at

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_13,

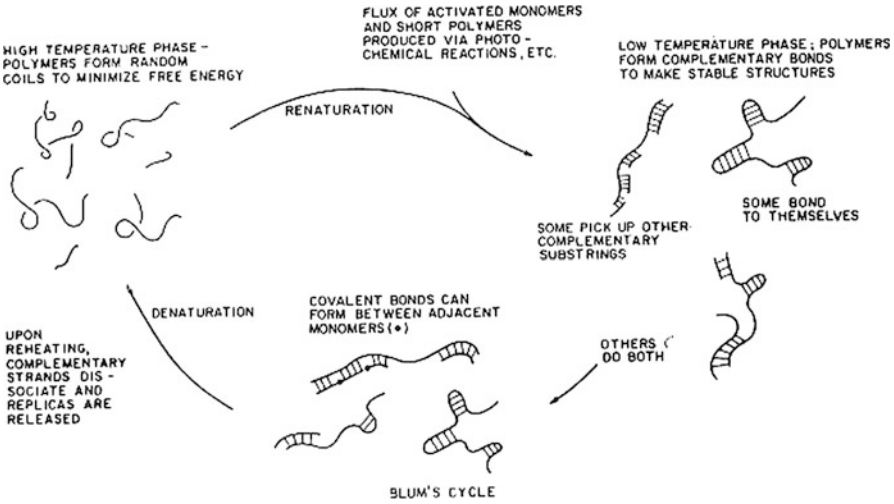


Fig. 13.1 The proposed model of the origin of biological information (and life) based on the concept of *frustrations* (Anderson 1983, 1987). Due to the presence of *frustrations*, some polymer chains cannot self-conjugate, thereby exposing single-stranded segments to environment to act as templates for self-replication (Reproduced from Anderson 1983, 1987)

least one pair of components whose spins are parallel to each other and hence of a non-minimal energy. Anderson and his colleagues represented the nucleotide sequence of an RNA molecule as a string of binary digits or spins, designating G as + +, C as − −, A as + −, and U as − + (which obeys the Watson–-Crick pairing rule). This allowed them to calculate the free energy (i.e., spin glass Hamiltonian, a mathematical function mapping spin configuration to the total energy of the spin system) of RNA molecules described as linear strings of spins. Furthermore, they defined what is referred to as the "death function" *D(S)* as a nonlinearly decreasing function of the *spin glass Hamiltonian*:

$$D(S) = 1/\{\exp[-H(S) + \rho N] + 1\} \tag{13.1}$$

where *H(S)* is the spin glass Hamiltonian (or the total energy of the spin system S), ρ is proportionality constant and *N* is the number of spins in the system (which is less than ten in the case studied in Fig. 13.2 below). Repeated applications of Eq. 13.1 to a collection of short RNA sequences showed that certain sequences died out with time (see the 7- and 8-mers in Fig. 13.2) whereas certain others (see the 11- and 12-mers) grew with repeated "thermal cycling," reminiscent of the selective growth of some nucleotide sequences in living systems. A similar finding was reported by Zeldovich et al. (2007a, b, 2008) (see Sect. 14.7).

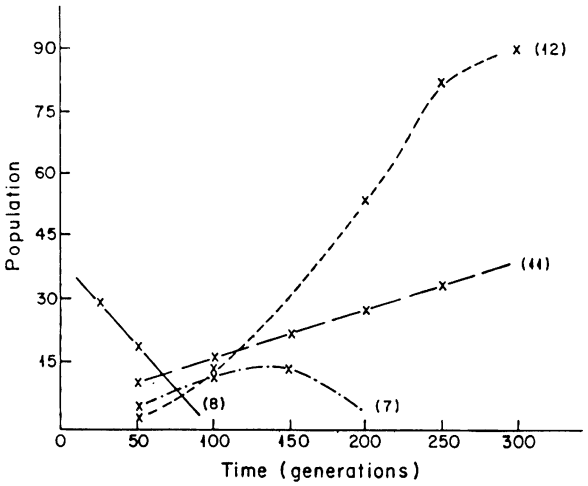


Fig. 13.2 The temporal evolution of RNA fragments obeying the death function, Eq. 13.1

13.2 The Conformon Model of the Origin of Life

Frustrations embedded in multicomponent physical systems including primitive RNA molecules embody both sequence *information* and mechanical *energy*, but Anderson and coworkers utilized only the *sequence information* in synthesizing complementary RNA fragments (see Fig. 13.1), thereby satisfying the *symbolic aspect* of Pattee's principle of *matter-symbol complementarity* (Pattee 1969, 1996; Ji 1999b) but not the energetic aspect. Consequently Anderson's model did not capitalize the mechanical (or conformational) energy associated with (or stored in) frustrations embedded in RNA to drive the synthesis of polymers. Anderson had to assume that "energy-rich" monomers, that is, nucleoside triphosphates (or nucleotides), were already available in the primordial RNA soup, but the presence of nucleoside triphosphates in the primordial soup may be very unlikely in view of its chemical instability, even if they were assumed to be formed by accidental coupling of five molecules belonging to the three different molecular classes – a base, a sugar, and an inorganic phosphate.

To overcome what I believed to be the deficiency of the Anderson model of the origin of biological information ("deficient" from the perspective of the *matter-symbol complementarity*), I modified the Anderson model by utilizing not only the *sequence information* (as he did) but also the *conformational energy* stored in frustrations (which he ignored). This is tantamount to assuming that the *frustrations* embedded in RNA molecules are *conformons* (sequence-specific conformational strains) (Ji 2000). The resulting *conformon-based* model of the origin of biological information (see Fig. 13.3) was named "the Princetonator" to reflect the facts (1) that it is an example of self-organizing chemical reaction–diffusion systems (as indicated by the suffix, *-ator*) and (2) that it is an extended version of the model of the origin of biological information originally proposed by Anderson and his

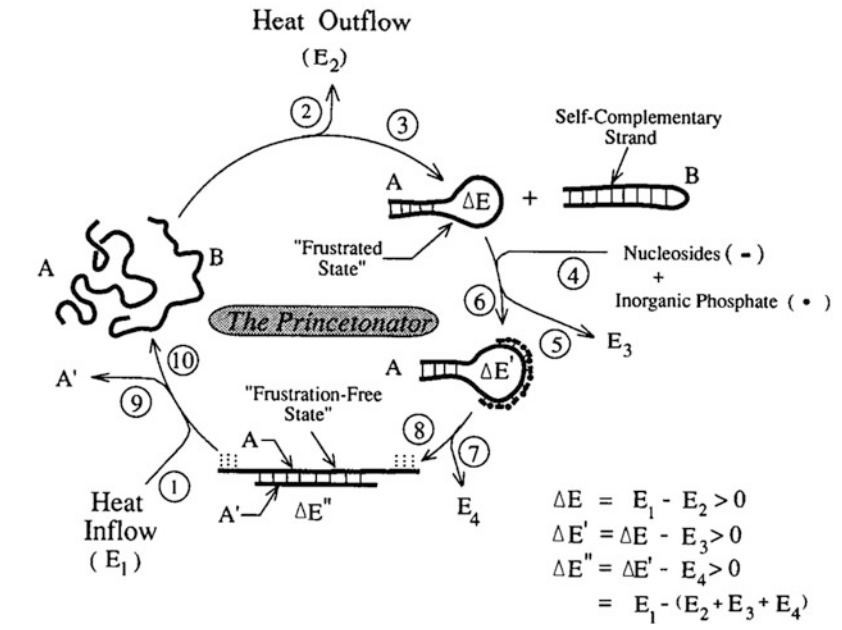


Fig. 13.3 A conformon-based model of the origin of self-replicating molecular systems that is constructed on the basis of the assumption that *frustrations* embedded in RNA carry both *sequence information* and *mechanical energy* and hence are examples (tokens, species) of *conformons* (Ji 2000) (Chap. 8). The key features of this model is that the thermal cycle of the earth's surface produce conformons in primitive RNA templates, which can drive the synthesis of RNA fragments that are complementary to a portion of the templates, the repetition of which leads to a complete replication of some RNA templates but not others. Conformons are equivalent to frustrations entrapped in sequence-specific loci in primordial biopolymers (Reproduced from Ji 1991)

group at Princeton (Fig. 13.2). The *Princetonator* contains the following key postulates (Ji 1991, pp. 224–225):

1. On the surface of the primordial earth about 3.5 billion years ago, there existed a pool (often called the "primordial soup") of at least two short biopolymers, A and B, most likely RNA molecules.
2. Due to thermal cycling (caused by the daily rotation of the earth or other cyclic motions on the earth such as tidal waves), the components of the primordial soup underwent periodic binding (e.g., due to low temperature; see Steps 3, 6, and 8 in Fig. 13.3) and de-binding (e.g., due to high temperature; see Step 10) processes.
3. During the low temperature phase, some biopolymers form a complete intramolecular binding (see B after Step 3) and some others form an incomplete intramolecular binding due to the presence of frustrations (see the bulge in A after Step 3) entrapping a part (ΔE) of the total energy flux, ($E_1 - E_2$), through

the primordial soup. The bulge (i.e., frustration) is located in sequence-specific sites and carries mechanical energy, ΔE, thus qualifying them as conformons (Ji 2000) (Sect. 8.1).
4. The bulge acts as a template for binding a set of monomers (i.e., nucleosides consisting of a ribose ring covalently linked to a base [symbolized as a dot connected to a bar] and inorganic phosphate ions [symbolized as a filled circle]) (Step 6).
5. The binding of the monomers and inorganic phosphate moieties to the bulge is postulated to trigger a conformational transition of the template causing covalent bond formation between nucleosides and adjacent inorganic phosphates to produce a string of nucleotides (see Step 8).
6. During the high temperature phase, the bound RNA fragments dissociate into monomers (see Step 10), producing unchanged B and A with a part of it reproduced (as A′), which has a finite probability of being elongated further through the repetition of the thermal cycling, eventually reproducing the original template A completely.

Pattee (1969) pointed out a set of logical and physical constraints that must be met by any satisfactory theory of the origin of life and biological information:

1. *The primeval ecosystem language* – The global set of geophysical and geochemical constraints of the primeval earth surface that were conducive to the spontaneous generation of self-replicating molecular systems or molecular *switches* (defined below).
2. *Complex molecular interactions leading to a very simple result – Communication* among molecules obey simple rules relative to the complex mechanisms underlying their *interactions*: Communication is in some way a simplification of complex dynamical interactions.
3. *Switches* – Physical devices whose function it is to turn on or off some physical or formal processes driven by energy dissipation. Networks of switches often referred to as "sequential switching machines" or "automata," can duplicate many of the most complex biological processes including human thought itself.
4. *Open-ended evolvability* – Not all self-replicating systems can also evolve. In order for self-replicating systems to evolve in an open-ended manner, special requirements additional to those of self-replication must be satisfied.
5. *Stability* – Of the many possible self-replicating systems that could have evolved spontaneously in the primeval ecosystem, only those with *stability*, *reliability,* and *persistence* survived.
6. The "von Neumann limit" – There exists a critical limit to the complexity of the network of switches which must be exceeded in order to effectuate self-replication. Since such a limit was first recognized by von Neumann, it is here suggested that the indicated limit be referred to as the "von Neumann limit," that is, the minimal level of the complexity (or organization) of the physical systems that are needed for an open-ended evolution.

All of these requirements appear to be satisfied by the combination of the original model of the origin of biological information proposed by Anderson (1983, 1987) and its modified version, the Princetonator (Ji 1991, pp. 224–225), as summarized in Table 13.1.

Table 13.1 The logical and physical requirements for the mechanism of the origin of *molecular messages* as specified by H. Pattee (1969) are met by the combination of the Anderson model of the origin of biological information (Fig. 13.2) and the Princetonator (Fig. 13.3)

Pattee's constraints on mechanisms of the origin of life (Pattee 1969)	Satisfied by	
	Anderson's model	The princetonator
1. Primeval ecosystem	The "RNA soup" on the surface of the earth subjected to thermal cycling	
2. Simple rules		*Conformon* production and utilization
3. Switches		Frustrated regions of RNA harboring *conformons* (see Fig. 13.3)
4. Open-ended evolvability		*Thermally accessible* conformations (called *virtual conformons* (Ji 1991, p. 136)) of RNA fragments that can drive self-replication when reified to real conformons upon coupling to exergonic chemical reactions, obeying the generalized Franck–Condon principle (Ji 1991, pp. 50–56) (Sect. 2.2.3). Due to thermal motions implicated, there is a finite probability of errors occurring during the conformon-driven copolymerization process, thus leading to mutations and open-ended evolution (Pattee 1995)
5. Stability		It is possible that n catalytically active molecular species (CAMS) must be colocalized in a small spatial volume (to be called the catalytic site) to effectuate spontaneous copolymerizations (see the Franck–Condon state defined on p. 433 in Ji 1974a and Fig. 1 in Ji 1979). If the probability of such a colocalization is P and the average probability of individual CAMS being located in the catalytic site is p, the following relation holds: $P = p^n$. This simple power law indicates that the *stability* and the *probability of spontaneous formation* of the self-replicating systems (SRS) increases and decreases, respectively, with increasing n. That is, the larger the value of n, the smaller is the probability P and the greater would be the stability of SRS against its accidental destruction by thermal motions
6. von Neumann limit		The *von Neumann limit* below which no SRSs can evolve may be identified with the exponent n in the relation, $P = p^n$, because n is determined by the balance between two opposing processes, namely, the spontaneous generation of SRSs (whose probability decreases with n) and the stability of SRSs (whose probability increases with n). We may refer to n as the *von Neumann exponent*

What is noteworthy about *the Princetonator* is that it is based on the same molecular entity, the conformon that has been found to account for the mechanisms of energy coupling underlying oxidative phosphorylation (Sect. 11.5), muscle contraction (Sect. 11.4.3), and active transport (Sect. 8.5) and of enzymic catalysis (Sect. 11.3.3). If the Princetonator is valid, it would mean that the same physical entity, the conformon that was thought to be responsible for the origin of life 3.5 billion years ago may be still responsible for the molecular mechanisms underlying life here and now. In the next section, it will be argued that the conformon also plays a crucial role in the evolution of life. These considerations motivate me to suggest the following postulate:

> The conformon not only was responsible for the origin of life 3.5 billion years ago but has also been responsible for the phylogeny and ontogeny of organisms ever since. (13.2)

We may refer to Statement 13.2 as the "Conformon Theory of the Origin of Life, Phylogeny, and Ontogeny (CTOLPO)." Since the origin of life, phylogeny, and ontogeny reflect aspects of life, Statement 13.2 could be alternatively called the "Conformon Theory of Life," which in turn is synonymous with the so-called *Fourth Law of Biology*, Statement 11.45, which simply states that

> Conformons are necessary and sufficient for life. (13.3)

Chapter 14
Principles and Mechanisms of Biological Evolution

The year 2010 marked the 150th anniversary of the historic publication of Darwin's (1809–1882) "Origin of Species" in which he proposed his *theory of evolution by natural selection* (Darwin 1859). Evolution (to be defined below) is a controversial topic (Miller 2008; Carroll 2006) and has been attracting the interest of both scientists and lay public, ranking among the most widely discussed subjects on the Internet (see Table 14.1). For example, *evolution theory* has been visited by more people than *Einstein's relativity theory* as of August 2009 and is comparable to the topic of Obama's cabinet in the number of visitors.

There are two kinds of empirical data that are involved in debates on evolution – macroscopic (or phenomenological) data such as those Darwin collected during his 5-year trip (1831–1836) around the world on the HMS Beagle including the Galapagos Islands, and microscopic (or molecular) data such as those on the role of DNA in genetic inheritance that became available about a century after the publication of Darwin's *macroscopic* theory of evolution. Since fact-based debates on evolution must utilize either one or both of these two kinds of empirical data, we can logically divide all debates on evolution into *four* main classes or categories, depending on the kinds of empirical data that inform the debates (see Table 14.2).

All the debates on evolution before molecular biology began around the mid-twentieth century and belong to what may be referred to as the Type I debates (see the third row in Table 14.2). The *evolution-creation debates* that began in Darwin's days and continue today (see Row 3 in Table 14.1) are mostly between scientists and some Christians and exemplify the Type I evolutionary debates. Macroscopic data on evolution are of such a nature that they may not be able to provide an objective basis for rationally resolving any Type I evolutionary debates. In contrast, new kinds of debates, here called Types II and III, arose as the results of analyzing experimental data on the molecular biology of inheritance that began most notably with the discovery of DNA double helix by Watson and Crick (1953) and the subsequent discovery of the genetic code (see Table 11.11), and these debates are waged among biologists and other scientists and have the potentials of being resolved rationally, unlike Type I debates.

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_14,

Table 14.1 The intense public interest in topics related to biological evolution and its scientific versus religious interpretations as surveyed by Google as of August 5, 2009

Topic	Hits (10^6)
1. Intelligent design debate	21.3
2. Evolution theory	9.16
3. Evolution versus creationism	4.26
4. Darwin's theory	2.04
5. ID versus evolution debate	0.64
6. Origin of life theories	3.65
7. Einstein's relativity	1.11
8. Big Bang theory	10.2
9. Obama's stimulus package	15.3
10. Obama's cabinet	10.4
11. Market economy	70.0
12. Washington DC news	121.0

Table 14.2 Four types of debates on biological evolution

	Based on	
Type	Macroscopic data	Microscopic data
I	+	–
II	–	+
III	+	+
IV	–	–

Type II debates arise when a given set of molecular data obtained from biological experiments can be interpreted in terms of more than one molecular mechanisms, for example, the relative importance of random mutations versus nonrandom recombinations in determining the genotype variations of an organism. A molecular mechanism is defined here as a set of molecular processes that is thought to account for a given empirical observation. Type III evolutionary debates are concerned with the question as to how the macroscopic and microscopic aspects of biological evolution can be bridged. Similar problems of connecting the macroscopic and microscopic events were encountered and successfully resolved in simpler sciences, that is, *physics* and *chemistry,* in the past by introducing major novel concepts (see Rows 1 and 2 in Table 14.3). Similarly, connecting the *macroscopic* Darwinian theory of evolution and the *microscopic* theories of molecular and cell biology may require invoking one or more new concepts as suggested in the last three rows of Table 14.3, which may turn out to be true or may be falsified and replaced by better theories in the future. Finally, for a logical completeness, it is necessary to include Type IV debates on evolution that are based neither on macroscopic (e.g., fossil records) nor microscopic empirical data (e.g., coevolution of DNA sequences among different species) but only on religious beliefs such as those found in the Old and New Testaments of Christianity or in other similar religious writings.

It was about a century ago that newly emerging experimental data forced physicists to abandon *Newtonian mechanics* as a universal theory and replace it with *quantum mechanics* (Plotnitsky 2006). The quantum mechanical revolution in

Table 14.3 The historical development of scientific theories from the macroscopic to the microscopic levels

Field		Theory	
		Macroscopic	Microscopic
1. Physics	(a) Mechanics	Newtonian Mechanics (Newton 1678)	Quantum Mechanics (Bohr et al. 1925)
		Hydrogen Line Spectra (Balmer 1885)	Bohr's Atomic Model (Bohr 1913)
	(b) Thermodynamics	Entropy, $dS = dQ/dT$ (Clausius 1865)	$S = k \ln W$ (Boltzmann 1872–1875)
		Blackbody Radiation (Kirchhoff 1859)	Quantization of Energy (Planck 1900)
2. Chemistry	(c) Periodic Table	Regularities in Chemical Properties (Mendeleev 1869)	Regularities of Atomic Structures (Bohr 1920–1923)
3. Biology	(d) Genetics	Heritable Factor (Mendel 1865)	DNA (Avery et al. 1944; Watson and Crick 1953)
	(e) Enzymology	Ensemble-Averaged Enzymology (Michaelis and Menten 1913)	Single-Molecule Enzymology explained by conformon theory (Lu et al. 1998; Ji 2008b) (Sect. 11.3)
	(f) Muscle Contraction	Sliding Filament Mechanisms (Huxley and Hanson 1960)	Single-Molecule Mechanics based on the conformon theory (Ishijima et al. 1998; Ji 2008b) (Sect. 11.4)
	(g) Cell Biology	The Cell Theory (Schleiden and Schwann 1938) (Swanson 1964)	The Cell as the Smallest Unit of Computation (*the computon*) driven by Conformons and the Cell Language (Ji 1985a, b, 1997a, 2002b) (Sects. 6.1.2 and 10.1)
	(h) Evolutionary Biology	Darwinian Theory of Evolution (Darwin 1859)	The cell theory of evolution (Kirschner and Gerhart 1998, 2005; Ji this chapter)

physics was sparked by seemingly simple experimental data provided by the spectral analyses (i.e., the analysis of the wavelength dependency) of light emitted by heated objects, either solid (as in the case of blackbody radiation) or gases (as in atomic line spectroscopy) (Sect. 11.3.3). The result of this revolution was the establishment of the novel concept that energy is absorbed or emitted by matter in discrete units referred to as *quanta*, later called *photons* or *quons* (see Table 14.3) (Herbert 1987).

The concepts of *energy* and *entropy* are the twin pillars of the science of heat (i.e., *thermodynamics*), the former being governed by the First Law (Sect. 2.1.3) and the latter by the Second Law (Sect. 2.1.4). Although not as spectacular as the quantum revolution that centered primarily on *energy* (see Row a in Table 14.3),

Table 14.4 A comparison between the *macro-to-micro transitions* in *physics* and *biology* that have occurred or are currently in progress in theory building. These transitions can be analyzed in terms of another dichotomy, namely, *energy* versus *information* as shown below

		Energy	Information
Physics	*Macro*	Continuous	Confined to the mental world
	Micro	Discrete (quantization of energy, quantum, quons)	Extended to physical processes (Wolfram 2002; Lloyd 2009; Ji 1999a)
		(1) Energy is quantized (Sect. 11.3.3)	
		(2) Wave/particle duality (Sect. 2.3.1)	
		(3) Heisenberg uncertainty principle (Sect. 2.3.1)	
Biology	*Macro*	Orthogonal to information	Orthogonal to energy
	Micro	Inseparable from information (i.e., fused with *information* to form *gnergy*) (Sect. 2.3.2)	Inseparable from energy (i.e., fused with *energy* to form *gnergy*) (Sect. 2.3.2)
		1. Information-energy complementarity (or gnergy as the complementary union of information and energy) (Sect. 2.3.2)	
		2. Gnergons (i.e., discrete units of gnergy) as the driving force for all self-organizations (Sect. 2.3.2)	
		3. Conformons (gnergons embedded in biopolymers) as the driving force for all goal-directed molecular motions in the cell (Chap. 8)	
		4. The cell as the unit of computation or the *computon* (Sect. 6.1.2)	
		5. The cell is the smallest physical unit that can evolve in the Darwinian sense (Sect. 14.2)	

there was a conceptual revolution of a sort that was centered on *entropy* about a quarter of a century earlier than the quantum revolution (see Row b in Table 14.3): L. Boltzmann (1872–1875) introduced the concept of *statistical weights* (Volkenstein 2009, p. 64) (or its cognates "information," "order," "disorder," etc.) into physics. Prior to Boltzmann, R. Clausius (1822–1888) defined the change in the thermodynamic entropy, S, of a system as the ratio of two macroscopic observables, the heat absorbed by the system reversibly, dQ, and the temperature, T, at which this heat transfer takes place; that is, $dS = dQ/T$. Boltzmann connected the macroscopic entity S (or dS for small change in S) with microscopic entity W, the number of the molecular configurations or states compatible with (or accessible to) the macroscopic state of the system, that is, $S = k \ln W$, where k is the Boltzmann constant.

A *molecular revolution* also occurred in the field of chemistry in the first decades of the twentieth century in the form of the connection established between Mendeleev's periodic table of macroscopic properties of chemical elements and the atomic structures of the elements predicted by quantum mechanics (see Row c in Table 14.3).

Following what may be called the "molecularizing trend," the "molecular turn," or the "from-macroscopic-to-microscopic trend" in natural sciences as evident in Rows a through c in Table 14.3, I perceive a similar *molecular revolution* in biology (see also Table 14.4). In other words, I believe that there are many *macroscopic*

biological phenomena that have been accounted for in terms of their molecular counterparts, or molecular *mechanisms*. If this perception is accurate, what is (are) the novel concept(s) that has (have) enabled the bridging between the *macroscopic* and *microscopic* worlds in biology?

There may be five potential areas of biology that either have already or will have experienced in the coming decades the same kind of molecular revolutions that have transformed physics and chemistry throughout the twentieth century. These areas are (1) *genetics*, (2) *enzymology*, (3) *active mechanical processes* including muscle contraction and active transport, (4) *cell biology*, and (5) *evolution* (see Rows d through h in Table 14.3).

The first *molecular revolution* in biology occurred when Avery et al. (1944) demonstrated that the substance responsible for transmitting a phenotype from one cell to another was DNA, thus identifying Mendel's "heritable factor" with DNA, and when Watson and Crick (1953) discovered the double helical structure of DNA which suggested possible molecular mechanisms for replicating DNA. The second and third molecular revolutions occurred more or less simultaneously in the last decade of the twentieth century when the laser-based single-molecule manipulation techniques were invented and applied to studying single molecules of enzymes (e.g., cholesterol oxidase; see Sect. 11.3) and molecular motors (e.g., actomyosin system; see Sect. 11.4). The novel molecular concept that enabled the bridging of the gap between the traditional ensemble-averaged *enzymology* and *muscle contraction physiology* and their molecular mechanisms is here suggested to be *the conformon* discussed in Chaps. 8 and 11. The fourth molecular revolution in biology may be identified with the bridging of the phenomenological cell theory first formulated by Schleiden and Schwann in 1938 (Swanson 1964) and the modern molecular cell biology based on the concepts of the conformon described in Chaps. 8 and 11 and intracellular dissipative structures (IDSs, or more briefly *dissipatons*) discussed in Sect. 3.1. In addition to *conformons* and *IDSs*, a third novel element was introduced to biology at the cell level, namely, the *cell language theory* presented in Sect. 6.1 (see Row h in Table 14.3), the cell language being essential for the cell's role as the smallest unit of molecular computing in nature (Ji 1999a, 2002b). The fifth and final molecular revolution in biology may be identified with the realization that

> The unit of biological evolution is the living cell itself. Hence, without understanding the workings of the cell, it is impossible to understand the molecular mechanisms underlying biological evolution. (14.1)

Statement 14.1 will be referred to as the *Cell Theory of Evolution* (see Row h in Table 14.3), which is described in Sects. 14.2, 14.3, 14.4, and 14.5 as a possible *microscopic theory of evolution* that can account for or subsume the *macroscopic theory of evolution* proposed by Darwin in 1859, just as *quantum mechanics* formulated in the early decades of the twentieth century accounts for or subsumes the *Newtonian (or classical) mechanics* of the late seventeenth century (see Row a in Table 14.3). Statement 14.1 is consistent with the so-called *Principle of the Evolution-Development Complementarity* discussed below (see Statement 14.7).

Table 14.5 A summary of the consequences of the *macro-to-micro transitions* in physics and chemistry

	A	B	C	X
Physics (spacetime)	Space	Time	*Speed* of moving objects	$\sim 10^{10}$ cm/s
Biology (gnergy, or information-energy complementarity) (Sect. 2.3.1)	Information	Energy	*Mass* of machines	$10^3 \sim 10^{15}$ atoms[a]

[a] These numbers were estimated on the basis of the assumption that gnergy in the form of conformons (Chap. 8) and IDSs (Chap. 9) drive molecular machines (10^{-9} m in diameter as compared to the diameter of the hydrogen atom, 10^{-10} m) and cells (10^{-5} m in diameter), respectively

One possible difference between the macro- to microtransitions in physics and biology (Table 14.4) may be as follows:

> Just as *space* and *time* are separable for objects moving with speeds slow relative to the speed of light and fuse for objects moving with speeds approaching that of light, so *information* and *energy* are separable for macroscopic machines but become Inseparable and fuse into gnergy for molecular machines. (14.2)

Statement 14.2 may be referred to as the *symmetry principle of physics and biology* in the sense that the parameter-dependent relational transition specified by 14.3 and 14.4 remains *invariant* when physics is replaced by biology (see Table 14.5). We may represent this idea symbolically thus:

$$\mathbf{A} \llcorner \mathbf{B} \text{ when } \mathbf{C} << \mathbf{X} \tag{14.3}$$

$$\mathbf{A}^{\wedge}\mathbf{B} \text{ when } \mathbf{C} \sim \mathbf{X} \tag{14.4}$$

where A and B are two physical entities whose *relation* undergoes a transition (from $\llcorner$ to ^, or vice versa) when the numerical value of the parameter C approaches the critical threshold X, and the symbols, $\llcorner$ and ^, denote the *orthogonality* and the *complementarity*, respectively. (For the definition of the *complementary relation*, see Sect. 2.3.1.) If the *physics-biology symmetry principle* proposed in Table 14.5 turns out to be valid, biology may be endowed with the concept of *gnergy*, the complementary union of information and energy (Sect. 2.3.1), that is comparable to the concept of *spacetime* in physics.

14.1 Darwin's Theory of Evolution

Darwin's theory of evolution is a *macroscopic* theory formulated one and a half centuries ago in order to account for the then available *macroscopic* data about organisms (see Row h in Table 14.3) (Darwin 1859). Consequently, the key elements of Darwin's theory (see below) may be remote from, and shed little

light on, the microscopic (i.e., molecular) data on organisms that have been accumulating in biology over the past one and a half centuries. Just as Newtonian mechanics failed to account for microscopic observations (e.g., blackbody radiation, atomic line spectra, the photoelectric effect), so it would not be surprising if Darwin's theory of evolution will be found inadequate to account for certain molecular data on living systems (e.g., the role of DNA in inheritance and morphogenesis, the genetic codes, signal transduction cascades, the cell cycle, cell differentiation, genetic drift, etc.). This is why it is absolutely essential that a microscopic theory of evolution be constructed that can not only account for molecular data on living systems but also subsume the Darwinian theory of evolution, just as quantum mechanics subsumed Newtonian mechanics.

As pointed out by Mayr (1991), Darwin's theory of evolution is not a single theory but a system of at least four theories:

1. Organisms are not permanent but change in time.
2. Species multiply by branching into daughter species or by forming founder populations that evolve into new species.
3. Evolutionary changes occur gradually and not by the sudden production of new individuals belonging to a new species.
4. Evolution occurs through (a) variation of heritable traits and (b) selective survival of individuals adapted to their environment.

It is probably safe to assume that Items (1) and (2) have been confirmed by empirical data. Some evolutionary biologists may dispute the validity of Item (3) based on the theory of punctuated equilibrium (Eldredge and Gould 1972). Applying the generalized Franck–Condon principle (Sect. 2.2.3) to evolution, it can be predicted that phylogenesis (i.e., the evolutionary development of groups of organisms) will be rate-limited by the speed of geological changes (Ji 1991), which would be consistent with the idea of punctuated equilibria. Item (4) may also be viewed as confirmed by empirical data, although the microscopic mechanisms underlying the variation of heritable traits are still unknown.

Darwin's theory of evolution was constructed in the absence of any knowledge about (1) how variations of individual characteristics arose and (2) how these characteristics were transmitted from one generation to the next. The so-called *Modern Evolutionary Synthesis* (Mayr 1991) was formulated between the mid-1930s and the mid-1940s to fill these lacunae by invoking (1) *random mutations* as the source of genetic variations and (2) the *Mendelian genetics* as the mechanism of inheritance.

As already pointed out, Darwin's theory of evolution is a *macroscopic* theory (and to a large extent this is also the case with the Modern Evolutionary Synthesis) that was formulated at least a century before the full-fledged science of molecular biology was born with the discovery of DNA as the key molecule of inheritance, as succinctly summarized by Zimmer (2009):

> . . . While Darwin recognized that variation and heredity were the twin engines that made evolution possible, he did not know what made them possible. It would take almost a century after the publication of On the Origin of Species for biologists to determine that the answer was DNA . . . (14.5)

Unlike the impression created by Statement 14.5, DNA is not the whole solution to the problems of evolution but only a part of the solution. According to the so-called *Kirschner-Gerhart thesis*, Statement 14.6 given in Sect. 14.2, the complete solution to the evolutionary problems may lie in our understanding *how the living cell works*.

14.2 The *Cell Theory of Evolution*

There is no doubt that *evolution* results from complex interactions between organisms and their environment over the geological time scale. Evolution implicates a system of complex interactions that may be schematically represented as in Fig. 14.1.

If Fig. 14.1 is valid, the evolving phenotype (i.e., evolution) is a function of three variables that are irreducible.–

1. The genotype at time n that varies among different individuals of a group.
2. Environmental conditions that change from n to (n + 1) with speeds much slower than the lifetime of individual organisms, and
3. Mechanisms of interactions between individual organisms and their environment constrained by developmental mechanisms. That is, organisms are postulated to be genetically endowed with the capacity to survive only within a fixed range of environmental conditions and die otherwise.

Variables (1) and (3) are determined by *cell biology* and variable (2) by *geology*. The scheme shown in Fig. 14.1 may thus be viewed as a diagrammatic representation of the *cell biology of evolution* that seems consistent with the prediction made by M. Kirschner and J. Gerhart (1997):

> . . . with the explosion in molecular biology, cell biology could assert itself in evolutionary thought and allow a reinterpretation of evolution as a cellular process. (14.6)

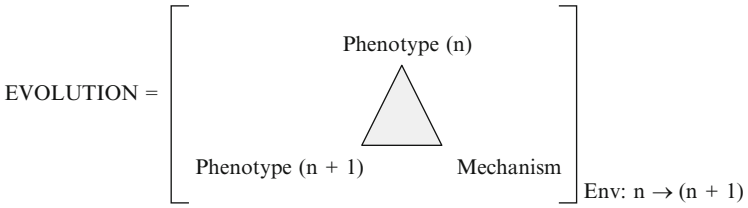


Fig. 14.1 A diagrammatic representation of the biological evolution. Evolution is viewed as the emergence of cell phenotype (n + 1) from cell phenotype (n) as the result of the interaction between the cell (symbolized by the *triangle*) and the environment as Environment (n) changes to Environment (n + 1) (Notice that this diagram is similar to [or isomorphic with] the diagram defining "function" in Fig. 6.9, suggesting that what evolves is function, not just structures or processes)

For future reference, we will refer to Statement 14.6 as the *Kirschner-Gerhart thesis*. Evidently, the *Cell Theory of Evolution* (see Row h in Table 14.3) is consistent with the Kirschner-Gerhart thesis.

The four key concepts involved in evolutionary discourse, namely, *genotype*, *phenotype*, the *culling (or selective) influence of environment*, and *developmental mechanisms* (as in EvoDevo discussions [West-Eberhard 1998, 2003; Carroll 2006]), have been organized in Fig. 14.1 using the same *triadic template* that has been used to define Peircean *signs* (Fig. 6.2), *functions* (Fig. 6.9), *genes* (Fig. 11.5), and *dissipative structures* or *dissipatons* (Fig. 3.3). The fact that the same *triadic template* applies to so many fundamental entities in biology increases our confidence that there is something universal about the *diagram* used in Fig. 14.1 and elsewhere, justifying the naming of it as the *Peircean triadic template* or the *Peircean triadic network*.

Evolution and *development* both can be viewed as natural consequences of the interactions between *cells* and their *environment*. Evolution involves environmental changes that are much slower (by a factor of 10^2 or more?) than the environmental changes involved in development of an organism. Thus we can distinguish between two time scales – *synchronic* and *diachronic* – borrowing these terms from linguistics (see Sect. 4.5 for a related discussion). *Synchronic* events are those events that occur on the same *time scale* as the life span of organisms (usually less than about 10^2 years for the human-centric point of view) and *diachronic* events are those events that take place on the *diachronic time scale* on the order of geological times (greater than 10^2 years). Using these terms, it may be asserted that

> Evolution and development are different manifestations of the same cell-environment interactions occurring at two distinct time scales – *diachronic* and *synchronic*. (14.7)

If these speculations are valid in principle, the solutions to the fundamental problems in *evolution* and *development* may be intimately linked so that they can be achieved simultaneously or appear in synchrony. Since *diachronicity* and *synchronicity* can be viewed as representing the complementary aspects of time, we may refer to Statement 14.7 as the *Principle of the Evolution-Development Complementarity (PEDC)*.

According to the Law of Requisite Variety (LRV) (Sect. 5.3.2) (Heylighen and Joslyn 2001; Ji 1991, p. 221), no simple machines can perform complex tasks. Applying this law to cell biology, it was concluded in Sect. 5.2.3 (see Statement 5.10) that

> No simple cells can survive complex environment. (14.8)

Due to the Second Law of thermodynamics (*The entropy of the Universe increases with time*) (Sect. 2.1.4), it is inevitable that

> The natural environment of living systems become more complex with time on the geological time scale. (14.9)

Unlike human-made machines whose complexity is *passive* (i.e., remain constant unless altered by external forces), the complexity of organisms appears to be

active in the sense that organisms expend free energy to actively *complexify* their internal states (e.g., basal metabolic rates of cells being greater than the minimum levels needed for survival under given environmental conditions, EEG waves in resting brains), which must have been the consequence of biological evolution, leading to the following two equivalent statements:

> The biological evolution results from the greater probability of survival of those organisms that are capable of actively complexifying their internal states. (14.10)

> Organisms that are capable of actively complexifying their internal states have the greater probability of surviving complex environment. (14.11)

Underlying Statements 14.10 and 14.11 are the basic assumptions that there are two kinds of complexities in nature (Sect. 5.2.3), namely, "passive complexity" that does not require any expenditure of free energy to be maintained (e.g., random molecular motions in a volume of gas at equilibrium, the nucleotide sequences of DNA in dead cells, random mutations) and "active complexity," the complexity that disappears when free energy supply is blocked (e.g., *facilitated variations* of Kirschner and Gerhart (2005), the diversity of nucleotide sequences of DNA resulting from *recombination* in living cells). Just as active transport at the microscopic level is a unique biological phenomenon, not observed in nonliving systems, so *active complexity* at the molecular level may be unique to living systems, not observable in nonliving systems which can exhibit only *passive complexity*. I maintain that most, if not all, of the discussions on complexity in computer science and physics is about *passive complexity*, ignoring *active complexity*, just as physicists focused on studying passive transport (e.g., diffusion of gases and molecules) before *active transport* was discovered in living systems. An evidence for active complexity may be provided by the so-called Huynen–van Nimwegen exponent in Eq. 14.31 discussed in Sect. 14.7.

Combining Statements 14.9, 14.10, and 14.11 allows us to assert the following relation:

$$\text{SLT} + \text{LRV} + \text{ACSRS} = \text{Biological Evolution} \tag{14.12}$$

where SLT stands for the *Second Law of Thermodynamics* (Sect. 2.1.4); LRV stands for the *Law of Requisite Variety* (Sect. 5.3.2); and ACSRS is the acronym for *Actively Complexifying Self-Reproducing Systems* exemplified by the living cell theoretically represented by the Bhopalator (Sect. 10.1). In a certain sense, Eq. 14.12 can be said to embody two "selection rules" and a connector: SLT represents what may be referred to as the "external selection rule" or the "external filter" that is imposed on organisms from outside, ACSRS as the "internal selection rule" or the "internal filter" that allows only those organisms to develop that obey the genetic instructions encoded in DNA, and LRV that acts as the connector between the external world and the internal world of organisms. Stated in words, Eq. 14.12 asserts that:

> The Second Law of Thermodynamics and the Law of Requisite Variety are the necessary and sufficient conditions for actively complexifying self-reproducing systems to evolve. (14.13)

Alternatively,

Biological evolution is the natural consequence of the existence of actively complexifying self-reproducing systems (ACSRS) on this planet that obey the Second Law of Thermodynamics and the Law of Requisite Variety. (14.14)

For convenience, we may refer to Statements 14.13 and 14.14 as the *Cell Theory of Evolution (CTE)*. If proven correct, these statements may qualify to be referred to as the *Principle of Biological Evolution* (PBE). It should be pointed out that Statements 14.13 and 14.14 may be unique among the currently available theories of biological evolution in that it, for the first time, introduces not only *LRV* but also the concepts of *active complexification (AC)* and the physical agent implementing AC, that is, actively complexifying self-reproducing systems (ACSRS), as necessary conditions for biological evolution, in addition to the *Second Law*, which has often been claimed to be the sole driving force for biological evolution by some biologists including Brooks and Wiley (1986).

14.3 The Principle of Maximum Complexity

The concepts of *active* and *passive complexities* were introduced in Sect. 14.2 in analogy to *active* and *passive transports* in cell biology. The *complexity* of a system can be defined simply as the number of bits required to describe the system. The description of a system entails characterizing (1) the *boundary conditions* of the system, and (2) the position and motions of the system components as functions of time that are determined by (or obey) the laws of physics and chemistry. In most cases, the boundary conditions of living systems are *dynamic*, which in general requires more bits to describe and hence more complex than if they were *static*.

The dichotomy of *active* and *passive* complexities is related to two other dichotomies (see Rows 1, 2, and 3 in Table 14.6) – (1) the dichotomy of *dissipative* and *equilibrium* structures of Prigogine (1977, 1980) (Sect. 3.1) and (2) the dichotomy of *open* and *isolated* thermodynamic systems.

Table 14.6 The dichotomy of the *local* and *global* perspectives in thermodynamics

	Perspective	
	Local (*synchronic*)	Global (*diachronic*)
1. *Information*	*Active complexity*	*Passive complexity*
2. *Energy*	Dissipative structures (*dissipatons*)	Equilibrium structures (*equilibrons*)
3. *System*	Open	Isolated
4. *Environment*	Obeys the law of maximum entropy	Impermeable to energy and matter
5. *Laws*	"The law of maximum complexity" (LMC)[a]	The law of maximum entropy (LME)

[a] This law states that

The active complexity of living systems increases toward a maximum. (14.15)

According to the Second Law of thermodynamics, the entropy of an isolated system increases toward a maximum (Sect. 2.1.4) as indicated in Row 5 above. Analogously, some open systems such as organisms that are endowed with the abilities (1) to self-reproduce and (2) to increase their complexity actively may exhibit the tendency to increase their complexity from one generation to the next (i.e., on a phylogenetic time scale), obeying what is here referred to as the *Law of Maximum Complexity* (LMC) (see Row 5, Table 14.6). Thus defined, LMC is a law that is applicable to living systems (as both individuals and groups) and seems to capture the essential characteristics of living systems which may be identified with what Kirschner and Gerhart (1998) refer to as the *evolvability* of life.

The Law of Maximum Complexity (LMC), or alternatively the *Maximum Complexity Principle* (MCP) (in analogy to the *Maximum Entropy Principle*, another name for the Second Law), may be logically derived from the Second Law of Thermodynamics (SLT) (Sect. 2.1.4) and the Law of Requisite Variety (LRV) (Sect. 5.3.2), if we can assume that

1. The environment of living systems embody "passive complexity" which increases with time as the result of the operation of SLT (equivalent to Statement 14.9.
2. Living systems embody "active complexity" which is kept at least as complex as that of their environment in order to maintain the homeostasis of self-replication (equivalent to Statements 14.10 and 14.11).

We can represent this derivation in the form of a syllogism:

1. **SLT**: The passive complexity of the environment of living systems increases with time.
2. **LRV:** Living systems must increase their complexity actively to keep up with the increasing environmental complexity in order to maintain self-replication.
3. **LMC:** Therefore, the active complexity of living systems must increase with time in order for them to survive. Or algebraically thus:

$$\mathbf{LMC} = \mathbf{LRV} + \mathbf{SLT} \tag{14.16}$$

If this syllogism is true, it may be concluded that LMC represents another version of the principle of biological evolution (PBE) and hence is closely related to or is an alternative expression of Statements 14.13 and 14.14.

14.4 Evolution as a Triadic Relation

I think *evolution* and *emergence* are closely related. Emergence may be defined simply as the appearance (over varying time scales) of the observable C from the interaction between at least two material entities, say, A and B, none of which can exhibit C individually, because C results from a unique mechanism, M, of interactions between A and B:

$$\mathrm{A} + \mathrm{B} \xrightarrow{\mathrm{M}} \mathrm{C} \tag{14.17}$$

In Fig. 2.8, M has been referred to as "renormalization," namely, the regrouping of material entities to form a new entity that exhibits properties not possessed by its precursors. The process of emergence, 14.16, appears to be repeated in nature (or occurs recursively) at least at eight distinct levels as shown in Table 14.7.

The content of Table 14.7 evidently reveals qualitative symmetry. It is suggested that Table 14.7 is symmetric with respect to Process 14.16 in the sense that Process 14.16 remains *invariant* when applied to various fields, from physics to chemistry to biology to sociology to cosmology. If we can apply Noether's theorem (Agarwal 1977; Ramond 1981; Ryder 1985) (according to which a symmetry of mathematical equations embodying physical theories always implies the existence of a *conserved quantity*) to the apparent symmetry revealed in Table 14.7, it may be concluded that there exists a *conserved quantity* whose identity is unknown. What can it be? One possibility is that this conserved quantity is *Gnergy*, the complementary union of *information* and *energy* that has been postulated to underlie all self-organizing processes in the Universe (Ji 1991, 2004b) (Sect. 2.3.2), including what may have preceded the Big Bang such as the "pre-Bing Bang" activity predicted by Gurzadyan and Penrose (2010). If this conjecture turns out to be true, Gnergy may be considered to represent the *ultimate symmetry* of our Universe perhaps subsuming the supersymmetry that unifies fermions and bosons (Han 1999).

The term "emergence" is more widely used in physics (especially in condensed matter physics and statistical mechanics) than in biology, while the use of the term "evolution" is almost exclusively confined to biology (except perhaps in the Big Bang cosmology). One prominent example of a mutually antagonistic use of these two terms is provided by R. Laughlin's statement quoted below from his book, *A Different Universe: Reinventing Physics from the Bottom Down* (Laughlin 2005). He accepts *emergence* but rejects all *evolutionary explanations* in biology:

> . . ., I think a good case can be made that science has now moved from an Age of Reductionism to an Age of Emergence, a time when the search for ultimate causes of things shifts from the behavior of parts to the behavior of the collective . . .. The transition to the Age of Emergence brings to an end the myth of the absolute power of mathematics . . . (pp. 208–209)

> Evolution by natural selection, . . . , which Charles Darwin originally conceived as a great theory, has lately come to function more as an antitheory, called upon to cover up embarrassing experimental shortcomings and legitimize findings that are at best questionable and at worst not even wrong. Your protein defies the laws of mass action? Evolution did it! Your complicated mess of chemical reactions turn into chicken? Evolution! The human brain works on logical principles no computer can emulate? Evolution is the cause! . . . (pp. 168–169)

Emergence and *evolution* may not be as alien to each other as have been depicted above. On the contrary, they may be inseparably connected to each other in a complex manner as indicated in Statement 14.17:

> Evolution is synonymous with Property X emerging from Precursor Y through Mechanism Z. (14.18)

Statement 14.17 can be represented diagrammatically as shown in Fig. 14.2, utilizing, again, the Peircean triadic template that appears in Fig. 14.1 (see also Sect. 6.2.11).

Table 14.7 A "periodic table" of emergence. The crudely estimated half-time of the emergence at each level is indicated in the parentheses in the unit of seconds. What is periodically and recursively occurring in this table is Process 14.16

Field (time scale)	C	A	B	M
1. Physics ($\sim 10^{-12}$ s)	Rigidity superconductivity superfluidity (Anderson 1972)	Atoms	Atoms	Coupled motions of atoms
2. Chemistry ($\sim 10^{-6}$ s)	Spontaneous reorganization of atoms in molecules (e.g., formation of H_2O)	H_2	O_2	Electronic rearrangements via molecular collisions or absorption of photons
3. Enzymology (~1 s)	Environmentally selected reorganization of atoms in molecules (e.g., selection of L- isomers from a mixture of L- and D-optical isomers)	Molecule	Molecule	Electronic rearrangements within active sites of biopolymers
4. Cell biology ($\sim 10^{2}$ s)	Organized motions of groups of molecules and ions (e.g., chemotaxis, mitosis, cell cycle, release of autoinducers)	Molecules and ions	Molecules and ions	Cell-controlled organization of intracellular physicochemical interactions (i.e., interactomes)
5. Developmental Biology ($\sim 10^{6}$ s)	Organized motions of cells (e.g., quorum sensing, ontogeny)	Cells	Cells	Cell–cell communication using the cell language
6. Sociology ($\sim 10^{10}$ s)	Organized motions of organisms (e.g., ant nest building, social network formation on the Internet)	Organisms	Organisms	Organism–organism communication using symbolic languages
7. Evolutionary Biology ($\sim 10^{13}$ s)	Emergence of new phenotypes (see Fig. 14.1)	Organisms	Environment	Variations of individuals, reproduction through social interactions, and natural selection via social and environmental interactions
8. Cosmology ($\sim 10^{15}$ s)	Organized motions of particles, planets, stars, galaxies, clusters, superclusters (e.g., hydrogen atoms, hydrogen molecules, Moon, Earth, the sun, the solar system, the Milky Way Galaxy)	Particles	Particles	Interactions among particles mediated by the gravitational, electroweak, and strong forces under the guidance of cosmological symmetry principles such as the recently suggested gnergy tetrahedron (Ji 2004b)

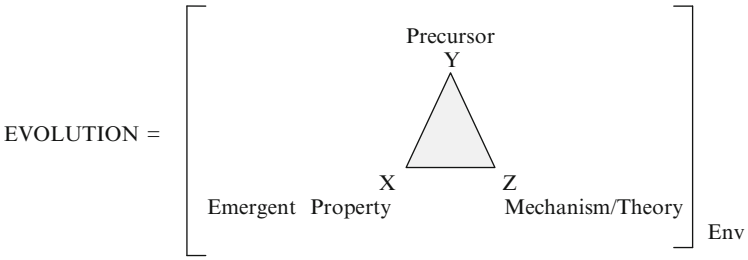


Fig. 14.2 A triadic definition of evolution. It is suggested here that Y is related to Firstness, X to Secondness, and Z to Thirdness in the triadic metaphysics of C. S. Peirce (1839–1914) (Sect. 6.2). This figure is qualitatively similar to Fig. 14.1

Table 14.8 Evolution as a triadic relation *type* with its *tokens* in physics, biology, and the spiritual world. The symbols X, Y, and Z are defined in Statement 14.17 and Fig. 14.2

	Evolution		
Levels	Property X	Precursor Y	Mechanism Z
Physics	Rigidity	Hadrons	Expanding universe
	Superconductivity	Leptons	
	Superfluidity	Bosons ("equilibrons")	
Biology	Self-reproduction	Ions	Thermal cycling caused by the revolution of the earth
	Adaptability	Molecules ("equilibrons")	
	Differentiation	Chemical reactions ("dissipatons")	
Religion	Self-control	Cells	Social interactions through the ages (?)
	Self-sacrifice	Brains	
	Belief in truth, good, and beauty	Social groups ("Nouons")	

It should be noted that *Evolution* is represented by the whole triangle (see the square brackets) and *Emergence* by one of its three edges, that is, Y-X. As indicated in Table 14.8 below, physical evolution differs from biological one because their mechanisms of evolution are different – one is cosmological in spatiotemporal scale and the other is local, that is, earth- and biosphere-bound.

Laughlin's treatment of the concept of *evolution* in the above quotations appears to go against the mainstream view of contemporary biologists (Salthe 2009). Theodosius Dobzhansky (1900–1975) (1973) has remarked that

> Nothing in biology makes sense except in the light of evolution. (14.19)

To a physical-organic-chemist-turned theoretical cell biologist who has spent more than three decades studying living systems, Statement 14.18 rings true. More recently, Fodor and Piatelli-Palmarini (2010, p. 30) expressed what they thought was the opposite of Statement 14.18:

> . . . nothing in evolution makes sense except in the light of developmental biology. (14.20)

According to the Principle of the Evolution-Development Complementarity, Statement 14.7, these seemingly opposite views of Dobzhansky and Fordor and Piatelli-Palmarini may reflect the complementary aspects of life.

Laughlin might have come to disbelieve in the relevance of evolutionary explanations for living structures and processes perhaps because to him evolution is a phenomenon secondary to emergence: that is, all that is needed to understand life is the concept of *emergence*, just as all collective properties of condensed matter physics can be so accounted for (see Row 1 in Table 14.8), although, as he admits, they cannot (yet) be derived mathematically from the basic laws of physics. In contrast to such a view, we can as equally well justify the claim that "emergence" and "evolution" are intimately linked as indicated in Fig. 14.2, not only in biology but also in physics. In other words, it may be legitimately asserted that collective properties of matter such as superconductivity and superfluidity *emerge* from a large amount of matter through *cosmological evolution* just as life has *emerged* from a large number of material components through *biological evolution*. (Superconductivity and superfluidity may be unique to our Galaxy, just as life may be unique to the Earth among many similar planets in the Universe.) It seems thus reasonable to conclude that "emergence" is impossible without "evolution," since "evolution" provides the mechanism of "emergence," or equivalently, that "emergence" can be viewed as a consequence of "evolution."

Evolution is here understood as a complex system of physicochemical processes involving both *variations* of the properties of the evolving system and the *selection* of systems by their environment solely based on system's characteristics. A corollary of the above assertion would be that, if evolution is regarded as an *antitheory* (defined by Laughlin as ideological thinking that leads to "the explanation that has no implications and cannot be tested" (Laughlin 2005, p. 168), so necessarily would emergence be an antitheory. That is, there seems to be no difference between physicists explaining the collective properties of condensed matter in terms of "emergence" and biologists explaining living processes in terms of the concept of "evolution." Both (*tokens*) may belong to the same *type* of logical reasoning.

As already mentioned, it is possible that evolution is a general phenomenon in our Universe and as such applies not only to physics and biology but also to the mental and spiritual worlds, as indicated in the last row of Table 14.8.

Table 14.8 incorporates the idea of I. Prigogine (1917–2003) that there are two (and only two) types of structures in the physical universe – "equilibrium structures" (or *equilibrons*) and "dissipative structures" (or *dissipatons*) (see Sect. 3.1). These two entities are postulated to serve the role of Precursor Y for Property X in physical and biological evolutions. The 3×3 symmetry of the table entailed coining a new term to label the Precursor Y for Property X in the spiritual/mental evolution (see the last row). "Nouons" (from Greek "nous" meaning mind) is recommended for the precursor of the mental and spiritual qualities. *It is here assumed that, when a large number of independent minds work together and cooperate, a new human phenomenon emerges which can be identified with the mental and the spiritual.*

Salthe (1993, 1996) advanced the following definitions (reflecting current usage in biology): (1) development = predictable directional change and

(2) evolution = irreversible accumulation of historically mediated information. Probably the most fundamental difference between *physical* and *biological* evolutions (in the sense defined in Table 14.8) is that the former does not but the latter absolutely depends on *self-replication*. Since the physical Universe can evolve without self-replication while biological systems cannot develop nor evolve without cellular self-replication, the following generalization may hold:

Self-replication is necessary for development but not for evolution. (14.21)

Several corollaries of Statement 14.20 can be formulated:

Physical systems can evolve but not develop; Biological systems can both develop and evolve because they can self-replicate. (14.22)

Self-replication is the complementary union of development and evolution. (14.23)

Self-replication of individual organisms in synchronic time leads to development: Self-replication of groups of organisms in diachronic time leads to evolution. (14.24)

There are two kinds of *emergence* in biology – *ontogeny* (development) and *phylogeny* (evolution). The difference between *ontogeny* and *phylogeny* is that the former involves individual organisms developing within their life spans (or on the "synchronic" timescale) while the latter involves groups of organisms that evolve on the "diachronic" timescale (Sect. 4.5), which is much slower than the synchronic timescale. In other words,

What develops is individual organisms over a synchronic timescale; what evolves is groups of organisms over a diachronic time scale. (14.25)

Statement 14.24 is equivalent to Statement 14.23 and can be viewed as defining the meanings of "synchronic" and "diachronic" times (or time scales) in terms of the well-established difference between *development* and *evolution* in biology. Statement 14.24 is in turn equivalent to the following statement:

Synchronic time is developmental, i.e., finite and cyclical; diachronic time is evolutionary, i.e., infinite and unidirectional. (14.26)

It is possible to represent Statement 14.23 diagrammatically as shown in Fig. 14.3. The main points of Fig. 14.3 can be summarized as follows:

1. The *synchronic time* (or developmental time) and *diachronic time* (or evolutionary time) are orthogonal/complementary in the sense that focusing on (or prescinding) one automatically excludes the other from view.
2. The *synchronic time* and *diachronic time* axes define a space (to be referred to as the *self-replicator space* or the *EvoDevo space*) in which every point represents a self-replicator or the living cell, the material system capable of both *development* and *evolution,* and clusters of points represent taxons, clades, or species of organisms.
3. The time in EvoDevo space (to be referred to as the *biological time*, in contrast to the physical or Newtonian time) is two-dimensional consisting of the *synchronic* and *diachronic* axes that are orthogonal. The biological time can be depicted as a spiral motion consisting of a series of coupled cyclical (as indicated by the curved red arrow) and translational (as indicated by the straight red arrow) motions as represented by a series of gray disks.

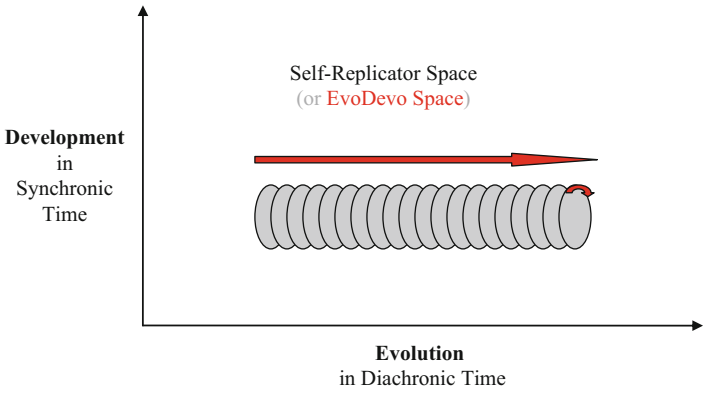


Fig. 14.3 A diagrammatic representation of the orthogonalities 1) between *development* and *evolution* on the one hand and (2) between *synchronic* and *diachronic* times on the other. The series of the *gray* disks symbolizes a spiral motion (see the *curved red arrow*) advancing from *left* to *right* consisting of (1) the *cyclical motions* in the plane of each disk which is orthogonal to the *x*-axis and parallel to the *y*-axis, and (2) the *translational motion* of the disk along the *x*-axis. When viewed at low resolution, the spiral appears as the arrow of time (see the *straight red arrow*). Each circular disk, therefore, may be thought of as the "atom of evolutionary time (AET)." See text

4. The *EvoDevo space* may be analogous to the *phase space* in physics (consisting of the position axis and the momentum axis that are orthogonal). Just as each point in the phase space represents the state of a system of many particles and the evolution of such a system is depicted as a bundle of line trajectories, each point in the EvoDevo space represents an organism, clusters of points represent groups of organisms, bundles of line trajectories represent the development of organisms (groups, taxons, clades), and bifurcating bundles of line trajectories represent the tree of life.
5. Just as the phase space is essential for *statistical mechanics* in physics, so the EvoDevo space may be essential for *infostatistical mechanics* (defined in Sect. 4.9) that accounts for living structures and processes, that is, life.

An interesting analogy may be drawn between the *evolutionary debate* between anti-Darwinians (favoring the *variation generation* as the cause of evolution) and *neo-Darwinians* (claiming the *natural selection* as the evolutionary cause) on the one hand and the controversy, on the other hand, about interpreting DNA microarray data based on the *transcriptional control* or on both the *transcriptional/transcript-degradation controls* Ji et al. 2009a). It is well established that RNA levels measured with DNA microarrays are determined by two opposing processes – "transcription" and "transcript degradation" (Figs. 12.5 and 12.27) (Sect. 12.8), which can be schematically depicted as in Fig. 14.4.

Before Perez-Ortin and his group in Valencia (Garcia-Martinez et al. 2004) and others measured both *RNA levels* (or *transcript levels*, TL) and *transcription rates* (TR) simultaneously in budding yeast (see Fig. 12.6), most experimenters utilizing microarrays assumed that RNA levels were determined by transcription rates alone

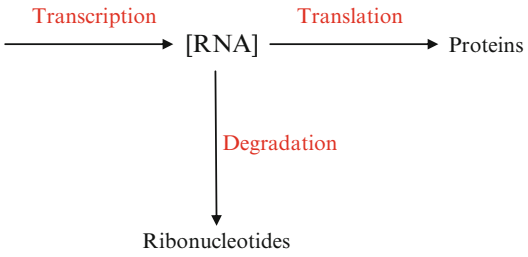


Fig. 14.4 The intracellular RNA levels denoted as [RNA] controlled by *transcription* and *transcript degradation*

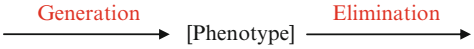


Fig. 14.5 Evolution of novel phenotypes as a dynamic balance between *phenotype generation* and *phenotype elimination*

(i.e., assumed the *transcriptional control stance*), so that whenever RNA levels rose, it was interpreted as an indication that the corresponding transcription rate increased. But the Garcia-Mainez et al. (2004) data clearly demonstrate that there is no such one-to-one correlation between RNA levels and transcription rates as evident in Fig. 12.6, leading to the conclusion that the transcript-degradational control must play an important role. The debate between *neo-Darwinains* and *anti-Darwinians* may be analyzed in a similar way:

1. New phenotypes emerge as a result of the balance between two opposing processes – "phenotype generation" and "phenotype elimination":
2. Phenotypic variations can result from either *genotypic variations* (i.e., involving DNA sequence changes) or *epigenetic mechanisms* (i.e., without involving any DNA sequence changes).
3. Genotypic changes can be caused by *random mutations*, *recombinations*, *horizontal gene transfers,* or *self-organized variational mechanisms* (as a part of *active complexification processes* postulated to be inherent in the living cell (see Sect. 14.2).

Any successful theory of evolution that can replace neo-Darwinian mechanism of evolution must take into account both *variation generation* and *elimination* as well as all the complex mechanisms indicated in (2) and (3) above. Neo-Darwinians seem to ignore the *generative process*. On the other hand, anti-Darwinians may be ignoring the importance of *selection* (or *elimination*). If the scheme presented in Fig. 14.5 is correct, both *variation generation* and *natural selection* (i.e., elimination) would be important in evolution, just as the *transcription* and *transcript-degradation* steps are equally important in determining RNA levels in cells (Ji et al. 2000a).

14.5 The Gnergy Principle and Biological Evolution

During the past several decades, many biologists have been suggesting that the Second Law is the driving force for the biological evolution. Some even asserted "Evolution as Entropy" (Brooks and Wiley 1986). It is agreed that the Second Law is a necessary condition for life, but it is obviously not a sufficient one, since thermodynamic forces alone are not sufficient to drive living processes. If thermodynamic forces were sufficient to produce life, life should have originated at the time of the Big Bang 13.7 billion years ago, since the thermodynamic force of the Universe must have been at its peak at that time. The thermodynamic force has been decreasing ever since the Big Bang and it was not until about 12 billion years after the Big Bang (3.5 billion years ago) that the first form of life emerged on this planet. What took it so long? It was certainly not due to the lack of thermodynamic force. It is suggested here that the necessary and sufficient condition for life is a combination of *thermodynamic force* (i.e., free energy) and *information* (i.e., the environmental and boundary conditions needed for self-reproduction or self-replication on this planet), the combination of which isbeing referred to as gnergy (see Sect. 2.3.2), and that it took 12 billion years for the informational aspect of the gnergy responsible for life to become satisfied by the surface of this planet.

The author postulated in (Ji 1991, pp. 152–163, 230–237) that all self-organizing processes in the Universe, including the evolution of life, are driven by gnergy, the complementary union of *information* (gn-) and *energy* (−ergon) (Sect. 2.3.2). Consistent with this thesis, it was found in Sect. 11.3 that the single-molecule experimental data on cholesterol oxidase can be interpreted only in terms of both *conformational energy* and *evolutionary information* (i.e., gnergy).

If the above reasoning is valid, it may be concluded that, to understand the biological evolution in its fullest detail, it would be necessary to develop a new field of inquiry wherein both *thermodynamics* (i.e., the study of energy and entropy) and *informatics* (i.e., the study of information, taking into account not only its *amount* as is done by current information theories but also its *meaning* and *values* (Volkenstein 2009, p. 160)) play fundamental roles in modern biology on an equal footing. Such a new field of study may be referred to as "gnergetics." So defined, gnergetics would be indistinguishable from or accommodate "infostatistical mechanics" (Sect. 4.9), the EvoDevo space (Fig. 14.3), "synergetics" of Haken (1983), the "theory of self-organization" (Prigogine 1977, 1980; Kondepudi and Prigogine 1998), "infodynamics" of Salthe et al. (Salthe 1996), the "coordination dynamics" (see Sect. 15.12) of Kelso (1995), and the Gibsonian information discussed by Turvey and Kugler (1984).

14.6 The *Thermodynamics* and *Informatics* of the Control Underlying Evolution and Development

There are three essential ingredients for any goal-directed processes, including development (the goal of which is for a fertilized egg to become a mature adult organism) and evolution (the goal of which is assumed to be the development or the

Table 14.9 The Principle of Dynamic Balance (PDB): X = any physicochemical entity; E = energy; S = entropy; I = information (Volkenstein 2010, pp. 142–144); dS_i = the entropy production due to irreversible process (Kondepudi and Prigogine 1998, p. 88); dS_e = the entropy change of the system due to the energy and matter exchange between the system and its environment (Kondepudi and Prigogine 1998, p. 88)

Function	ΔX	X_+	X_-	Thermodynamic laws
1. Structure	ΔE	E_+ (or Q)	E_- (or W)	The first law (*principle of conservation of mattergy*)
2. Process	ΔS (or dS)	S_+ (e.g., d_iS)	S_- (or d_eS)	The second law (*principle of disorganization*)
3. Control (*communication, organization, development, selection, and evolution*)	ΔI	I_+	I_-	The fourth law (?) (*principle of organization*)

emergence of self-replicating systems that can survive under increasingly complexifying environment). These three ingredients are (1) *energy* (i.e., energy-matter or mattergy) to ground (i.e., to provide a material basis for) a process, (2) *entropy* to cause a process (since, according to the Second Law of thermodynamics, no process can occur without entropy production), and (3) *information* to control a process, that is, to provide the constraints in the form of boundary and initial conditions. The relation among these three entities is compared in Table 14.9. This table is organized on the basis of the principle here called the *Principle of Dynamic Balance* (PDB), the same principle also operating in the triadic control mechanism postulated in Sect. 15.3, which is deduced on the basis of the goal-directed changes in genome-wide RNA levels in budding yeast undergoing glucose–galactose shift (Sect. 12.3). The Principle of Dynamic Balance can be expressed algebraically as shown in Eq. 14.26:

$$\Delta X = X_+ - X_- \tag{14.27}$$

where X is any observable (or state variable) of a physical system, ΔX is the net change in the observable, X_+ is any physicochemical process that contributes to increasing X, and X_- is any physicochemical process that contributes to decreasing X.

It is interesting to note that PDB can be utilized to express the content of the First Law of thermodynamics by equating X with energy, X_+ with heat (normally designated as Q), and X_- with work (designated as W) (see the second row of Table 14.9). PDB can also be utilized to express the Second Law by equating X with entropy (designated as S), X_+ with any process that contributes to increasing the entropy of the thermodynamic system under consideration (such as irreversible process and the import of high-entropy materials into the system), and X_- with any process that contributes to decreasing the entropy of the system (such as the synthesis of low-entropy materials in the system or the import of low-entropy material into the system from environment). The well-known *entropy balance equation of Prigogine* (EBEP), that is, Eq. 14.27,

$$dS = d_iS + d_eS \tag{14.28}$$

where dS is the change in the entropy content of a nonisolated system, d_iS is the entropy increase due to irreversible processes occurring inside the system, and d_eS is the entropy change (either positive or negative) of the system due to the exchange of matter and energy with its environment. Despite the apparent formal similarity between Eqs. 14.26 and 14.27, there is an important difference. PDB is a *difference* equation whereas the entropy balance equation of Prigogine (EBEP) is a *summation* equation. Another significant difference between PDB and EBEP is that, whereas PDB includes both entropy-producing (i.e., S_+) and entropy-consuming (i.e., S_-) processes inside the system, EBEP recognizes only the entropy-producing processes inside the system, excluding any entropy-consuming ones (e.g., biosynthesis in organisms), and hence must be viewed as incomplete.

Perhaps one of the most novel features of Table 14.9 is the appearance of *information, I,* and its cognate concepts such as *communication*, *selection*, *organization, control*, *development,* and *evolution* in a row that is separate from the row for *entropy*, graphically illustrating the independence of *information* from *entropy* (or vice versa) in contrast to the views of Jaynes (1957a, b); Brillouin (1953, 1956), and others who view *information* and *entropy* as two different names for a fundamentally identical entity. Their argument (see Volkenstein 2009, p. 63) is largely based on the formal similarity between the mathematical expression for the thermodynamic entropy, Eq. 14.28, formulated by Boltzmann (1844–1906), and the equation for information proposed by Shannon (see Eq. 4.2) which can be reduced to Eq. 14.29.

$$S = k \ln P \tag{14.29}$$

where k is the Boltzmann constant and P is the number of the microstates compatible with the microstate of the system under consideration (also called the statistical weights of the microstates).

$$I = K \log_2 P \tag{14.30}$$

where I is the information associated with an event that can occur in P different ways and K is a proportionality constant (Volkenstein 2009, p. 142). The formal similarity between the equations for S and I is indeed striking. The entity defined by Eq. 14.28 is referred to as *thermodynamic entropy* or the Boltzmann–Clausius entropy (to be designated as S_T) and is defined by Eq. 14.29 as the *informational entropy, information-theoretic entropy,* or the Shannon entropy (Volkenstein 2009, p. 145) (to be designated as S_I). Whether or not S_T and S_I are similar not only on the *formal level* (as seen above) but also on the *substantial level* may critically depend on the nature of P, the number of different ways that an event can occur or the number of different ways an object can be described ΔE. If it is accepted that there are indeed three fundamental entities, ΔE, ΔS, and ΔI, as indicated in the second row of Table 14.9, and if ΔE and ΔS are associated with the First and Second Laws

of thermodynamics, would it be too far-fetched to infer that there may be a new law of thermodynamics that is associated with ΔI that controls, selects, and organizes spontaneous processes in nature? Such a conjectured law is referred to as the Fourth Law of thermodynamics, or the Principle of Organization in Table 14.9. This Fourth Law seems consistent with the classification scheme of the thermodynamic laws given in Fig. 2.2 and with the two laws described in Table 4.1, namely, the Laws of Requisite Variety and Requisite Information.

14.7 The Zeldovich–Shakhnovich and the MTLC (Molecular Theory of the Living Cell or the Bhopalator) Models of Evolution: *From Sequences to Species*

Unlike the past models of biological evolution that are based on phenomenological population genetics, the newly emerging microscopic/molecular models of evolution increasingly utilize the genome-wide molecular information provided by the thermodynamic stabilities of proteins (e.g., Fig. 12.26) (Koomin et al. 2002; Zeldovich et al. 2007a, b; Zeldovich and Shakhnovich 2008) and comparative genomic data such as shown in Fig. 14.6. For example, the microscopic physical model of evolution proposed by Zeldovich et al. (2007a, b, 2008) quantitatively accounts for not only the protein stability distribution in Fig. 12.26 (see the solid curve) but also the power-law behavior of the frequency distribution of gene family sizes (Fig. 14.6).

The gene family size (GFS) distribution curves in Fig. 14.6 can be characterized in terms of four numbers: N = the number of the genes in the genome of an organism; n_i = the number of genes in the ith gene family, a gene family being defined as a set of genes sharing some common features such as nucleotide sequences, protein folds, and/or functions; f_i = the frequency of the occurrence of the ith gene family size in a genome; m = the number of gene families in a genome. These numbers are related as follows:

$$N = \sum_{i=1}^{m} f_i n_i = AUC \tag{14.31}$$

where AUC is the area under the curve of GFS distribution.

Figure 14.6 contains the following valuable features that may shed important light on the fundamental mechanisms underlying cell structures and functions driving both evolution and development:

1. The distributions of gene family sizes (GFSs) obey a power law

$$P(S) = cS^{-\gamma} \tag{14.32}$$

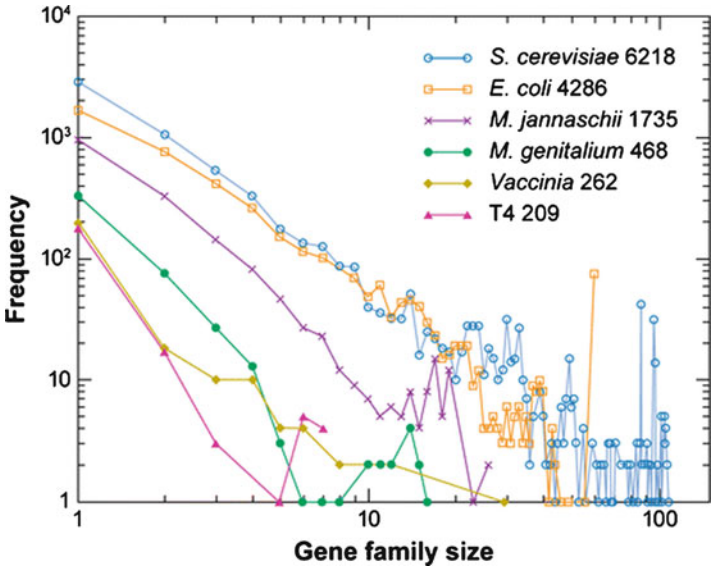


Fig. 14.6 The frequency distribution of gene family sizes (GFS) in the complete genomes of two bacteria (*Escherichia coli*, *Mycoplasma genitalium*), an Archaea (*Methanococcus janaschii*), a eukaryote (*Saccharomyces cerevisiae*), the vaccinia virus, and the bacteriophage T4. For example, in the *S. cerevisiae* genome, there are about 500 families with 3 genes, 50 families with 10 genes and 2 families with 50 genes. The gene family sizes were determined from the output of the Smith-Waterman algorithm which compares two or more gene sequences (Huynen and van Nimwegen 1998). The power-law exponent, γ, is called the Huynen–van Nimwegen exponent which is thought to be proportional to the complexity of organisms and it is -2.81 for *S. cerevisiae*, -2.84 for *E. coli*, -3.27 for *M. janaschii*, -4.02 for *M. genitalium,* and -3.8 for vaccinia. The number following the names of a species indicates the predicted number of protein-coding regions in that species (Figure reproduced from Zeldovich and Shakhnovich 2008)

where P(S) is the probability or the frequency of the occurrence of gene family size S within a genome (there being 3 to 700–800 gene families, depending on genomes), c is the normalization constant, and γ is the exponent of the power law. Huynen and Nimwegen (1998) found that the numerical values of γ ranged from -2.8 to -4.0 across a dozen different genomes. Taking the logarithm of both sides of Eq. 14.31 and plotting log P(S) against S predicts a straight line with slope $-\gamma$ and *y*-intercept c, in approximate agreement with the plots shown in Fig. 14.6.

2. Different genomes have different number of protein-coding regions (i.e., genes), from 6,218 for *Saccharomyces cerevisiae* to 468 for ***Mycoplasma*** *genitalium,* and this is reflected in the different sizes of the areas under the curves (AUCs): The AUC of *S. cerevisiae* is much greater than the AUC of *M. Genitalium,* for example.
3. For a given genome size (i.e., species), the power-law relation between GFSs and associated frequencies becomes poor (i.e., noisy) as GFSs increase beyond some thresholds. For example, see the noisy plots in Fig. 14.6 for *S. cerevisiae, Escherichia Coli,* and *Methanococcus jannaschii* as GFSs increase beyond about 20 genes.

4. As pointed out by Huynen and van Nimwegen (1998), the exponent γ of the power law underlying the GFS distribution increases with genome size N. From their Fig. 2, the following equation was obtained:

$$\gamma = 0.94 \log \mathrm{N} - 4.38 \tag{14.33}$$

For the convenience of future discussions, it may be convenient to refer to Eq. 14.31 as the *Huynen–van Nimwegen (HN) equation* and γ as the Huynen–van Nimwegen (HN) exponent, Fig. 14.6 from which this equation derives as the *Huynen–van Nimwegen (HN) plot,* and the individual curves in the Huynen–Nimwegen plot as *Huynen–van Nimwegen (HN) curves.*

The molecular model of evolution proposed by Zeldovich et al. (2007a, 2008), to be referred to as the *Zeldovich-Shakhnovich model* for brevity, is based on the following six assumptions:

(a) *An organism can be treated as a set of genes.*
(b) *The genetic code transforms genes into amino acid sequences of proteins.*
(c) *The lattice protein folding model transforms the amino acid sequence of a protein into its native conformation, that is, the most stable conformation, or the conformation with the lowest Gibbs free energy of folding.*
(d) *The probability P_{alive} that an organism is alive is proportional to the probability $P_{nat}{}^{(i)}$ that protein i is in its native conformation*:

$$P_{alive} \sim min_i P_{nat}{}^{(i)} \tag{14.34}$$

where the symbol min_i indicates the least stable of all the proteins, each labeled with the index, i, with i = 1 through N, the number of proteins in the genome.
(e) *Therefore, the dead rate, d, of an organism is negatively related to the probability*

$$d = d_0(1 - P_{nat}{}^{(i)}) \tag{14.35}$$

where d_0 is the original dead rate of an organism before undergoing genetic mutations.
(f) *The probability P_{nat} of the native state of the least stable protein in the genome is postulated to be inferable from the amino acid sequence of the protein using the 3×3×3 lattice model with the Miyazawa-Jernigan potential (Miyazawa and Jernigan* 1996*):*

$$P_{nat} = e^{(-E\_0/T)} / \left(\sum_{i=0}^{M} e^{(-E\_i/T)} \right) \approx 1/(1 + e^{(-\Delta E/T)}) \tag{14.36}$$

where E_0 (or E_0) is the energy of the ground-state conformation of a protein, E_i(or E_i) is the energy of the ith conformation of the protein, M = 103,346 is

the total number of accessible conformations, T is the absolute temperature, and ΔE is the sum of the energy differences between the ith and ground state conformations of the protein with i running from 1 to M.

The Zeldovich–Shakhnovich model based on these assumptions plus the secondary constraints (explained below) has been simulated on a computer, resulting in a set of novel findings, including (1) the emergence of "dominating protein sequences (DPSs)" reminiscent of Andersons's finding (Sect. 13.1), (2) the exponential population growth following the appearance of DPSs, and (3) the power-law distributions of protein family sizes (which are directly related to gene family sizes through the genetic code) (see Fig. 4a, b in Zeldovich and Shakhnovich 2008), and (4) the asymmetric distribution of protein stability data (see the solid curve in Fig. 12.31).

The secondary constraints implemented in the computer simulation of the Zeldovich–Shakhnovich model include: (1) random mutations of a nucleotide in a randomly selected gene with constant rate m per unit time per DNA length (with no mutation allowed for stop codons to ensure constant length of protein sequences), (2) duplication of randomly selected genes within an organism's genome with constant rate u, and (3) birth of an organism via duplication of an already existing organism with constant rate b.

Although the Zeldovich–Shakhnovich model provides what appears to be the first successful microscopic mechanism (connecting nucleotide sequences to organismic properties) to account for Observation (*1*) above (Zeldovich et al. 2007a), it does not explain Observations (*2*)–(*4*). To account for these observations, it is here suggested that at least two laws – the Law of Requisite Variety (LRV) (see Sect. 5.3.2) and the Principle of Rule-Governed Creativity (RGC) (see Sects. 6.1.4 and 12.10), and two new concepts, that is, active versus passive complexities (Sect. 5.2.3) and equilibrium structures (equilibrons) versus dissipative structures (dissipatons) (Sect. 3.1.5), needs to be utilized as detailed below:

Observation (1) The key point of the model proposed by Huynen and van Nimwegen (1998) to account for the power law distribution of gene family sizes is that "all the genes within a family are affected in the same (or at least a similar) way by the environment." That is, "gene families have to behave in a coherent fashion within the genome; that is, the probabilities of duplication of genes within a gene family are not independent of each other." In the following discussion, I will refer to this feature of the Huynen–van Nimwegen model as the Huynen–van Nimwegen constraint (HVC). In the Zeldovich–Shakhnovich model (Zeldovich et al. 2007a, b; Zeldovich and Shakhnovich 2008), HVC is implemented by what is called the "weakest link," which Zeldovich et al. postulated to be the lowest free energy conformation of the least stable of the proteins in a genome, the probability of which was calculated using Eq. 14.35. Another possibility suggested by the molecular theory of the living cell proposed in this book is that HVC is satisfied by a gene family, X, acting as a dissipaton (i.e., IDSs; see Sect. 12.5) carrying out a critical cell function Y under environmental condition Z. Function Y of an organism is said to be critical under environment Z, if inhibiting or removing Y leads to the demise of the organism under Z. "Critical" in this sense is synonymous

with the expression "weakest link" used in the Zeldovich et al. model (Zeldovich et al. 2007a, b; Zeldovich and Shakhnovich 2008). We may refer to this suggestion as the XYZ postulate. The XYZ postulate can be viewed as a species (or an example) of HVC, since X represents a set of genes sharing some common features and since the malfunctioning of X will lead to the inhibition of Y and hence to cell death under environmental condition Z. In other words, the set of genes constituting X can "behave in a coherent fashion within the genome" as required by HVC. Furthermore, if we represent the probability of X as P(X), then the probability of cell death can be calculated using Eq. 14.34 with P(x) replacing $P_{nat}^{(i)}$:

$$d = d_0(1 - \ P(X)) \tag{14.37}$$

Although I believe Eq. 14.36 is biologically more realistic than the Zeldovich–-Shakhnovich model, Eq. 14.34, it is probably computationally less realistic, since P (X) is the probability of a process which is likely "catalyzed" by a set of proteins encoded in a gene family and hence unlikely to be as simple as the Boltzmann distribution, Eq. 14.35, underlying the Zeldovich-Shankhnovich model (2007a, b; Zeldovich and Shakhnovich 2008).

Observation (2) According to the *cell language theory*, cells utilize microscopic or molecular language called the *cell language* or *cellese* whose principles are found similar (or isomorphic) to those operating in the human language or *humanese* (Sect. 6.1.2). Thus, genes (proteins) are akin to words, complexes of genes (proteins) are akin to sentences, and a DNA molecule or a genome is akin to a book or a text of instructions for survival under a given set of environmental conditions. A language, either natural or cellular, is thought to obey the *Law of Requisite Variety* (LRV) (Ji 1997a): that is, *no simple language can describe complex environment, and no simple organism can survive complex* environment (see Sect. 14.2). *Therefore, different genomes have different sizes most likely because they contain the instructions that are needed for organisms to survive their environment* that have different amounts of complexities (as measured in bits; see algorithmic information discussed in Sect. 4.3). For example, *S. cerevisiae* has a larger genome (with 6,218 predicted protein-coding regions) than *E. coli* (with 1,735 predicted structural genes), probably because the complexity of the environment under which *S. cerevisiae* can survive is much greater than the complexity of the environment under which *E. coli* can survive. Based on this reasoning, we can conclude that *the size of a genome reflects the algorithmic complexity (or the algorithmic information content)* (see Fig. 4.1) *of the environment* under which the associated organism has survived. Since the size of a genome is related to the AUC of the Huynen–Nimwegen plot, we can therefore infer that the AUC of the Huynen–Nimwegen plot reflects the complexity of the environment under which a species has survived:

AUC of the Huynen-Nimwegen Plot $\approx$ **Algorithmic Complexity of the Environment under which a Species has** (14.38)

Observation (3) The Huynen–Nimwegen curves in Fig. 14.6 that belong to living cells (and not viruses) can be divided into two regions – the *deterministic region* showing a one-to-one correlation between GFSs (i.e., n_i) and their frequencies (i.e., f_i) and the *nondeterministic* (also called *noisy*, *chaotic, unpredictable,* or *creative*) regions where there is no correlations between GFSs and their frequencies. The boundaries between these two regions are located at the GFS values in the rage of 10–30 genes. In other words, the Huynen–Nimwegen curves are partly deterministic and partly chaotic, reminiscent of the *rule-governed creativity* (*RGC*) in the human language (Sect. 6.1.4). Similar dichotomous behaviors were observed in the genotypic similarity versus phenotypic distance (GSvPD) plots of the budding yeast transcriptomics discussed in Sect. 12.11. *One possible rationale for the unpredictable, chaotic, and creative regions of the Huynen–Nimwegen curves may be that such unpredictability reflects the arbitrariness of signs in cellese (*Sect. 6.1.4*), which is thought to be necessary for maximizing communication among cells using cellese* (see the *Maximum Information Principle* in Ji 1997a).

Observation (4) The exponent, γ, of the Huynen–van Nimwegen equation, 14.31, represents the slope of the Huynen–van Nimwegen curve of a genome. This slope increases (i.e., becomes less negative) with increasing genome size N as evident in Fig. 14.6, with the possible exception of vaccinia. Focusing on cells, it is evident that cells with smaller genomes tend to have smaller (or more negative) slopes, indicating that *cells with smaller genome sizes utilize large gene families less frequently than the cells with larger genome sizes*. One possible explanation for this intriguing observation is provided by the *cell language theory* coupled with the concepts of *equilibrons* versus *dissipatons* on the one hand and *passive* versus *active complexities* on the other. This explanation entails the following principles and assumptions:

1. As already alluded to above, genes are analogous to *words*, a set of genes (such as those encoding metabolic pathways) are analogous to *sentences*, and genomes are analogous to *books*.
2. There are two aspects to words, sentences, and books just as there are two aspects to music – the *sheet music* (which is an *equilibron*) and the *audio music* (which is a *dissipation*, since "no energy, no sound"). These genes and genomes can act as *equilibrons* (as when encoded in DNA, RNA, or protein sequences) or as *dissipatons* (as when expressed as transient structures such as molecular motors in action, ion gradients, and active metabolic pathways).
3. Gene families acting as dissipatons are the units of cell functions, not individual genes (as frequently believed).
4. Cells embody two kinds of complexities – *passive* and *active* complexities (Sect. 5.2.3) (see also Eqs. 14.10 and 14.11). Transiently organized sets of genes and enzymes for the purpose of executing gene-encoded cellular processes under a given environmental condition constitute active complexification processes (also called self-organization in Sect. 3.1, or SOWAWN machines in Sect. 2.4.3).
5. According to the Principle of Maximum Complexity, the *active complexity* of living systems increases with the complexity of their environment (Sect. 14.3).

Table 14.10 Some of the key experimental data on proteomics and comparative genomics that are relevant to modeling evolution and their possible explanations provided by the Molecular Theory of the Living Cell (MTLC) developed in this book and by other models of evolution

	Explanations provided by		
Observations	MTLC (this book)	Hunen and van Nimwegen (1998)	Zeldovich et al. (2007a, b, 2008)
1. Protein stability distribution (Fig. 12.26)	Universal principle of thermal excitations (Sect. 12.12) (qunatitative) (see Fig. 12.25f)	*Not explained*	*Not explained*
2. Power-law distribution of gene family sizes (Eq. 14.31 and Fig. 14.6)	Gene families as dissipatons and as functional units (Sects. 3.1.5 and 14.7) (qualitative)	Gene families as coherent units; i.e., genes in a family are affected in the same way (quantitative)	Gene sequence Conformations Organismic Survival Species (Sect. 14.7) (quantitative)
3. Variable genome sizes (Fig. 14.6)	Law of requisite variety (Sects. 5.3.2 and 14.7) (qualitative)	*Not explained*	*Not explained*
4. Huynen–Nimwegen equation (Eq. 14.31)	The exponent γ as a quantitative measure of the *active complexity* of an organism (Sects. 5.2.3 and 14.7) (qualitative)	*Not explained*	*Not explained*
5. Compatibility with the model of evolution proposed in Fig. 14.7	Compatible with nodes A, B, C, D and E	Compatible with nodes A and E	Compatible with nodes A and E

Based on these principles and assumptions, it is here suggested that the exponent, γ, of the Huynen–van Nimwegen plot of an organism (Fig. 14.6) represents a *quantitative measure of the active complexity* of the organism, that is, the larger the value of γ, the more actively complex the organism is, or the more complex is the environment under which the organism can survive.

In Table 14.10, a brief comparison is provided among the various models of biological evolution in terms of their ability to account for some of the key experimental findings in proteomics and comparative genomics that any viable models of biological evolution should be able to account for. The model of evolution described in this book (to be referred to as the *MTLC-based model*, where MTLC stands for "molecular theory of the living cell") provides explanations for all of the four key observations listed above – one quantitative and three qualitative. In contrast, the models of Huynen and Nimwegen (1998) and Zeldovich et al. (2007a, b, 2008) both account for only one of the four observations, namely, the power-law distributions of gene family sizes, Eq. 14.31.

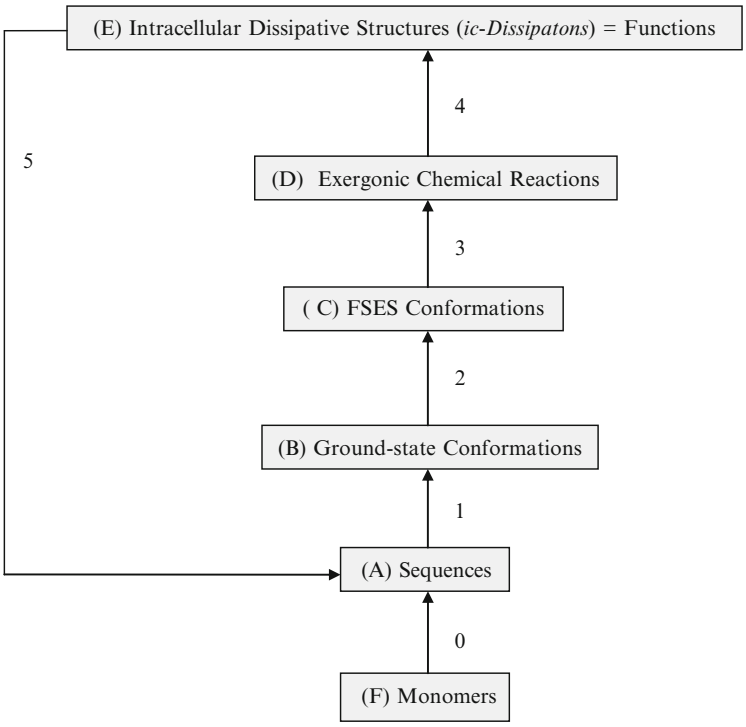


Fig. 14.7 *The MTLC-based model of biological evolution*: A molecular theory of biological evolution of unicellular organisms constructed by incorporating the *Zeldovich-Shakhnovich model of evolution* (see text) into the *Bhopalator model of the living cell* (Sect. 10.1) within the framework of the *molecular theory of the living cell* (MTLC) developed in this book. See text for the explanations to the six key steps proposed above, labeled from 0 through 5. FSES stands for "Functionally Significant Excited State" as compared to denatured state of proteins; *ic-dissipatons* refers to the intracellular (ic) dissipative structures which are postulated to be the ultimate driving force for all cell functions and hence synonymous with *intracellular functions* encoded in the genome (Sect. 12.5)

The MTLC-based model of biological evolution is schematically represented in Fig. 14.7. The model consists of six nodes, denoted as A through F, and six steps (or links) from 0 through 5, which can be viewed as causal links:

Step 0 Biological evolution involves two qualitatively distinct processes – (1) the origin of life or self-replicating systems (also called organisms) out of the primordial chemical soup (see Step 0), and (2) the adaptation and speciation of organisms (see Steps 1 through 5). The mathematical models of evolution proposed by Huynen and Nimwegen (1998) and Zeldovich et al. (2007a, b, 2008) do not address the problem of the origin of life but assume that organisms were already present in the biosphere. In contrast, the model of evolution described in Fig. 14.7 includes both the origin of life, Step 0, as presented in Sect. 13.2, and the process of evolution, Steps 1 through 5 described throughout this book.

Step 1 The sequence information of biopolymers (DNA, RNA, and proteins) affects the three-dimensional shapes (also called conformations) of biopolymers primarily driven by the tendency for biopolymers to assume the most stable conformations accessible to them under a given environmental condition or the tendency for biopolymers to assume conformations with as small Gibbs free energy content as possible. We will refer to this tendency as the *Principle of Gibbs free energy minimization* (PGFEM).

Step 2 In order for sequence information to be causally effective, biopolymers must be thermally excited to reach Functionally Significant Excited States (FSESs), that is, they must undergo thermally induced transitions from ground-state conformations (GSCs) to FSESs. FSESs are thought to be identical with thermally excited conformations of biopolymers, including nearly denatured conformations, that have been selected by evolution due to their catalytic activities contributing to cell survival. The evidence for this step is provided by that fact that both the single-molecule enzymological data and the protein stability distribution can be fit into the blackbody radiation-like equation, Eq. 12.26 (see Fig. 12.30, Panel f).

Step 3 According to the Second Law of Thermodynamics, FSESs cannot lead to any measurable effects unless they are coupled to (i.e., catalyze) some exergonic chemical reactions. The molecular mechanism responsible for the coupling between FSES and exergonic chemical reactions is thought to obey the generalized Franck–Condon principle discussed in Sect. 2.2.3.

Step 4 The Principle of Self-Organization (Sect. 3.1) ensures that, under a right set of initial and boundary conditions, a set of exergonic chemical reactions can generate space- and time-organized and goal-directed chemical concentration, electrochemical, and mechanical gradients inside the cell collectively called IDSs (Intracellular Dissipative Structures) or intracellular dissipatons (Sect. 3.1.5).

Step 5 Most importantly, the IDSs or dissipatons described in Step 4 above are endowed with biological functions (see the *IDS-Cell Function Identity Hypothesis* in Sect. 10.2), some of which may assume a *critical role* under some environmental conditions – *critical* in the sense of affecting the life of the whole organism, of which such IDSs are a part, leading to the selection of the right kinds of cells (including their genes, RNAs, and proteins, etc.) most fit to survive the prevailing environmental conditions. In other words,

> Biological evolution selects organisms primarily based on functions (i.e., IDSs) and only secondarily based on nucleotide sequences. (14.39)

Statement 14.38 would be true if a cell function can be supported or realized by more than one set of genes, just as a given protein fold can be realized by more than one amino acid sequences (Chothia 1992). Thus, Statement 14.38 may be referred to as the *Function First and Sequence Second* (FFSS) *Postulate* or as the *Dissipatons First and Equilibrons Second* (DFES) *Postulate*, since sequences are equilibrium structures and functions are dissipative structures (Sect. 3.1.5).

Table 14.11 The key principles, laws, and concepts underlying the six steps of the MTLC-based model of biological evolution shown in Fig. 14.7

Steps	Principles, laws, concepts
0	Conformons (Chap. 8)
1	Protein folding controlled by both Gibbs free energy and genetic information, i.e., gnergy (Sects. 2.3.2, 4.9, 4.11 and 11.1)
2	Universal principle of thermal excitations (Sect. 12.12)
3	Generalized Franck–Condon principle, also called the principle of slow and fast processes (Sect. 2.2.3)
4	Principle of Self-Organization (Sect. 3.1)
5	Law of Requisite Variety (Sect. 5.3.2)
	IDS-cell function identity hypothesis (Sect. 10.2)
	Functions first and sequences second postulate (Statement 14.38)

What distinguishes the MTLC-based model of biological evolution schematically presented in Fig. 14.7 and those proposed by Huynen and van Nimwegen (1998) and by Zeldovich et al. (2007a, b, 2008) is that all of the key steps implicated in the model are associated with at least one clearly formulated physical principle, law, or concept. These are listed in Table 14.11 without any detailed explanations, since they have already been explained in the indicated chapter and sections of this book.

According to the MTLC-based model of evolution depicted in Fig. 14.7, the evolution of organisms depends on five critical entities operating properly, namely, sequences (or genes, RNAs, proteins) (designated as node A), ground-state conformations of critical proteins (node B), functionally significant excited states of critical proteins (node C), the critically important exergonic chemical reactions (e.g., respiration, active transport, muscle contraction) (node D), and critically important IDSs (node E). Unlike the Zeldovich-Shakhnovich model where the probability that an organism is alive, P_{alive}, is directly related to the probability that the *weakest-link protein* (i.e., the protein whose malfunctioning leads to death) be in its native (i.e., functional) state, $P_{nat}^{(i)}$, as indicated by Eq. 14.33, which leads to the rate equation for organismal death, Eq. 14.34, the MTLC-based model of evolution suggests an alternative equation, Eq. 14.39, that can be obtained by replacing $P_{nat}^{(i)}$ in Eq. 14.33 with P(E):

$$P_{alive} \propto P(E) \tag{14.40}$$

where $\propto$ symbolizes proportionality, and P(E) is the probability that the critical IDS (i.e., node E in Fig. 14.7) under a given environmental condition is in its "native state" or "functional state." The rate of organismal death predicted by the MTLC-based model of evolution (BME), then, can be obtained by inserting P(E) to Eq. 14.34, leading to Eq. 14.40:

$$d = d_0[1 - P(E)] \tag{14.41}$$

where d is the rate of organismic death increased or decreased relative to a reference death rate, d_0, by altering P(E) through affecting any one of the underlying four entities (i.e., nodes D, C, B, or A) in the MTLC-based model that happens to be the weakest link under a particular environmental condition. The following predictions can be made based on Eq. 14.40:

1. No evolution can proceed without changing the average P(E) of a population.
2. Because of the postulated "many-to-one mapping between the nth and the (n + 1)th nodes," not all changes in sequences, protein stabilities, excited states of proteins, or exergonic chemical reactions are expected to lead to the corresponding changes in P(E).

The MTLC-based model of evolution shown in Fig. 14.7 may be alternatively referred to as the "five-causes mechanism of cell death (FCMCD)," since there are at least five key mechanisms by which the death of an organism may be effected, depending on the environment under which the organism of interest maintains life; i.e., by altering (1) sequences (or DNA, RNA, or proteins by mutations, recombinations, deletions, insertions etc.), (2) ground-state conformations, (3) excited-state conformations, (4) chemical reactions, and/or (5) IDSs (i.e., intracellular dissipatons) directly.

As will be discussed in Chaps. 18 and 19, the MTLC-based model of evolution provides an unexpected and useful theoretical framework for *biomarker* (i.e., disease-related cell states) *identification*, *molecular diagnosis*, *drug target discovery research*, and *drug therapy* in personalized medicine.

Chapter 15
Multicellular Systems

15.1 The Morphogenesis of *Drosophila melanogaster*

The morphogenetic processes of *Drosophila melanogaster* (fruit fly) and *Homo sapiens* are homologous (i.e., similar) since they have been found to utilize closely related sets of genes in highly conserved manner. Because of easy genetic manipulations possible with insects relative to humans, most of our current knowledge about the molecular basis of animal morphogenesis has come from researches performed on *Drosophila*.

The life span of *Drosophila melanogaster* is about 30 days, and it takes 10 days for a fertilized *Drosophila* egg to become an *adult* fly. After fertilization, the *Drosophila* zygote begins mitosis (i.e., nuclear division), but cytokinesis (i.e., division of the cytoplasm) does not occur in the early stages of the embryo, resulting in a multinucleate cell called a *syncytium* (also called *syncytial blastoderm*). Because of the common cytoplasm shared by all the nuclei of the syncytium, morphogen (i.e., diffusible molecules regulating morphogenesis) gradients play a key role in controlling the pattern of transcription of individual nuclei. At the tenth nuclear division, the nuclei migrate to the periphery of the embryo, and at the thirteenth nuclear division, the 6,000–8,000 nuclei are partitioned into separate cells forming the *cellular blastoderm*. The embryogenesis, that is, the process of a fertilized egg to develop into an embryo, takes about 15 h in *Drosophila*.

Lécuyer et al. (2007) used the fluorescence *in situ* hybridization (FISH) technique to determine the localization in the embryo of approximately 25% of the mRNA encoded in the *Drosophila* genome. They found that the majority of sampled mRNAs (i.e., 71% of 3,370 genes, or 2,360 genes) are localized in the early embryo as illustrated in Fig. 15.1. Their study demonstrates that mRNA localization in *Drosophila* embryo is heterogeneous and suggests that such a distribution of mRNA in embryo may be a widespread biological phenomenon playing a fundamental role in organizing cellular architecture.

The patterns of distribution of mRNA molecules in cells measured with microarrays can be either spatial (Fig. 15.1) (Lécuyer et al. 2007) or temporal

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_15,

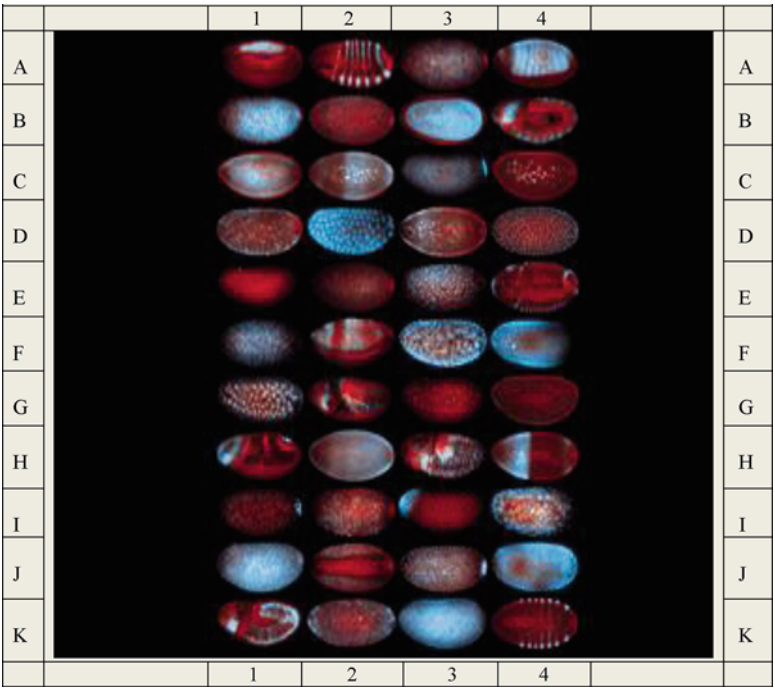


Fig. 15.1 Asymmetric distribution of mRNA molecules in *Drosophila* visualized with fluorescent in situ hybridization (FISH) technique (Lécuyer et al. 2007). The mRNA molecules are depicted in *blue* and nuclei in *red*. There are a total of 44 embryo images in this figure in 11 rows and 4 columns. To identify individual images, rows are labeled with capital letters and the columns with Arabic numerals. Thus, Image A1 will designate the image on the first row and the first column, and Image K4 will designate the image on the last row and the last column, etc. (The embryo images were reproduced from Lécuyer et al. 2007 by permission of *Cell* obtained through Copyright Clearance Center)

(Figs. 12.1, 12.2, 12.3). Both the RNA distributions in *time* and *space* are expected to obey the *Triadic Control Principle* (TCP) described in Fig. 15.2. Just as the majority of workers in the field of DNA microarray technology in the past decade committed false-positive and false-negative errors in interpreting their data due to ignoring TCP (Ji et al. 2009a), so it can be predicted that researchers employing the FISH technique to measure spatial distributions of mRNA signals such as shown in Fig. 15.1 can make similar errors in interpreting their data if TCP is not taken into account. For example, if an mRNA signal was found to be high in the anterior region relative to the posterior region in a syncytial *Drosophila* blastoderm (e.g., see I3 in Fig. 15.1), the usual interpretation is that the transcription rate of the associated gene is higher in the anterior region than in the posterior region, or that the associated gene is *expressed* in the anterior region but not in the posterior region of the embryo (see Table 1 in Lécuyer et al. 2007). But, in the absence of independent data, it would be impossible to rule out the alternative possibility

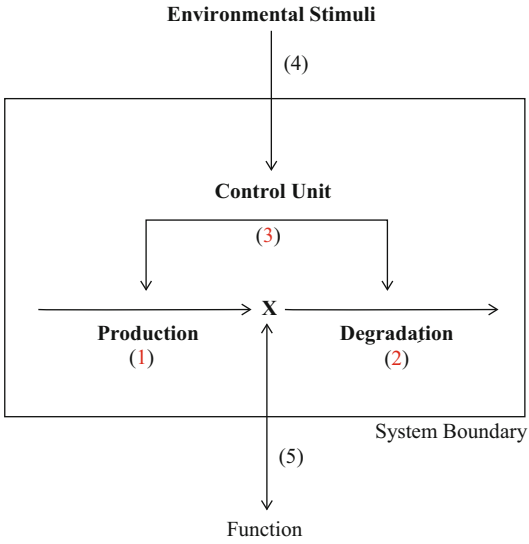


Fig. 15.2 A diagrammatic representation of the "triadic control principle" (TCP), also called "triadic control hypothesis" (TCH), or the "triadic control mechanism" (TCM). Please note that Processes 1, 2, and 3 are *internal* to the system (whence the notion of triadic control) and X is the *effector unit*. Process 4 is environmental input, and Process 5 is the environmental message-triggered function (or output) of the system immediately caused or effectuated by X

that the same observation may be the result of a decreased rate of transcript degradation in the anterior region of the embryo relative to the posterior region without any gradient in the transcription rate of the associated gene between these two regions. Adopting the first interpretation and inferring the associated gene to be responsible for the observed mRNA gradient thus can lead to a false-positive (or Type I) error if the alternative interpretation turns out to be true.

The structural elements forming the anterior-posterior axis in *Drosophila* are already put in place during egg formation (or oogenesis) before fertilization. Developing oocyte is polarized by mRNA molecules differentially bound to cytoskeletal elements (if the local mRNA concentration is determined predominantly by transcription and not by transcript degradation; see the Triadic Control Principle explained in Fig. 15.2). The genes coding for these mRNA molecules are called *maternal effect genes*. The differentially bound mRNA molecules get translated upon fertilization to form concentration gradients of the resulting proteins across the egg cytoplasm. *Bicoid* and *hunchback are* two maternal effect genes playing the most important roles in patterning anterior parts (head and thorax) of the *Drosophila* embryo, and *Nanos* and *Caudal* are maternal effect genes that are important in determining posterior abdominal segments of the embryo. Maternally synthesized *bicoid* mRNA molecules preferentially accumulate in the anterior end of developing *Drosophila* eggs, and *Nanos* mRNA accumulate at the posterior end of the eggs, resulting in oppositely directed gradients of *bicoid* and *nanos* mRNA molecules. When these mRNA molecules are translated into proteins, Bicoid and Nanos gradient are formed along the anterior-posterior axis. *Hunchback* and *caudal* mRNA molecules are evenly distributed throughout the interior of egg cells, but their protein products are distributed unevenly because (1) Bicoid protein inhibits the translation of *hunchback* mRNA and Nanos protein inhibits the translation of

the *hunchback* mRNA, and (2) Bicoid and Nanos proteins are unevenly distributed across the *Drosophila* egg.

The Bicoid, Hunchback, Nanos, and Caudal are transcription factors that regulate the transcription of gap genes such as *Krüppel, giant, tailless, and Knirps*. Gap genes are part of a larger family called the *segmentation genes* that determine the segmental body plan of the embryo along the anterior-posterior axis. They are called "gap genes" because their expression leads to the formation of gaps in the normal pattern of structure or the formation of broad bands in the embryo.

The maternal effect genes, including *bicoid* and *nanos*, are required during oogenesis. The transcripts or protein products of these genes are found in the egg at fertilization, and form morphogen gradients. The pair-rule genes divide the embryo into pairs of segments. These genes encode transcription factors that regulate the expression of the segment polarity genes, whose role is to set the anterior-posterior axis of each segment. The gap genes, pair-rule genes, and segment polarity genes are together called the segmentation genes, because they are involved in segment patterning.

The order of the expression of the set of genes, maternal effect genes, gap genes, pair-rule genes, and segment polarity genes leads to an increasingly differentiated and diversified *spatial compartmentation* of the volume occupied by the *Drosophila* embryo which in turn leads to increasing the "active" complexity of the embryo," active" because such *compartmentations* would be impossible without dissipating free energy. The concepts of "active" and "passive" complexities were defined in Sect. 5.2.3. Therefore, it appears logical to define what may be referred to as "the active complexity of the embryo" (ACE) as the number of bits in the shortest string of symbols that describes the geometric compartmentation of an embryo, including the body segmentations:

$$\begin{array}{c}\textbf{Active Complexity of}\\ \textbf{the Embryo (ACE)}\end{array} = \begin{array}{c}\textbf{Algorithmic Complexity of the Geometric}\\ \textbf{Compartments of the Embryo}\end{array} \tag{15.1}$$

Once the concept of active complexity of embryo (ACE) is defined, it is simple to take the next logical step and define what may be called the "information density of the embryo" (IDE) as the ratio of ACE and the geometric volume of the embryo (GVE):

$$\begin{array}{l}\textbf{Information Density of the Embryo (IDE)}\\ = \textbf{Spatial Complexity of the Embryo (ACE)}/\textbf{Geometric Volume of the Embryo (GVE)}\end{array} \tag{15.2}$$

It is important to differentiate the IDE from what may be called the "information density of the genome" (IDG), defined as the ratio of the algorithmic complexity of the nucleotide sequences of the genome over the geometric volume of the genomic DNA molecules, since embryo is dissipative structures (or dissipatons) and the genome, as defined here, would be an equilibrium structures (or equilibrons)

(Sect. 3.1). To use a familiar metaphor, embryos are akin to *audio music* and the genomes are akin to *sheet music*. Because the quality of audio music depends on many more factors (such as the artistic skills of the musician, the kinds of instruments employed, the environmental factor, etc.) than the quality of a sheet music, the information content of audio music is much greater than the information content of a sheet music. One characteristic of sheet music is that it can be handed down from one generation to another without any change. As evident in Fig. 15.1, both the genome and the volume of the *Drosophila* embryo remain more or less constant during most of the embryogenesis, but the algorithmic information content of the embryo (and hence the IDE) obviously increases as the *Drosophila* embryogenesis progresses. The genomic information density of a species tends to increase over generations (i.e., on the diachronic timescale, not on the synchronic timescale; see Sect. 14.4 and Fig. 14.3 for the definitions of "synchronic " and "diachronic " timescales), leading to Statement 15.3:

> The information density of the genome increases with diachronic time; the information density of embryos increases with synchronic time. (15.3)

Statement 15.3 is consistent with the Law of Maximum Complexity, Statement 14.15, described in Sect. 14.3.

The transcription factors coded for by segmentation genes also regulate the *Law of Maximum Complexity*. These genes are located in Drosophila chromosome 3, and the order of the genes on the chromosome determines the order in which they are expressed along the anterior-posterior axis of the embryo. The Antennapedia group of homeotic selector genes includes *labial, antennapedia, sex combs reduced, deformed,* and *proboscipedia*. *Labial* and *deformed* genes are expressed in head segments (where their protein products activate the genes defining head features), and *sex-combs-reduced* and *antennapedia* genes encode the proteins that specify the properties of thoracic segments. In *Drosophila*, antennae and legs are created by the same program except a single transcription factor. When this transcription factor is mutated, the fly grows legs on its head in place of antennae, a phenomenon known as the *antennapedia mutation* (http://zygote.swathmore.edu/droso4.html).

The antennapedia homeodomain is a sequence-specific transcription factor from *Drosophila* encoded by the Antennapedia (*antp*) gene. The antennapedia homeodomain (Antp) is a member of a regulatory system that gives cells specific positions on the anterior-posterior axis of the organism. Antp aids in the control of cell development in the mesothorax segment in *Drosophila*. The homeobox domain (or homeodomain) binds DNA through a helix-turn-helix structural motif.

Homeobox genes (about 180 base pairs) were discovered in 1983, and the proteins they encode, the *homeodomain proteins* (~60 amino acid residues long) have been found to play important roles in the developmental processes of many multicellular organisms. They have been shown to play crucial roles in embryogenesis and have a wide phylogenetic distribution. Hundreds of homeobox genes have been described in baker's yeast, plants, and all animal phyla (Bürglin 1996).

15.2 The Role of DNA, RNA, and Protein Gradients in *Drosophila* Embryogenesis

At the syncytial blastodermal stage of Drosophila embryo (see K3 in Fig. 15.1), we can recognize three kinds of macromolecular gradients:

1. The *DNA gradients* high in the periphery of the embryo and low in its interior (as can be inferred from the RNA Images A2, B4, E4, and K4 in Fig. 15.1),
2. The *RNA gradients* along the anterior-posterior axes (see Images A4, C2, D3, F2, G2, H2, H4, J3, and K4), the dorsal-ventral axes (see Images A1, A2, and B4), and other directions (see Images E4, G2, H1, H3, I3, and K4), and
3. The *protein gradients* that can be inferred from RNA gradients since no RNA would be synthesized or degraded without the associated catalytic proteins or enzymes. Protein gradients must also be present to act as molecular transporters or motors (Chap. 8) responsible for generating DNA and/or RNA gradients.

A macromolecular gradient has two fundamental properties – (1) the property intrinsic to the macromolecule (hence to be referred to as the *intrinsic* or *single-molecule property*) and (2) the property arising from its being a part of a gradient (to be referred to as the *extrinsic* or *collective property*). Of course, any gradient can be of two distinct kinds – (1) the *spatial gradient* (more *here* than *there*) such as those asymmetric RNA localization images given in Fig. 15.1, and (2) the *temporal gradient* (more *now* than *before*) such as the RNA trajectories shown in Figs. 12.1 and 12.2a. The shape (i.e., the cooperative property of a macromolecule) of a gradient may be compared to an *audio music* and the intrinsic property of a macromolecule to a *sheet music*. In this analogy, the cellular genome is a master sheet music and the RNA and protein gradients are the audio music in two different media or channels having different effective ranges or fields of activity (see Row 3 in Table 15.1). Another way to characterize the roles of DNA, RNA, and protein gradients in an embryo is in terms of the concept of *molecular computing* or a *system of molecular computers* that are communicating with one another (to accomplish a common task) using the cell language (Sect. 6.1.2) mediated by intercellular protein messengers (see Row 5 in Table 15.1). Viewed in this manner, the RNA localization (or gradient) images such as displayed in Fig. 15.1 can be considered to represent an instantaneous computing activity (observed through the lens of RNA) that is being carried out by the *Drosophila* embryo as it develops toward an adult fruit fly.

15.3 The Triadic Control Principle (TCP)

The analysis of the genome-wide variations of the RNA levels in budding yeast undergoing glucose-galactose shift (see Sect. 12.3) strongly indicates that the intracellular concentration of RNA molecules is constantly *controlled* by the cell

Table 15.1 The roles of DNA, RNA, and proteins in *Drosophila* embryogenesis

	DNA	RNA	Protein
1. *Average size* (arbitrary unit)	3	2	1
2. *Diffusibility* (arbitrary unit)	1	2	3
3. *Effective range of action*	(a) Nucleus	(a) Nucleus (b) Cytoplasm	(a) Nucleus (b) Cytoplasm (c) Extracellular space
4. *Catalytic activity*	No	Almost none	Yes
5. *Function*	Secondary memory (Sect. 11.2.6)	Primary memory (Sect. 11.2.6)	Soft transistor (Sect. 5.1.1)
	Optimal form for information reproduction	Optimal for information retrieval Molecular computing Cell language (Table 6.3)	Optimal form for energy transduction[a]

[a]From chemical to mechanical forms, i.e., conformons (Chap. 8)

to meet its needs by balancing the *rates of production* (V_P) and the *rates of degradation* (V_D) of RNA (see Steps 1 and 2 in Fig. 15.2). Depending on the needs of the cell, the concentrations of intracellular levels of specific RNA molecules are *actively maintained* at one of the following three dynamic states:

1. *Dynamic steady states* (when $V_P = V_D$),
2. *Ascending states* (when $V_P > V_D$), and
3. *Descending states* (when $V_P < V_D$).

Recent evidence indicates that V_P and V_D are space- and time-dependent, often regulated by microRNAs (Makeyev and Maniatis 2008), thereby qualifying space- and time-dependent RNA levels as members of *dissipative structures* and, more specifically, members of IDSs or r-dissipatons (see Sect. 3.1.2).

The Triadic Control Principle (or Hypothesis) depicted in Fig. 15.2 is so called because of the existence of two opposing processes, 1 and 2, under the control of a third process, 3. The source of the control signals, or the agent of the cell control, is postulated to be the *cell itself* which is in constant communication with its neighbors and environment (by exchanging information carried by diffusible molecules or through local electric fields) and perform molecular computation under the guidance of DNA programs (sheet music). This postulate is consistent with or equivalent to the postulate that the cell is the smallest DNA-based molecular computer or *the Computon* (see Row 9 and Footnote 7 in Table 6.3) (Ji 1999a). The modifier, "triadic", also implies (1) that there are three, and only three, classes of the processes underlying cell functions, namely, *production, degradation*, and

control of production and degradation, and (2) that there exists a hierarchy among these three processes:

$$\textbf{Production} > \textbf{Degradation} > \textbf{Control} \tag{15.4}$$

where the symbol, " $\mathbf{A} > \mathbf{B}$", reads as "**A** must precede **B**" or "**A** is a prerequisite for **B**". Scheme (15.4), when applied to Fig. 15.2, suggests (1) that **X** must be produced before it can be degraded, and (2) that the production and degradation processes of **X** must be in place before they can be controlled. This is reminiscent of a similar hierarchical relation that obtains among the three fundamental aspects of reality that Peirce referred to as Firstness, Secondness, and Thirdness (Sect. 6.2.2).

If the system under consideration is the cell, then the function of the cell is postulated to depend on the presence of a set X of molecules and ions inside the cell. If the system under consideration is a subcellular compartment of a developing embryo such as the peripheral compartment of a syncytial blastoderm, then the function of such a compartment is thought to depend on the set X of molecules and ions present in that compartment as a balance between their input into and output from the compartment. The concentrations or levels of the members of X can be controlled by regulating their rates of *production* (or input) and *degradation* (or output). The vertical double-headed arrow indicates an identity relation. The horizontal arrows indicate irreversible processes driven by free energy dissipation. The numerals 1, 2, and 3 refer to the hierarchical relation shown in Inequality (15.4): Without 1, no 2; without 2, no 3. The source of the control signals is postulated to be the cell itself which communicate with its neighbors and environment as indicated above.

The nature of X in Fig. 15.2 can be any material or physical entities controlled by the system under consideration, including activated genes, pre-mRNAs, mRNAs, nc-RNAs (Amaral et al. 2008, Mattick 2003, 2004), microRNAs (Hobert 2008, Makeyev and Maniatis 2008), small-molecular-weight entities such as glucose, ATP, P_i, NADH, and metal ions. X need not be confined to the cell and can represent any material entities that play fundamental role in living systems such as blood level of hormones, glucose, and other metabolites, blood content of an organ, and the space- and time-dependent number of electrically active neurons in the brain, etc. In Table 15.2, the triadic control mechanism is applied to five different levels of biological organization, listing specific examples of the key components of the mechanism in a self-explanatory manner.

Enzymes may be viewed as one of the simplest material systems whose behaviors can be accounted for in terms of the *triadic control mechanism* depicted in Fig. 15.2. Enzymes can exist in at least two conformational states, *ground state* and *activated state* (characterized by the presence of sequence-specific conformational strains, i.e., *conformons*; see Figs. 11.30 and 14.7). The activated state of an enzyme is produced by substrate binding (Jencks 1975) and/or exergonic chemical reactions through generalized Franck–Condon mechanisms (see Fig. 8.1 and Sect. 11.4). The activated state of an enzyme is caused to *relax* back to its ground state when it performs a molecular work, be it catalysis (i.e., lowering the

Table 15.2 The triadic control principle or mechanism applied to five levels of biological organization

Level	Production	X	Degradation	Control	Function
1. Subcellular	*Substrate binding, chemical reactions*	*Conformational strains*[a] *of biopolymers* (Chap. 8)	*Molecular work processes* (e.g., catalysis, active transport)	*Evolutionary information encoded in biopolymers* (Sect. 11.3.3)	*Time- and space-organized molecular processes* (e.g., active transport, gene expression)
	Transcript-ion (transcriptosome)	*RNAs* (Chap. 12)	*Transcript degradation* (degradosome)	*Biochemical signals* (e.g., ATP, transcription factors, miRNAs)	*Controlling metabolic activities* (e.g., glycolysis, respiration, cell cycle, morphogenesis)
	Phosphorylation (kinases)	*Phosphoproteins* (e.g., activated enzymes)	*Dephosphorylation* (phosphatases)	*Biochemical signals* (e.g., cholesterol, cAMP, ATP)	*Cell type-specific cell functions* (production of key metabolites)
2. Cellular	*Mitosis*	*Cells*	*Apoptosis*	*Intercellular messengers*	*Morphogenesis, organogenesis, carcinogenesis*
3. Tissue	*Blood inflow*	*Tissue blood content*	*Blood outflow*	*Hormones, nerve signals*	*Tissue-specific activities* (e.g., brain activity)
4. Organ (e.g., blood)	*Activation* (e.g., by proteolysis)	*Activated coagulation factors*	*Inactivation* (by proteolysis, protein phosphatases)	*Biochemical signals* (e.g., from ruptured vessels)	*Homeostasis of organ function* (e.g., prevention of blood loss, i.e., hemostasis)
5. Body	*Vasoconstriction,* ↑*cardiac output*	*Blood pressure*	*Vasodilation* ↓*cardiac output*	*Renin, angiotensin, aldosterone*	*Homeostasis of body perfusion* (microcirculation)
	Activation (e.g., pleasurable stimuli)	*Reward system activity*	*Deactivation* (e.g., painful stimuli)	*Habit, will*	*To promote the survival of individuals and species*

[a]Also called *conformons* (Chap. 8)

activation energy barrier) or exerting mechanical forces on its environment as in active transport (Sect. 8.5) or muscle contraction (Sect. 11.4). It is postulated that the *control information* that determines the number of conformons stored in an enzyme at any given time is encoded in the amino acid sequence of the enzyme which in turn determines the 3-dimensional shape of the enzyme under a given environmental condition. The function of the enzyme can be very broadly identified as the time- and space-organized biopolymer motions in the cell driven by exergonic chemical reactions, including not only molecular motor and pump functions but also basic catalysis such as covalent modification of substrates in solution.

15.4 The Synchronic vs. Diachronic System–Environment Interactions

In biology, we can recognize two distinct classes of *system-environment interactions* – (1) the *individual-environment interactions* (IEI) and (2) the *population-system interactions* (PEI) (see Row 1 in Table 15.3). IEI takes place over a

Table 15.3 Synchronic and diachronic interactions between living systems and their environment

		Interactions	
		Synchronic	Diachronic
1.	Systems	Individual organisms	Populations of organisms
2.	Timescale (see Fig. 14.3)	Synchronic time (or *developmental time*)	Diachronic time (or *evolutionary time*)
3.	Mechanisms of interactions	Force-mediated	Code-mediated
4.	Principles obeyed	Laws of physics and chemistry (Secondness)[a]	Rules, codes, conventions (Thirdness)[a]
5.	Fields	Molecular biology	Evolutionary biology
		Chemical biology	Paleontology
		Epigenetics[b]	Genetics[c]
		(Synchronic biology)	(Diachronic biology)
		"Semantic biology"	
		Cell biology (*genomics*)[d]	
		Physiology	
		"Evolutionary developmental biology (or EvoDevo)"	
		"Developmental evolutionary biology"	
		"Biosemiotics"[e]	
		"Biongnergetics"[f]	

[a]Related to the metaphysics of Peirce (see Sect. 6.2.1)
[b]The study of the effects of genes (other than their nucleotide sequences) on the phenotypes of individuals here and now
[c]The study of the effects of genes (i.e., their nucleotide sequences) of individuals on the phenotypes of their offspring
[d]Genomics is here defined as a combination of *epigenetics* and *genetics*
[e]The study of molecular signs (e.g., DNA, RNA, protein domains) in living systems (Sect. 6.2) (Sebeok 1990, Hoffmeyer 1996, Pattee 2008)
[f]The study of information (*gn-*) and energy (*−erg*) transductions in living systems (Ji 1985a, b)

relatively short timescale characteristic of individual life spans. In contrast, PEI occurs over a much longer timescale determined by the life span of populations or species. In Sect. 14.4, the former timescale was referred to as the *synchronic time* and the latter as the *diachronic time*. Hence, we may refer to IEI as *synchronic interactions* and PSI as the *diachronic interactions*. (For related discussions, see Sects. 2.6 and 4.5.)

Since all physical interactions are force-mediated, "physical interactions" and "synchronic interactions" are synonymous. There are four forces in nature – gravitational, electromagnetic, weak, and strong forces. The electromagnetic and weak forces are often combined as the electroweak force. Forces and energies are mathematically related to each other through the Second Law of Newtonian mechanics. Hence, "force-mediated" and "energy-mediated" can be used interchangeably. "Code-mediated" processes include all template-mediated processes in molecular and cell biology such as enzymic catalysis, replication, transcription, translation, receptor-mediated processes, and signal transduction in cell. These interactions are referred to as "diachronic interactions" because it takes a long time for the codes involved to develop and change, relative to the time it takes for a code to effectuate its functions, for example, as a template for copying activities.

What goes on in biological systems (i.e., enzymes, cells, tissues, animals, plants, etc.) obey the laws of physics and chemistry just as what goes on in nonbiological systems (e.g., rocks, machines, mountains, stars) do. But what distinguishes biological systems from nonbiological systems is the rules, codes, and conventions embodied in their boundary conditions or structures that harness or constrain the operation of the laws of physics and chemistry to accomplish their goals (see Row 4 in Table 15.3) (Bernstein 1967, Polanyi 1968, Pattee 1982, 2008). In other words, biology has two complementary aspects – law-governed and the rule-governed as pointed out by Pattee (182, 2008). Thus, it seems natural to divide biology into two branches, for example, *chemical biology* vs. *evolutionary biology* (see Row 5 in Table 15.3), depending on which of these two aspects of biology is being emphasized.

The dichotomy of the *law-governed* and *rule-governed* aspects of biology seems to be first recognized and has been systematically investigated by Pattee (1968, 1969, 1982, 1995, 1996, 2001, 2008) under the rubric of the *symbol-matter complementarity* during the past several decades. In (Ji 1999b), I referred to Pattee's idea as the "von Neumann-Pattee principle of sign-matter complementarity" (VPPSMC) and pointed out the close theoretical relation existing between VPPSMC and the *information-energy complementarity* (IEC) or the *gnergy principle* (Sect. 2.3.2) formulated in the 1990s by extending Bohr's principle of complementarity from quantum mechanics to biological phenomena including the operation of enzymes and molecular machines in living cells.

The *von Neumann-Pattee principle of sign-matter complementarity* (Pattee 1982, 2008, Ji 1999b) and the information-energy complementarity (Ji 1991, 1995) may be viewed as theoretical attempts to integrate both law-governed (i.e., *causal*) and rule-governed (i.e., *codal*) aspects of biology. A similar view has been expressed by Barbieri (2003, 2008a, b, c) who has been attempting to integrate the *syntactic* and *semantic* aspects of molecular biology under the umbrella of *biosemiotics* in

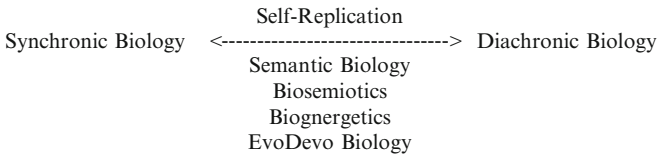


Fig. 15.3 A classification of biology into three branches, two of which (synchronic and diachronic biologies) may be viewed as the complementary aspects of the third (semantic biology, biosemiotics, biognergetics, or EvoDevo biology). "Gnergy" is defined as the complementary union of information (gn-) and energy (−ergy) in analogy to light being the complementary union of waves and particles (Sect. 2.3.2), and "biognergetics" is the study of living processes viewed as being driven ultimately by *gnergy* or its discrete units, *gnergons*

agreement with (Hoffmeyer 1996, 2008, Pattee 2008). These theoretical developments coincide with the recent trend in experimental biology to integrate developmental biology and evolutionary biology, the trend often referred to as "evolutionary developmental biology" (EvoDevo) or "developmental evolutionary biology" (Carroll 2006, Kirschner and Gerhart 1998, West-Eberhard 1998, 2003). The newly emerging biology that attempts to integrate the traditionally independent developmental biology and evolutionary biology into a coherent system of knowledge and applications has been given numerous names by independent authors, some of which are listed in the last row of Table 15.3. The last row of Table 15.3 can also be represented diagrammatically as shown in Fig. 15.3, which highlights *self-replication* as the single most important process that glues together all of the three branches of biology.

15.5 The Dissipative Structure Theory of Morphogenesis

Morphogenesis is a dynamic process consisting of many component processes taking place in an organism coordinated in space and time. In short,

> Morphogenesis is a dissipaton composed of a set of component dissipatons that are organized in space and time. (15.5)

The *dissipative structure-* or *dissipaton-based* approaches to cell biology described in the previous chapters (e.g., Sects. 3.1, 9.1, and 12.4) suggest the following set of generalizations as theoretical guides for formulating molecular mechanisms underlying morphogenesis:

1. There are two classes of structures in the Universe – equilibrium structures (*equilibrons*) and dissipative structures (*dissipatons*) (Sects. 3.1, 9.1). The key difference between *equilibrons* and *dissipatons* is that the former can exist without using up free energy while the latter requires continuous dissipation of free

Table 15.4 Examples of *equilibrons* and *dissipatons* in the Universe

Size	Equilibrons	Dissipatons
Macroscopic	Chairs, tables, cold candle sticks, rocks, secondary memory of a computer	Candle flames, sounds, city traffic flow patterns, primary memory of a computer
Microscopic	X-ray structures of proteins, RNA and DNA, linear sequences of nucleotides in genes, molecular structures of ATP, NADH, and glucose	Membrane potentials, cytosolic gradients of ions and metabolites, spatiotemporal patterns of changes in RNA levels in cells and embryos (Figs. 9.1, 15.1)

energy for their existence. Thus, anything that disappears when free energy supply is blocked belongs to the family of *dissipatons* while anything that remains unaffected by the blockade of free energy supply belongs to that of *equilibrons*. Some examples of these two classes of structures are given in Table 15.4.

2. There are many examples of *dissipatons* produced inside the cell, including the time-dependent changes in RNA levels in budding yeast measured with DNA microarrays which correlate with cell functions (Figs. 9.1, 12.2a) (Ji et al. 2009a). These so-called RNA kinetic patterns (also called "RNA trajectories", *ribons,* or *RNA waves*; see Sect. 12.7) can be visualized on a 2-dimensional plane as shown in Figs. 12.10 and 12.11.
3. One of the most distinct features of the molecular theory of the living cell being developed in this book is what is here referred to as the *Dissipaton-Cell Function Identity (DCFI) Hypothesis* which was also referred to as the *IDS-Cell Function Identity (ICFI) Hypothesis* in Sect. 12.5. This hypothesis asserts that *dissipatons* and *cell functions* are the two sides of the same coin. That is, *dissipatons* and *cell functions* are the internal (or *endo*) and external (*exo*) views, respectively, of the same phenomenon known as the living cell.
4. If we designate intracellular *dissipatons* associated with some cell function as X, the following generalization holds, because the activity (or level) of X must be able to undergo either an increase or a decrease whenever the cell needs in order to adapt to changing environment. Therefore, there must exist two processes, one producing X and the other destroying it as depicted in Fig. 15.2.
5. All cell functions can be accounted for, at least in principle, in terms of **X**, a set of molecules (e.g., enzymes, ATP, ions, RNA, etc.) whose kinetic patterns (also called behaviors, trajectories, or dissipatons) "cause" or "are correlated with" cell functions. This is the content of the *DCFI hypothesis* mentioned in 3 above.
6. Finally, it is suggested here that Fig. 15.2 can be applied to what goes on in the *extracellular space* (ECS), if we assume that there exists $\mathbf{X}'$ in ECS which is both produced (from **X** as a part of **F**) and destroyed in a manner similar to **X** in Fig. 15.2 so as to maintain its kinetic patterns to produce all extracellular structures and processes needed for all cell functions including morphogenesis. We will refer to this idea as the *Dissipative Structure Theory of Morphogenesis* (DSTM). Figure 15.4 schematically depicts the elements of DSTM.

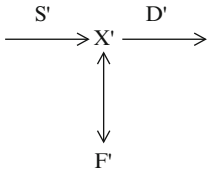


Fig. 15.4 An *external* (or exo) view of the "dissipative structure theory of morphogenesis" (DSTM). $\mathbf{S}'$ = synthesis of $\mathbf{X}'$ in extracellular space (ECS). $\mathbf{D}'$ = destruction of $\mathbf{X}'$ in ECS. $\mathbf{F}'$ = Extracellular functions, including the construction and destruction of extracellular matrix, the production and control of pericellular ion, metabolite, and intercellular messenger gradients. $\mathbf{X}'$ includes extracellular matrix proteins, and $\mathbf{S}'$ includes exocytosis of precursor proteins of $\mathbf{X}'$, and $\mathbf{D}'$ includes the various matrix metalloproteinases. In contrast, Fig. 15.2 can be viewed as an *internal (or endo) view* of the "dissipative structure theory of morphogenesis"

15.6 The Tree-Ring-and-Landscape (TRAL) Model of Evolutionary and Developmental (EvoDevo) Biology

Dendrochronology, the science of tree-ring dating, uses tree rings as a means to determine not only the age of trees but also to reconstruct the climate changes, since climate affects the tree growth and tree rings thus serve as a historical record of climate changes. The American astronomer A. E. Douglass (1867–1962) originally developed this technique in the first half of the twentieth century in order to understand cycles of sunspot activity. He reasoned that changes in solar activity would influence climate patterns on the earth which would in turn affect tree-ring growth patterns. In other words, Douglass correctly inferred the sequence of events shown in Fig. 15.5.

The main purpose of dendrochronology as developed by Douglass was to infer the sunspot activities from the tree-ring growth patterns. The purpose of morphogenetic research in biology is to understand how DNA and environmental changes bring about the shape changes in organisms within their lifetimes, that is, to understand the molecular mechanisms by which DNA and environment interact to bring about morphogenesis (Fig. 15.6).

Figures 15.5 and 15.6 have more common features than may appear on the surface. First, the tree ring is a relatively simple example of morphology. Second, sunspot activities and the associated climate changes constitute a part of the environment of organisms. Third, although not explicitly indicated in Fig. 15.5, tree rings are affected not only by sunspot activities and associated climate changes but also by the genome (i.e., DNA) of trees because different species of trees produce different tree-ring patterns even under identical environmental conditions. Therefore, Fig. 15.6 is a more comprehensive representation of the causal relations underlying morphogenesis and hence subsumes Fig. 15.5 and *dendrochronology*.

It is interesting to note that the causal scheme shown in Fig. 15.6 can be applied to either *developmental biology* or *evolutionary biology*, depending on the timescales adopted. On the time scale of individual organism's life span

Fig. 15.5 Tree rings can record sunspot activities, because sunspot activities affect climate which in turn influences tree-ring growth

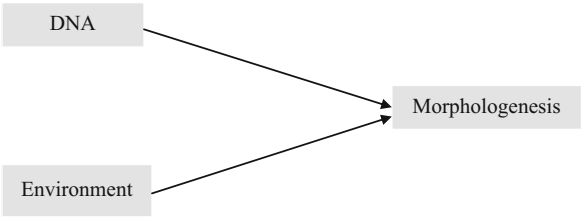


Fig. 15.6 DNA and environment as independent cause of the morphology of organisms. The main question in morphogenesis is: What are the mechanisms by which the combination of DNA and environment brings about the morphology of organisms. Please note that environment includes sunspot activities

(i.e., in synchronic time; see Table 15.3), Fig. 15.6 represents developmental biology; on the time scale of species life span which may be as long as hundreds or more life span of the individual members of a species under consideration (i.e., diachronic time scale), the same figure can represent evolutionary biology. Thus, it may be necessary to recognize two kinds of timescales in biology – developmental (or synchronic) and evolutionary (or diachronic) times – and these timescales may be said to be *complementary* to each other in the sense that focusing on one automatically excludes the other from view just as focusing on the wave nature of light (or forest) automatically excludes the particle nature of light (or trees) from view in physics and *vice versa*.

We may express this situation as in Statement 15.6:

> The biological time is complementary union of developmental (or synchronic) time and evolutionary (or disachronic) time. (15.6)

Statement 15.6 may also be referred to as the *EvoDevo duality of life* in analogy to the *wave/particle duality* of light in physics.

Both developmental and evolutionary processes can be represented using the language of *renormalizable networks* discussed in Sect. 2.4. The network characteristics of development and evolution are summarized in Table 15.5.

Of course, different species have different life spans, which can range from 1 day to 10^6 days. So what distinguish synchronic from diachronic timescales are not the absolute lengths of time measured with a clock as done in physics but rather the number of replication cycles of organisms which is unique to biology. In other words, synchronic and diachronic times are measured relative to the unit of the life span of organisms whereas the conventional time in physics is measured with a *clock*, which naturally leads to the possibility of dividing time into *physical* and *biological* times as schematized in Fig. 15.7.

Table 15.5 The network representation of the *EvoDevo duality of life* in biology in analogy to the wave/particle duality of light in quantum physics

	Devo (development)	Evo (evolution)
1. *Node*	Fertilized egg cells	Organisms
2. *Edge*	Synchronic interactions (*within the life span of an individual organism*)	Diachronic interactions (*within the life span of a species*)
3. *Goal*	Mature organisms	Mature species

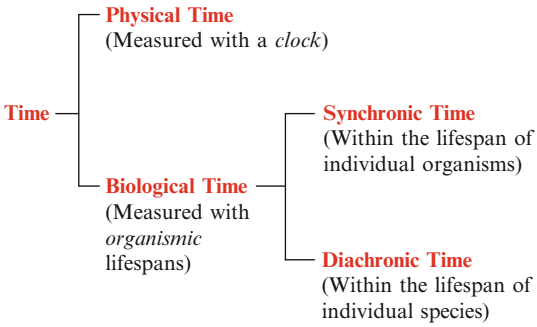


Fig. 15.7 *The dual dichotomy of time*. That is, dichotomizing time into *physical* and *biological* times on the one hand and the biological time into *synchronic* and *diachronic* times on the other

The synchronic time is confined within the life span of the organisms of a species (e.g., days for bacteria and decades for *Homo sapiens*) and the diachronic time extends beyond individual life span and implicates hundreds or more of them, depending on the nature of the evolving traits under consideration.

Dichotomizing time into physical and biological times as shown in Fig. 15.7 appears reasonable in view of the fact that there are two distinct kinds of irreversible processes in nature – (1) *physical irreversible processes* such as diffusion of gases and radioactive decays of some elements, and (2) *biological irreversible processes* including cell division and cell death which have never been observed to be reversible. Any irreversible processes can be used as a *clock* to measure time. One major difference between *physical time* and *biological time* is the constancy of time interval or duration in the former (in non-relativistic frameworks) (Hawking and Mlodinow 2010) and the flexibility or variability of time interval or duration in the latter (e.g., the life span or generation time of bacteria is in hours as compared to that of humans which is in tens of years).

Just as dendrochronology as represented in Fig. 15.5 can be viewed as a subdiscipline of the EvoDevo duality of life as depicted in Fig. 15.6, the pattern of tree rings (combined with the image of landscape symbolizing the probability space) appears to provide a convenient *visual representation* of the EvoDevo duality of life as schematized in Fig. 15.8.

This so-called Tree-Ring-And-Landscape (TRAL) model of the EvoDevo duality of life can be applied to either *development* or *evolution* separately, not together, just as wave-measuring and particle-measuring apparatuses cannot be used together to study the nature of light (Bohr 1933, 1958, Herbert 1987). The TRL model, when

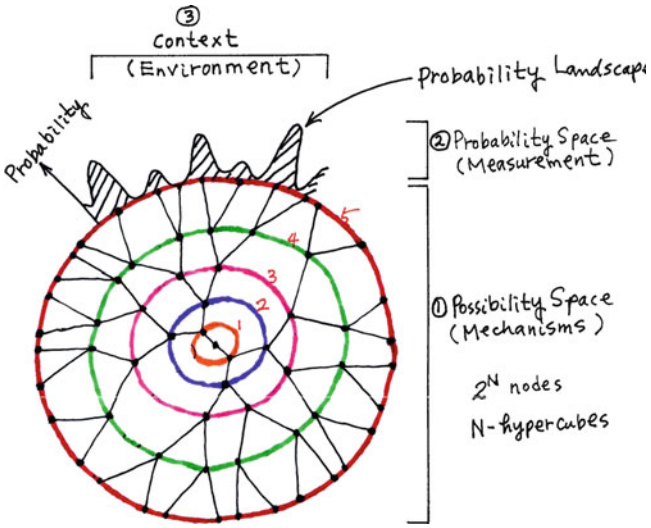


Fig. 15.8 The "Tree-Ring-And-Landscape" (TRAL) model of the EvoDevo duality of life (in analogy to the wave/particle duality of light). Each *circle* has 2^N cells, where N is the number of circles starting from the center which is assigned the value of $N = 0$. Each node has 2^n possible internal states, where $n =$ the number of genes in the cell

applied to *morphogenesis* (one of the three branches of developmental biology, the other two being *growth* and *differentiation*), has the following characteristics:

1. Each circle represents one *cell generation* which is exposed to an environment that may or may not change with time.
2. The number of *cells* (represented as nodes or vertices) on the Nth circle is 2^N, where N is the number of cell generations. When $N = 0$, there is one cell (at the center of the tree rings); when $N = 1$, there are two cells (or nodes) on the first circle; when $N = 2$, there are four cells on the second circle, etc.
3. The cells/nodes on any concentric circle carry a set of n genes in their DNA. The set of n genes can be represented in terms of a string of n 0′s and 1′s, enabling the functional state of the cell to be characterized by the patterns of the distribution of 0′s (inactive genes) and 1′s (activated genes). The total number of possible cell states is 2^n. In other words, each node on a circle has a set of 2^n possible internal states (not shown) that can be represented as a string of n 1′s and 0′s. (The n genes are renormalized as a node.)
4. Thus the TRAL model provides a convenient visual method for representing one (stem) cell growing into a system of 2^N cells, each cell occupying one of the 2^n cell states compatible with the prevailing environmental conditions:

   $2^N =$ cell number
   $2^n =$ cell states

5. The Nth circle (or ring) of the TRAL model can be described as an N-dimensional hypercube with 2N nodes, each node having characteristics

Table 15.6 The definition of the c-triad, assumed to be the necessary and sufficient condition for cell life including morphogenesis (Ji and Ciobanu 2003)

C-Triad	Description
1. *Computation*	Cells are evolutionarily programmed to express only those genes that promote the survival of the organisms (of which they are parts) under given environmental conditions
2. *Construction*	Cells manufacture their structural components and intercellular messengers before undergoing cell division, under the control of the environment (through synchronic interactions) and the genome (through diachronic interactions)
3. *Communication*	Cells communicate synchronically with one another by exchanging messenger molecules in order to cooperate to accomplish tasks beyond the ability of individual cells

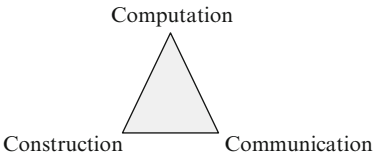


Fig. 15.9 A diagrammatic representation of the C-triad (Ji and Ciobanu 2003). The three processes are postulated to be both necessary and sufficient to account for the molecular mechanisms underlying the life of the cell

describable in terms of an n-bit string of 1′s and 0′. Thus, the circles of the TRAL model and hypercubes are mathematically equivalent or isomorphic. All the cells (i.e., nodes), except the original cell at the center, are connected by three links each forming a Y in the centrifugal direction (i.e., from the center toward the periphery), reflecting the fact that one cell gives rise to two cells with the precursor cell disappearing as the result of cell division.

6. Within any time period (e.g., an average cell cycle time), only one ring, that is, the outermost ring, is present or realized with all the associated precursor rings having disappeared into the past (unlike the real tree rings which accumulate).
7. The outermost ring is associated with a probability space erected perpendicular to it to encode the probabilities of observing particular gene-activity states of the cells on the ring determined by the current cellular environment, the gene-activity states being represented by strings of 2n 1′s (a gene turned on) or 0′s (a gene turned off).
8. The gene-activity state of a cell, in combination with the cell environment, is thought to determine the three fundamental activities of the cell, that is, computation, construction, and communication (see Table 15.6 and Fig. 15.9).
9. Therefore, the shape or topology of the probability landscape (to be referred to as the probability distribution function of cell states [PDFCS]) erected on the outermost ring (which resembles the topology of a landscape) is determined by both the current gene-activity states of the cells (which in turn determine

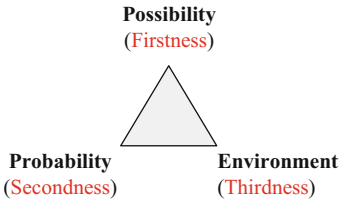


Fig. 15.10 The approximate correspondence between the triadicity of the TRAL model of life (Fig. 15.8) and the triadic metaphysics of C. S. Peirce (1903) (Sect. 6.2.2)

the activities of the C-triad) and their environmental conditions and carries all the information that can be observed/measured about an organism consisting of 2N cells, each cell endowed with n genes, that are organized in space and time, including its morphology. Thus defined, PDFCS described by the TRAL model is akin to the wave function in quantum mechanics (Herbert 1987, Morrison 1990).

10. The principle of dendrochronology is this: As the cells divide, the diameter of the tree increases with time. Due to the dependence of the rate of cell divisions on the temperature and other factors of the environment of the tree, the density of cells in the tree varies with the seasons of the year – the highest density being found every winter. So the ring structure of a tree results from the interactions between two processes – the cell division (which is internal to the tree) and the rotation of the Earth around the Sun (which is external to the tree). This principle of dendrochronology may be generalized and extended to morphogenesis, since a similar, although much more complex, process can account for the structures visible on the cross section of the *Drosophila* embryos which are the results of the interaction between the internal cell division/differentiation and the external alterations of environment (including temperature, humidity, morphogen gradients, etc.). Just as we can now read off the age (and the past environmental conditions) of a tree from tree rings, so we should in principle be able to read off the developmental and evolutionary history (or mechanisms) of *Drosophila melanogaster* from the molecular and cellular architectonics of the *Drosophila*.

One unexpected result of the TRAL model is that it provides a clear visual distinction between "possibility" and "probability". Possibility is Firstness of Peirce, probability is Secondness, and Environment is Thirdness by default (Sect. 6.2.2) (Fig. 15.10):

15.7 Quorum Sensing in Bacteria and Cell–Cell Communication Networks

Quorum sensing refers to the phenomenon exhibited by a group of bacteria that expresses select sets of genes *if and only if* there are a sufficiently large number of them around (hence "quorum") to cooperatively accomplish a gene-encoded task that cannot be accomplished by individual bacteria (Miller and Bassler 2001).

This phenomenon was discovered by two independent groups about 40 years ago (Fuqua and Greenberg 2002). The seemingly intelligent behavior of bacteria is the natural consequence of the following networks of structures and processes that interact with one another in an organized manner:

1. Bacteria possess the genes coding for diffusible intercellular messengers called *autoinducers*.
2. Bacteria possess the genes coding for the cell membrane receptors recognizing and importing the autoinducers present in the pericellular space.
3. Bacteria possess the genes that code for signal transducing proteins that, when activated by extracellular autoinducers binding to their target receptors, are able to search for and express the set of genes encoding the proteins that can implement quorum-sensitive or quorum-dependent effector functions.

An example of a bionetwork embodying these elements organized in space and time so as to exhibit quorum sensing is given in Fig. 15.11, which consists of nine nodes and seven edges. The network representation in this figure is a simple and convenient way of keeping track of all the main components and their interactions involved in effectuating quorum sensing. This bionetwork is best viewed as an example of *dissipative structures* at resting state and, when the system is activated to exhibit the phenomenon of quorum sensing, the system can be said to undergo a state transition from the resting to the activated states. Figure 15.11 is not an equilibrium structure because most of the structures shown in this figure would disappear upon cessation of free energy supply to the cell. An activated state of dissipative structures is characterized by a selective activation of a subset of the nodes of the bionetwork involved, leading to space- and time-organized physicochemical processes that appear to us observers as *quorum sensing*. The extracellular or cell–cell communication components of quorum sensing can be viewed as "intercellular dissipative structure" and represented as a bionetwork wherein cells themselves serve as nodes and molecule-mediated interactions among them as edges. Hence quorum sensing can be viewed as *a bionetwork of bionetworks*, reminiscent of the "renormalization" phenomenon in bionetworks discussed in Sect. 2.4. Thus the notion of bionetwork is one of those concepts in biology that can be applied to multiple levels *recursively* and hence may be at least partially responsible for the phenomena of *self-similarity* and *power laws* universally found in living systems (Gribbin 2004, Whitfield 2006).

It is surprising to find how simple the set of molecular structures and processes are that can give rise to the seemingly intelligent behaviors of bacterial quorum sensing. Quorum sensing in bacteria may be regarded as one of the simplest cases of *cellular intelligence* and *cellular computing*, and we can now confidently say that we have a more or less complete understanding of the molecular mechanisms underlying one of the simplest intelligent behaviors of organisms. That is, there is no mystery about *cellular intelligence*. It simply is yet another example of *self-organizing chemical reaction–diffusion processes* or *dissipative structures of Prigogine*. Hence, we may logically refer to the intelligent behaviors of cells as the X-ator following the naming tradition established in the field of self-organization (Babloyantz 1986), X indicating the name of the city most closely associated with the pioneering

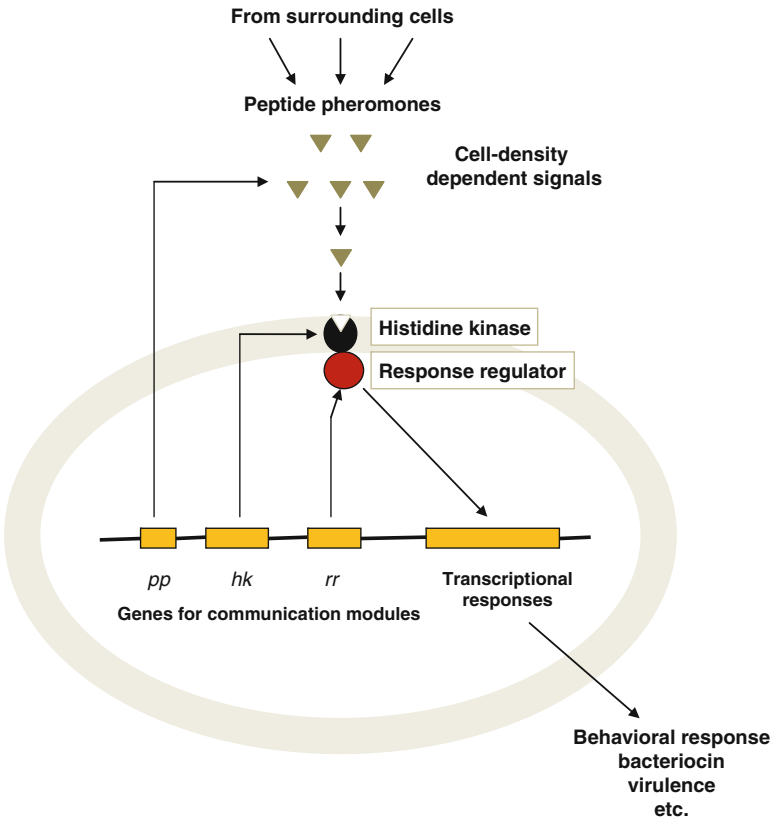


Fig. 15.11 Mechanisms underlying *quorum sensing* in bacteria. Quorum-sensing bacteria carry four classes of genes (see the four *dark bars* along the DNA symbolized by the horizontal line) coding for (1) pheromones (also called *autoinducers*, symbolized by *triangles*), i.e., small signal molecules secreted into the extracellular medium, (2) receptor (see the *dark sphere*) for recognizing pheromones (mainly from other bacteria) and having histidine kinase activity, (3) response regulator (see the *white sphere*) required to transduce the extracellular signal, and (4) genes required for behavioral responses such as production of bacteriocins (proteins that kill certain strains of bacteria), biofilm formation (for group protection), and virulence (ability to overwhelm host's immune system response) (Adopted from the figure published at http://www.sibelle.info/oped31.htm)

research on quorum sensing. To the best of my knowledge, Princeton is a good candidate for X, but unfortunately, the name Princeton has already been used to label the self-organizing reaction–diffusion system responsible for the origin of biological information proposed by P. Anderson and his coworkers at Princeton University in the early 1980s, namely, the Princetonator (Ji 1991a, pp. 224–225) (see Fig. 13.3). To get out of this dilemma, it is suggested here that a city nearby Princeton be *commandeered* to serve as Princeton's surrogate. Trenton may be the logical choice for this purpose, since Trenton is the capital city of the State of New Jersey where Princeton University is located. Hence, we may refer to any self-organizing

chemical reaction–diffusion system capable of exhibiting intelligent behaviors such as quorum sensing in bacteria as the *Trentonator*. Thus, quorum sensing in bacteria is the first Trentonator to be characterized in molecular terms. I would not be surprised if human intelligence will turn out to be the result of a set of elementary *Trentonators* that are spatiotemporally organized within our brains, nor if there exists a minimum number of neurons (10^2–10^3 ?) that is needed to form the basic Trentonator responsible for human intelligence.

15.8 Morphogenesis as a Form of Quorum Sensing

Morphogenesis or shape development is a multicellular phenomenon. Therefore, there is the distinct possibility that cells will cooperate in morphogenesis just as they do in quorum sensing. *Drosophila melanogaster* is the best studied model organism for morphogenesis. *Drosophila* morphogenesis starts with a fertilized single-celled egg which becomes a multicellular embryo with structured tissues and specialized cells and organs. This process occurs through many cell divisions, shape changes, and cell migrations called gastrulation. What is interesting about morphogenesis from a theoretical point of view is this: The initially symmetrical embryo undergoes a series of *symmetry breaking processes* to become a less symmetric structure. In other words, the *Drosophila* embryo undergoes state transitions from *disordered* to *ordered* states, to use the terminology of condensed matter physics of critical phenomena (Landau and Lifshitz 1990). Thus, *symmetry breakings* and *disorder–order transitions* may be regarded as two of the most fundamental processes in morphogenesis. The first mathematical model of symmetry breaking in morphogenesis was proposed by A. Turing in 1952 (Gribbin 2004) which is based on three elementary processes – (1) A catalyzes the formation of A and B, (2) B inhibits the formation of A, and (3) A and B have different diffusion constants. These three elements were necessary and sufficient to produce *symmetry breakings* in chemical concentration fields (Gribbin 2004, p. 127).

The simplest symmetry-breaking process in *Drosophila* morphogenesis involves what is known as "convergent extension," in which cells in a two-layer configuration migrate vertically so as to form one-layered cells with an increased horizontal length. Such cellular rearrangements are well within the capability of cells, since they are self-organizing chemical reaction diffusion systems endowed with the ability to execute the c-triad, i.e., *communication*, *computation*, and *construction* (see Table 15.6) (Ji and Ciobanu 2003). Consequently, *Drosophila* cells in this stage of development can (1) communicate with one another by synthesizing and secreting one or more morphogens (akin to autoinducers in bacteria) which diffuse away from the cells that produce them, (2) can compute the number of neighboring cells based on the combined concentrations of the morphogens secreted by neighboring cells, and (3) when the morphogen concentrations exceed a threshold value, can trigger the signal transduction cascade, leading to turning on or off of a set of genes needed to rearrange cells to produce the right embryological structure, for example, *convergent extension*. These same processes are involved in the phenomenon of quorum sensing in bacteria presented in Sect. 15.7.

Another fundamental feature of embryogenesis is that, throughout its process, there occur micro–meso correlations, because morphogenesis is ultimately directed by the molecular sequence information encoded in DNA which is located in the nucleus of individual cells. If this interpretation is right, it may be concluded that embryos are physical systems at critical points at the micro-, meso-, and macrolevels. In a sense, embryogenesis is a critical phenomenon, which may be referred to as a *bio-critical* phenomenon in contrast to the purely physical ones studied in condensed matter physics (Anderson 1972, Fisher 1998, Domb 1996).

15.9 Carcinogenesis as Quorum Sensing Gone Awry

Normal cells show the phenomenon of *contact inhibition*: that is, normal cells stop dividing when they make contact with adjacent cells. In contrast, cancer cells lose this ability and continue dividing in the presence of neighboring cells, thereby leading to piling up of cells on top of one another, a characteristic feature of tumor.

There appears to be the possibility that the same mechanism used by bacteria in their quorum sensing activity may be involved in normal-to-cancer cell transformation. This idea is explained in Table 15.7.

The key assumption underlying Table 15.7 is that the mechanisms of intercellular communication/cooperation observed in bacteria also operate in principle in normal density-sensitive cell growth which requires cell–cell communication through gap junctions (Evans and Martin 2002, Trosko 2007). When this cell–cell communication is compromised (dynamically as compared to statically, as explained below), carcinogenesis and angiogenesis may occur (Trosko 2007, Luiza et al. 2007). It is assumed here that what passes through gap junctions between adjacent cells is not just equilibrium structures (e.g., ions, ATP, etc.) but *dissipative structures* (or *dissipatons*), namely, the time-dependent patterns of changes in the concentrations of equilibrium structures comparable to what is referred to as RNA dissipatons (the patterns of distribution of RNA trajectories) in Sect. 12.8.2 (see also Sect. 3.2). If this idea turns out to be correct, one might predict that it is not the differences in gap junctional structures alone that

Table 15.7 The hypothesis that carcinogenesis is a form of quorum sensing gone awry

	Quorum sensing	Carcinogenesis
1. Signal	Autoinducers	Transcription signals (less than 1,000 Da)
2. Receptor	luxR	Gap junctions (connexons)
3. Gene expression induced by	High levels of autoinducers detected by luxR	High levels of transcription signals accumulating in cancer cells due to gap junction blockade
4. Intercellular communication	Enhanced	Inhibited
5. Dissipative structures	Concentration gradient of autoinducers	Concentration gradient of transcription signals (e.g., ions, ATP, NADH, etc.?)

characterize normal vs. cancer cells but the dynamic patterns (e.g., fluctuating levels of ions maintained as the balance between the input through the gap junctions on one part of a given cell and the output through the gap junctions on another part of the same cell) that differentiates the intercellular messages being exchanged between normal cells, between normal and cancer cells, and between cancer cells.

15.10 Symmetry Breakings in Morphogenesis and Cosmogenesis

There may be an interesting analogy between the Big Bang theory in cosmology and the developmental biology including morphogenesis. In both cases, relatively homogeneous (i.e., symmetric or disordered) (Landau and Lifshitz 1990) initial states are transformed into heterogeneous (i.e., asymmetric or ordered) states as a function of time (see Figs. 15.1 and 15.12 and Table 15.8). In other words, in both

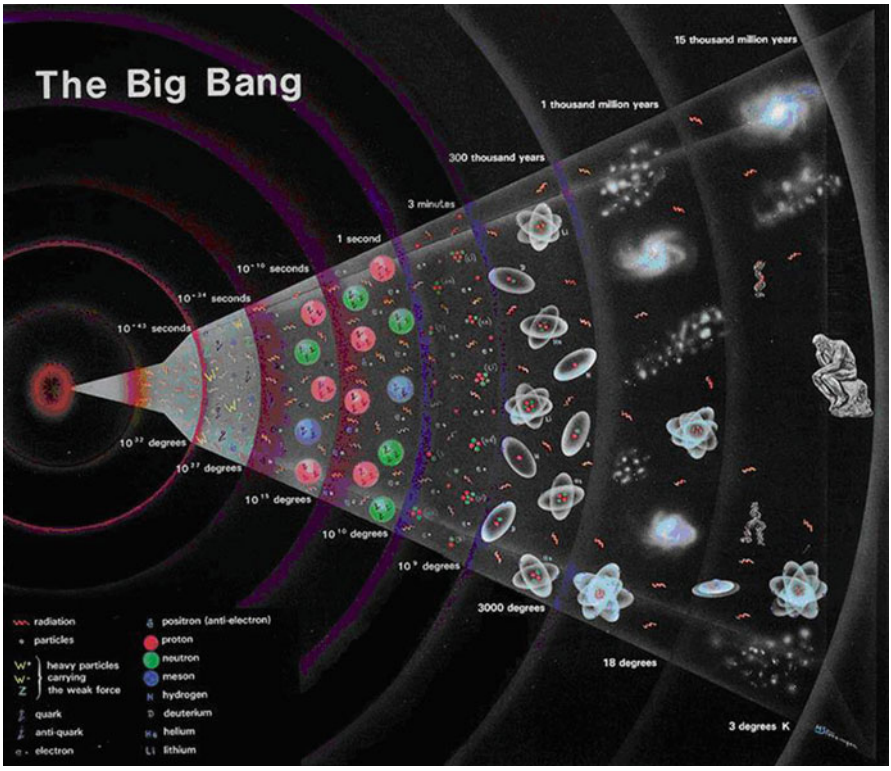


Fig. 15.12 The evolution (or morphogenesis) of the Universe. The initially *homogenous* (symmetric) mixture of electrons, quarks, gluons, and other particles becomes heterogeneous with time. The *geometric symmetry* (or homogeneity) of the Universe is continuously broken from the *left* to the *right*. After about 13.7 billion years, the Universe contains a *heterogeneous* (symmetry-broken) mixture of galaxies, stars, planets, and other objects (Reproduced from J. Gillies 2007)

Table 15.8 The history of symmetry breakings in the Universe

Concentric circles in Fig. 15.8	Time since time after the Big Bang	Temperature (degrees)	"Mattergy" (Sect. 2.3.1)
1	10^{-43} s	10^{32}	Radiation (i.e., energy), matter, antimatter
2	10^{-34} s	10^{27}	Radiation, matter, antimatter, quarks, gluons, W- and Z-particles
3	10^{-10} s	10^{15}	Radiation, matter, antimatter, quarks, anti-quarks, electrons, positrons
4	10^{-5} s	10^{10}	Radiation, electrons, positrons, protons, neutrons, mesons
5	3 min	10^{9}	Radiation, electrons, H, D, He, Li
6	3×10^{5} years	6×10^{3}	Radiation, H and other atoms
7	10^{9} years	18	Radiation, atoms, galaxies
8	15×10^{9} years	3	Radiation, stars, planets, DNA, *Homo sapiens*

cases, the algorithmic complexity of the systems involved (defined as the number of bits in the shortest string of symbols needed to describe an object or situation; see Sect. 4.3) increases, ultimately is driven by the increase in universal thermodynamic entropy (Sect. 2.1.4). This is why it seems logical to state that both the Big Bang and biological development (and biological evolution as well) can be viewed as examples of symmetry-breaking processes in space and time.

The cosmological symmetry breaking is generally known to be caused by the lowering of the temperature secondary to cosmological expansion (thus reducing the kinetic energy or momenta, i.e., velocity x mass, of particles) (see Fig. 15.12 and Table 15.8). However, biological symmetry breakings occur at constant temperatures (e.g., all the morphological changes shown in Fig. 15.1 occur within a narrow range of physiological temperatures), thus without slowing down thermal fluctuations or the Brownian motions of molecules and ions. Thus, we may associate *cosmogenesis* with "non-isothermal" or "cooling-driven" symmetry breakings (which will decrease *kinetic* energies of particles) and *morphogenesis* with "isothermal" or "constant temperature" symmetry breakings. In morphogenesis what is reduced may be construed to be the average distance between cognate binding surfaces of particles (including ions, molecules, biopolymers, and cells), thereby affecting their *potential* energies. Just as *momenta* (i.e., kinetic energies) and *positions* (affecting potential energies) are *complementary conjugates* in physics (Table 2.9), it may be that the *cosmological evolution* and *biological evolution* are also fundamentally related. There may be two (and only two) basic mechanisms of symmetry breakings in the Universe.

1. The "kinetic" mechanism where increased order results from reduced *kinetic energy* of binding partners, and
2. The "position" mechanism where increased order is caused by the reduction in the average distances between cognate particles (accompanied by decreased *potential energies*) in two ways – (a) via "passive" Brownian motions of binding partners and (b) via "active" translocation of binding partners driven by free energy dissipation.

We may refer to (2a) above as the "passive symmetry-breaking" mechanism, and (2b) as the "active symmetry breaking" mechanism. The cosmological (excluding biological) symmetry breakings may belong to the category of *passive symmetry breakings*, but living systems may utilize both *passive* and *active symmetry breakings*. These terms are related to the active and passive complexities discussed in Sect. 5.2.3.

An example of "active symmetry breakings" in morphogenesis is provided by the cell migration leading to germband expansion (Zallen 2006, Zallen and Wieschaus 2004) and an example of "passive symmetry breakings" is given by rosette formation among non-migrating cells in the germband of *Drosophila* (Zallen 2006). It seems possible that passively broken symmetry can be reversed, if some active mechanisms can intervene. This would mean that normal morphogenetic processes can implicate many active and passive symmetry-breaking processes organized in space and time, driven by free energy dissipation under the control of genetic information encoded in proteins, DNA, and RNA.

The cosmological symmetry breakings shown in Fig. 15.12 may have their counterparts in *biological symmetry breakings* exemplified by the development of a multicellular organism from a single fertilized egg cell. Biological symmetry breakings can be represented diagrammatically as bifurcation trees such as the inverted tree (Fig. 7.8) or the TRAL model (Fig. 15.8). If there are n cells in an adult organism, it will take (log n/log 2) generations of cell divisions for a fertilized egg cell to become an adult organism. Since there are about 10^{13} cells in the adult human body, it will take about 40 generations ($10^{13} \sim 2^{40}$) of cell divisions for a fertilized egg (see the node labeled 1 in Fig. 7.7 or the center node in Fig. 15.8) to mature into an adult human being with all its complexities. Figure 7.7, when rotated by 90° anticlockwise, resembles Fig. 15.12 in that the complexity (or order) of the system increases from left to right. If this comparison is valid, the Universe at the time of the Big Bang would be akin to a fertilized egg perhaps with superstrings acting as a "cosmological DNA" (Ji 1991).

Figure 7.7 was used to represent the postulate that enzymes can be viewed as coincident (event) detectors (Sect. 7.2.2). This notion can be better illustrated if Fig. 7.7 is rotated 90° clockwise. In this orientation, the leaves at the fifth level of branching (i.e., the nodes labeled 16–31) can be thought to represent Brownian particles or thermally fluctuating physicochemical processes, and the nodes at the next level (i.e., the nodes labeled 8–15) represent coincidence-detecting events. The leaves in Fig. 7.7 can be thought of as molecular events (e.g., enzymic reactions) which affect the next higher level (e.g., gene expression) which in turn affect the next higher level (e.g., cell divisions) and so on until the root (e.g., an embryo) is reached. Interpreted in this manner, Fig. 7.7 can be viewed as the mechanism for coupling genotype and phenotype, or microscale events and macroscale events, without any thermal gradients and hence as a system of dissipative symmetry breakings. In other words, these nodes are events (requiring x, y, z, and t to be specified and hence 4-dimensional in nature) that occurs if and only if two or more lower-level events occur more or less synchronously, that is, within a certain time window or bin, Δt, with intensities equal to or greater than the threshold, Θ (see Eq. 7.18 in Sect. 7.2.2). The root of the bifurcation tree, namely, node 1, is a

dynamic system whose structure and function are driven by a system of such coincident events, and we can identify such a system with an organism, unicellular or multicellular. Viewed in this manner, cells and their higher-order systems whose structure and properties ultimately depend on enzymes can be naturally associated with a 4-dimensional space. In other words, living systems are 4-dimensional and can be projected onto either the traditional 3-dimensional space of Euclid at a given time (span) or the one-dimensional space of time under a given spatial arrangement.

15.11 Allometry

Allometry is the study of the effect of the size of an organism, either unicellular or multicellular, on its function. For example, the linear relation between metabolic rates and body mass of different organisms shown in Fig. 15.13 is the subject of intense studies in the field of allometry. Whitfield defines *allometry* as follows (2006, p. 58):

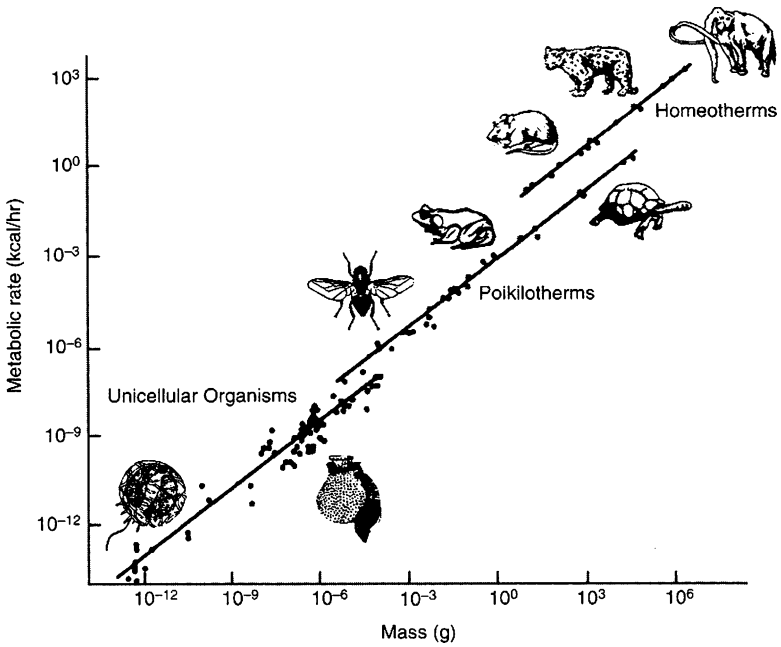


Fig. 15.13 The relationship between the metabolic rate of various organisms and their body mass (Reproduced from Whitfield 2006, p. 77 with kind permission from Novo Nordisk, Inc.)

> The relationship between metabolic rate and body weight is an example of a biological pattern called allometry, which compares how the value of any biological trait, such as metabolic rate or leg length, changes with the total size of a plant or animal. (15.7)

The so-called *quarter-power scaling laws* (Whitfield 2006, pp. 78–79) stating that many biological traits scale as body mass raised to the power of one or more quarters may be derived from the postulate that *the phenomenon of life is 4-dimensional because enzymes are coincidence detectors* (see Sect. 7.2.2). The *allometry equation* has the following deceptively simple form:

$$y = ax^b \tag{15.8}$$

where y is biological trait, either processes or structures, x is the total size of a cell, a plant or animal, and a is the *allometric coefficient*, and b is the *allometric exponent* which can be greater or less than 1. If b is greater than 1, for example, as in the case of deer antlers, the trait gets proportionately larger, and, if b is less than 1 as is the case with metabolic rate, it gets proportionately smaller so that, when the body size doubles, the metabolic rate increases by less than twofold.

During the past one and a half century, it has been found that, over a very wide range of body sizes of organisms (covering 27 orders of magnitude from unicellular organisms to whales), the metabolic rate scales as (or is proportional to) the body mass raised to the power of approximately (White and Seymour 2005). In Fig. 15.13, the metabolic rates of organisms from single cells to the elephant are plotted against their body masses on a log–log scale. The figure has three parallel lines, one each for *homeotherms, poikilotherms* (also called ectotherms), and *unicellular organisms*. They all have the same slope, that is, $b = 3/4$ but intercept the y-axis at different points, resulting in different values for a: The lower the intercept, the lower the *average* metabolic rate for each group. The allosteric exponent of shown in this figure is not the only possibility. There are many cases where it differs from and hovers around 2/3 (see Table 1 in White and Seymour 2005). It will be assumed here that the power law reflects at least some of the principles underlying the scaling phenomena in biology and that even the allometric exponent of 2/3 may be viewed as an example of the quarter-power scaling since 2/3 is equal to 2.666/4. Thus, any viable theory of allometric scaling should be able to provide a reasonable theoretical basis to account for the numerical values of both a and b in Eq. 15.8. It should be noted here that certain traits such as life span, heart beats, blood circulation time, and unicellular genome length scale as the body mass raised to the power of ¼, and the radii of aortas and tree trunks scale as body mass raised to the power of 3/8 or 1.5/4 (West and Brown 2004). These are examples of "quarter-power scaling," and the key question that has been challenging theoretical biologists for more than a century is why these exponents are multiples of 1/4, not 1/3 as expected on the basis of the scaling in the Euclidean space.

One of the currently most widely discussed and intensely debated theories to account for the 3/4 allometric exponent of the power law relating metabolic rate (y) to body mass (x) is the one proposed by West and Brown (2004, Whitfield 2006). Their theory accounts for the 3/4th scale exponent on the basis of the assumption that

> natural selection evolved hierarchical fractal-like branching networks that distribute energy, metabolites, and information from macroscopic reservoirs to microscopic sites. (West and Brown 2004) (15.9)

They further postulated that the hierarchical branching networks provided the following constraints:

1. Networks service all local biologically active regions in both mature and growing biological systems. Such networks are called space filling.
2. The networks' terminal units are invariant within a class or taxon.
3. Organisms evolve toward an optimal state in which the energy required for resource distribution is minimized.

It is interesting to note that the concept of networks employed by West and his coworkers (e.g., animal circulatory systems, plant vascular systems) focuses on the static spatial and geometric aspect of bionetworks, which may be viewed as belonging to the class of the *equilibrium structures* of Prigogine (Sect. 3.1.5). Since living systems are dynamic and better described in terms of *dissipative structures* (Prigogine 1977, 1980, Ji 1985a, b), and since living processes are almost always mediated by enzymes whose behaviors can be best characterized in terms of "temporal networks" in contrast to "spatial networks" as pointed out in Sect. 7.2.3, it may be reasonable to formulate an alternative theory of allometric scaling based on the notion of *dissipative network*, which are at least 4-dimensional in the sense that it takes four coordinates to characterize them, namely, x, y, x, and t.

Therefore, a simple explanation for the quarter-power scaling laws may be derived on the basis of the following assumptions:

1. The body mass (x) of an organism is not a geometric object (i.e., *equilibrium structure*) but a 4-dimensional entity, because it can be viewed as an organized system of cells and processes catalyzed by enzymes (acting as coincidence detectors) (see Fig. 7.8 in Sect. 7.2.3).
2. The number of cells (n) of an organism can be viewed as the projection of organisms on to the 3-dimensional Euclidean space (i.e., devoid of the time dimension).
3. The metabolic rate (y) of an organism is directly proportional to the number of cells constituting that organism (whose Euclidean volume is v), the proportionality constant increasing with both body temperature (T) and cell density, $d = n/v$, defined as the number of cells per unit body volume. (For simplicity, it will be assumed that the mitochondrial contents, or better the average respiratory activities, of cells are invariant among individual organisms and across species.)

Based on Assumptions (1) and (2), we can write:

$$n \sim x^{3/4} \Rightarrow n = ax^{3/4} \tag{15.10}$$

Based on Assumption (3), we can write:

$$y \sim n \tag{15.11}$$

Combining Eqs. (15.10) and (15.11) leads to:

$$y_i = a_i x_i^{3/4} \tag{15.12}$$

where y_i, a_i, and x_i are, respectively, the metabolic rate, the proportionality constant and the body size of the ith species with a distinct cell density, d_i, and habitat temperature, T_i. Because of Assumption (3), a_i is a function of both T_i and d_i:

$$a_i = f(d_i, T_i) \tag{15.13}$$

Taking the logarithm of both sides of Eq. (15.12) leads to:

$$\log y_i = {}^3\!/_3 \log x_i + \log a_i \tag{15.14}$$

Equation (15.14) predicts that, when the ith metabolic rate, y_i, is plotted against the ith body mass, x_i, on a double logarithmic coordinate system, a straight line with slope 3/4 would be obtained with different *y*-intercepts for different species, consistent with Fig. 15.13. Designating unicellular organisms as 1, poikilotherms as 2, and homeotherms as 3, the data in Fig. 15.13 make it clear that $a_1 < a_2 < a_3$, indicating that the metabolic rates per unit mass increase from unicellular organisms to poikilotherms to homeotherms. This observation is consistent with the *FERFAC* (Free energy requirement for Active complexity) hypothesis, Statement 15.20, which predicts that organisms with higher active complexities require higher energy expenditures, since the *active complexity* (Sect. 5.2.3) of the groups of the organisms considered here most likely increases in the same order as their intercept values, a_i.

The life span (LS) of an organism can be viewed as the projection of the living processes embodied in x on to the time dimension, which leads to:

$$LS_i = a_i x^{1/4} \tag{15.15}$$

where LS_i and a_i are, respectively, the life span and the proportionality constant of the ith species. Equation (15.15) is qualitatively consistent with the life span vs. body-mass plots found in the literature (e.g., see http:/www.senescence.info/comparartive.html) and (West and Brown 2004).

The key difference between the West–Brown–Enquist (WME) approach to developing a theory of allometric scaling and the one proposed in this book is that the former assumes that the 3/4 exponent can be derived mathematically from the species-specific physical characteristics of organisms (e.g., vascular trees of mammals, diffusion paths within cells in unicellular organisms), whereas the present approach regards the exponent as resulting from the universal property of all living systems, i.e., enzymic activity, regardless of differences in distribution networks among different individuals and species. It is possible that both approaches are relevant, since living systems embody two distinct processes – *transport* of matter between micro-meso (e.g., cells) and macro-sites (e.g., lung) and *transformation* of matter within cells. Based on the structural information of all living systems (e.g., role of mitochondrial membranes and lung alveoli membranes), it is likely that transport processes scale as the body mass raised to the power of 2/3 as was first suggested by Rubner in 1883 (White and Seymour 2005), and, based on the idea that

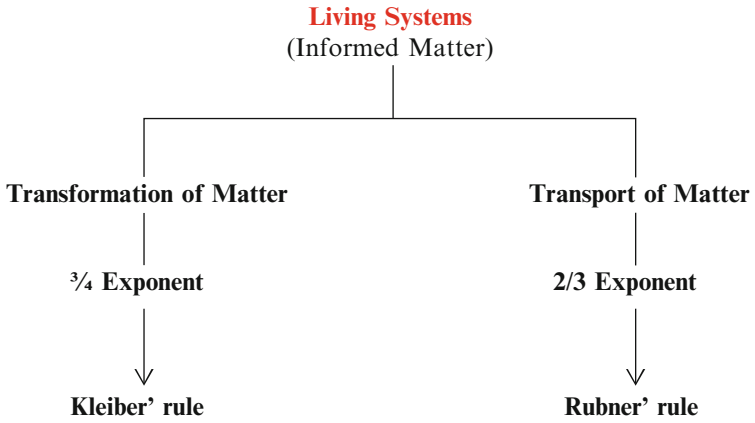


Fig. 15.14 The living systems as *informed matter* defined as the complementary union of matter/energy and information/life (see Table 2.5 in Sect. 2.3.1) that is supported by two dichotomous processes – *mass transformation* and *mass transport*, ultimately driven by chemical reactions catalyzed by enzymes acting as coincidence detectors (see Sect. 7.2.2)

enzymes are coincidence detectors serving as the nodes of temporal branching networks (Fig. 7.7), it can be suggested that transformation of matter in cells scale as the body mass raised to the power of 3/4, as proposed above. It is also possible that certain dynamic traits are rate-limited by *transport* of matter and that of certain others by *transformation* of matter, depending on the evolutionary, ontogenic, and physiological conditions of the organisms under consideration, thereby exhibiting either the 2/3 or 3/4 allometric exponents or some values in between as seems to be the case (see Tables 1 and 2 in White and Seymour 2005). These ideas are summarized in Fig. 15.14.

As evident in Fig. 15.15, the level of non-protein-coding DNA (i.e., dr-genes defined in Sect. 11.2.4) relative to protein-coding DNA (drp-genes, Sect. 11.2.4) is found to increase rapidly with increasing biological complexity, for example, from unicellular to multicellular organisms. The ratio of noncoding DNA to the total DNA does not change much from *Nanoarchaeum equitans* through *Rickettsia conorii* (spanning 67 unicellular species) but begins to rise sharply with *Rickettsia prowazekii,* continuing to rise through 19 species (multicellular species), reaching the maximum ratio with *Homo sapiens* (Mattick 2004). One plausible interpretation of the data in Fig. 15.15 is that the noncoding portions of DNA encode the information needed to organize in space and time the cells in multicellular organisms in order to maintain their functions. This idea can be expressed using the language of network sciences (Sect. 2.4) (Barabasi 2002, 2009):

> The coding regions of the DNA of a multicellular organism determine the intrinsic properties of the nodes of a bionetwork and the noncoding DNA regions determine both the interactions among the nodes and the space- and time-dependent control of their interactions in order to accomplish evolutionarily selected functions of the organism. (15.16)

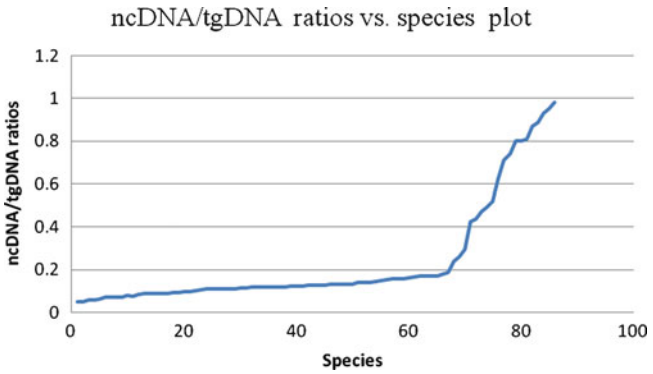


Fig. 15.15 The ratio of non-protein-coding (dr-genes, Sect. 11.2.4) to protein-coding DNA (drp-genes) in various species. The ratio does not change much from *Nanoarchaeum equitans* through *Rickettsia conorii* (spanning 67 species) but begins to rise sharply with *Rickettsia prowazekii*, continuing to rise through 19 species, reaching the maximum ratio of 0.983 with *Homo sapiens*. The data were downloaded from Taft and Mattiock 2012. ncDNA = noncoding DNA; tgDNA = total genomic DNA. The ncDNA/tgDNA ratio values were obtained from (Taft and Mattick, arXiv.org/ftp/q-bio/papers/0401/0401020.pdf, downladed on 01/04/2012; see also Mattick 2004). The coordinate values of the organisms plotted on the x-axis are: *1 = Nanoarchaem equitans, 2 = Thermotoga martima, 3 = Campylobacter jejuni, 4 = Wolinella succinogenes, 5 = Borrelia burgdorferi, 6 = Auifex aeolicus, 7 = Helicobacter hepaticus, 8 = Ureaplasma urealyticum, 9 = Treponoma pallidum, 10 = Archaeoglobus fulgidus, 11 = M. thermoautotrophicum, 12 = Mycoplasma pulmonis, 13 = Pyrococcus horikoshii, 14 = Mycobacterium tuberculosis, 15 = Mycobacterium bovis, 16 = Helicobacter pylori 26695, 17 = Dienococcus radiodurans, 18 = Helicobacter pylori J99, 19 = Caulobacter crescentus, 20 = Listeria monocytogenes, 21 = Listeria innocua, 22 = Fusobacterium nucleatum, 23 = Pseudomonas aeruginosa PAO1, 24 = Aeropyrum pernix, 25 = Coxiella burnetii, 26 = Chromobacterium violaceum, 27= Pasteurella multocida, 28 = Streptomyces coelicolor, 29 = Chlorobium tepidum TLS, 30 = Prochlorococcus marinus, 31 = Agrobacterium tumefaciens, 32 = Mycoplasma genitalium, 33 = Pyrobaculum aerophilum, 34 = Prochlorococcus MED4, 35 = Cloistridium acetobutylicum, 36 = Enterococcus faecalis, 37 = Xyella fastidosa, 38 = Eschelichia coli 0157:H7, 39 = Eschelichia coli K-12, 40 = S. enterica serovar Typhi CT18, 41 = Vibrio cholera. 42 = L. lactis sp. Lactis IL1403, 43 = Ralstonia solanacearum, 44 = Streptococcus MGAS315, 45 = Thermoanerobacter tengcogensis, 46 = Thermoplasma acidophilum, 47 = Brucella melitensis, 48 = Bacillus subtilis, 49 = P. syringae pv. Tomato DC300, 50 = Buchnera aphidicola (Ap), 51 = Methanococcus jannaschii, 52 = Mesorhizobium loti, 53 = Yersina pestis, 54 = Xanthomonas axonopodis, 55 = Haemophilus influenzae Rd, 56 = Bacillus halodurans, 57 = Xanthomonas campestris, 58 = Bacillus anthracis, 59 = Bacillus cereus, 60 = Buchnera aphidicola (Bp), 61 = Staphylococcus aureus N315, 62 = Staphylococcus aureus Mu50, 63 = Clostridium perfringens, 64 = Buchnera aphidicola (Sg), 65 = Nisseria meningitides, 66 = Prochlorococcus MIT9313, 67 = Ricke sia conorii, 68 = Rickesia prowazekii, 69 = Encephalitozoon cuniculi, 70 = Saccharomyces cerevisiae, 71 = Schizosaccharomyces pombe, 72 = Dictyostelium discoideum, 73 = Plasmodium falciparum, 74 = Plasmodium yoelii yoeli, 75 = Typanosoma brucei, 76 = Neurospora crassa, 77 = Arabidopsis thaliana, 78 = Caenorhabditis elegans, 79 = Oryza sativa L. ssp. japonica, 80 = Oryza sativa L. ssp. indica, 81 = Drosophila melanogaster, 82 = Ciona intestinalis, 83 = Fugu rubripes, 84 = Anopheles gambiae, 85 = Mus musculus, and 86 = Homo sapiens*

In Sect. 2.4.1, a bionetwork was defined as a network of nodes (**n**), such as proteins, RNA, and DNA, connected by edges (**e**) according to some topology (**T**) so as to accomplish a biological function (**F**), that is, **F** = **T(n,e)**. Statement 15.16 satisfies all the requirements of the definition of a bionetwork with the following identifications:

1. **F** = "evolutionarily selected functions of the organism"
2. **T** = "the noncoding DNA regions determine . . .the space- and time-dependent control of their interactions. . ."
3. **n** = ". . .coding regions of the DNA . . .determine the intrinsic properties of the nodes . . . "
4. **e** = "the noncoding DNA regions determine . . . the interactions among the nodes"

Therefore, based on the empirical data shown in Fig. 15.15 and the bionetwork theory described in Sect. 2.4.1, it is possible to make the following equivalent or related generalizations:

DNA of an organism encodes a bionetwork. (15.17)

DNA is a molecular representation of a bionetwork. (15.18)

Since DNA is a molecular representation of a bionetwork and since a bionetwork is a graph-theoretical representation of an organism, DNA is a molecular representation of an organism. (15.19)

Statement 15.19 may be referred to as the *Bionetwork Theory of DNA* (BTD), and it is here suggested that BTD complements the Watson-Crick theory of DNA (Watson and Crick 1953) which is mostly *structural* (or *node-centered*, in the language of network sciences).

At least 50% of the non-protein-coding DNA of the human genome has been found to code for RNA molecules that are not translated into proteins (Mattick 2004). Hence, Fig. 15.15 indicates that the level of RNA in cells most likely increases with biological complexity, making RNA levels inside the cell (and associated non-protein-coding DNA, or dr-genes; Sect. 11.2.4) a reliable index of the complexity (the active kind; see Sect. 5.2.4) of the phenotype of multicellular organism. Since maintaining complex structures of organisms would entail free energy dissipation, the following generalization follows:

The more complex an organism is, the more energy *the organism needs* to survive. (15.20)

We will refer to Statement 15.20 as the *Hypothesis of the Free Energy Requirement for Active Complexity of Living Systems* or more briefly as the *Free Energy Requirement for Active Complexity* (FERFAC) (for the definition of "active complexity", see Sect. 5.2.3). As discussed in connection with Fig. 15.13, the allometric data on the log–log relation between the body weight vs. the metabolic rate of various species, i.e., Eq. (15.14), strongly support the validity of the *FERFAC* hypothesis.

15.12 Micro–Macro Coupling in the Human Body

The human body is arguably the most complex material system in the Universe (besides the Universe Itself) in both its *structure* and *behavior*. The human body consists of approximately 10^2 joints, 10^3 muscles, 10^3 cell types, and 10^{14} neurons, each with multiple connections to other neurons (Kelso 1995). In addition, the motions of these components are not random but *coordinated* so that the body can perform macroscopic tasks essential for its survival under prevailing environmental conditions. The purpose of this section is to apply the theoretical principles and concepts developed in this book to elucidating the possible mechanisms underlying the phenomenon of the micro–macro coupling we experience in *coordinated motions* of our body.

Coordination dynamics originated in the study of the *coordination* and *regulation* of the movements of the human body (Bernstein 1967, Kelso 1995, Kelso and Zanone 2002, Kelso and EngstrØm 2006, Kelso 2008, 2009) but its principles are *scale-free,* i.e., *scale-independent,* and *universal* in that they apply to all material systems at all levels, including microscopic and macroscopic levels, that have more than one components interacting with one another to accomplish observable functions, leading to the following definition:

> Coordination dynamics is the study of the space-, time- and task-dependent interactions among the components of a dynamic system. (15.21)

We may recognize three broad branches of coordination dynamics on the basis of the distance scale over which coordination processes take place:

1. *Macroscopic Coordination Dynamics* (MacroCD) = the study of coordinated motions of the components of a system at the macroscopic scale (e.g., coordinated motions of left and right limbs, coordinated motions among the fingers of a hand),
2. *Mesoscopic Coordination Dynamics* (MesoCD) = the study of coordinated motions of the components of a system at the mesoscopic scale (e.g., morphogenesis; see Sect. 15.1), and
3. *Microscopic Coordination Dynamics* (MicroCD) = the study of coordinated motions of the components of a system at the molecular level (e.g., coordinated motions of the ATP-binding and Ca^{++}-binding domains of the Ca^{++} ion pump; see Figs. 8.6 and 8.7).

The human body movement depends on the successful coordination of all the components of the body on these three distance scales. The physicochemical systems embodying coordination dynamics at the three scales are distinct as schematically shown in Fig. 15.16. The theoretical concepts (*conformons*, *IDSs,* and *synergies*) that have been invoked as the mechanisms enabling the coordination dynamics at the three distance scales are indicted in Fig. 15.16, along with the suggested names of the associated dynamical systems (*RMWator*, *Bhopalator*, and *BocaRatonator*). *RMWator* and *BocaRatonator* are the two names used here for the first time, and the rationale for coining them is given in the legend to Fig. 15.16 and in Footnotes 24

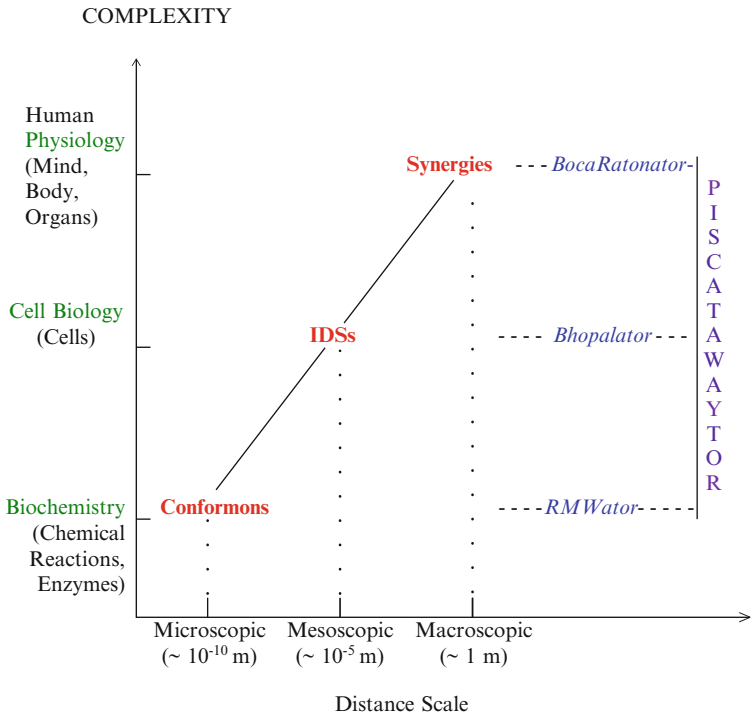


Fig. 15.16 Conformons, IDSs (Intracellular Dissipative Structures) (Sect. 3.1.2), and synergies as *microscopic*, *mesoscopic*, and *macroscopic* manifestations of *gnergons* (Sect. 2.3.2) or *dissipatons* (Sect. 3.1.2). The gnergon-based model of human behavior is here referred to as the "BocaRatonator" to acknowledge the seminal contributions made by Kelso and his colleagues at the Florida Atlantic University at Boca Raton, Florida. The term "RMWator" derives from **R** (Richland, to acknowledge Xie and his colleagues for their measurement of single-molecule enzymic activity of cholesterol oxidase while at The Pacific Northwest National Laboratory in Richland, WA), M (Minneapolis, to acknowledge Rufus Lumry and his colleagues' fundamental contributions to enzymology at the University of Minnesota at Minneapolis), and W (Waltham, to acknowledge the seminal work on enzyme catalysis carried out by William Jencks and his group at the Brandeis University in Waltham, Mass)

and 26 to Table 15.10. The theoretical model of the human body as a whole that is based on the *principle of self-organization* was referred to as *the Piscatawaytor* in (Ji 1991) (see Fig. 15.18). The various *ators* appearing in Fig. 15.16 are related as shown in Eq. (15.22) where CD stands for coordination dynamics:

$$\underset{(MicroCD)}{\text{RMWator}} + \underset{(MesoCD)}{\text{Bhopalator}} + \underset{(MacroCD)}{\text{BocaRatonator}} \qquad (15.22)$$

In December 2008, Professor Kelso visited Rutgers for 3 days and gave informative and inspiring seminars on *coordination dynamics* and the philosophy of *complementary pairs* to both my General Honors Seminar students and a

Table 15.9 The similarities and differences between the biological theories developed by J. A. S. Kelso and S. Ji

	Kelso (1984, 2008)	Ji (1974a, b, 2000, 2004a)
1. System studied	Human body	Molecular machines
2. Methods	Cognitive neuroscience	Chemistry
	Nonlinear dynamics	Molecular mechanisms
3. Principles invoked	Synergies	Gnergons[a]
	Biological information	Biological information
	Self-organization	Self-organization
	Complementarity	Complementarity
4. Direction of generalization	Macro → micro	Micro → macro
5. Philosophical generalization	Complementary nature (Kelso and Engstrøm 2006)	Complementarism (Ji 1993, 1995)

[a] Gnergons are discrete units of gnergy, the complementary union of *energy* and *information* (Sect. 2.3.2). Gnergons are thought to be necessary and sufficient for all self-organizing, goal-directed motions in all physical systems including the cell and the human body. Examples of gnergons include conformons (Chap. 8) and IDSs (Chap. 9)

University-wide audience. During his visit at Rutgers, we had an opportunity to compare the results of our researches over the past several decades in our respective fields of specialization and it did not take too long for us to realize that we have been studying the same forest called the human body albeit from two opposite ends – Kelso and his coworkers from the *macroscopic end* of human body movements and I from the *microscopic end* of molecular and cell biology. The similarities and differences between these two approaches and the results obtained are summarized in Table 15.9. Evidently, between us, we have covered the whole spectrum of *the science of the human body*, from *molecules to mind* (as Kelso poetically put it over breakfast one morning). One way to visualize how Kelso's poetic vision might be realized in material terms is shown in Fig. 15.17, the essence of which can be stated as follows:

> Mind controls cells; cells control molecules; molecules control energy supply and thereby cells and mind. (15.23)

Statement 15.23 reminds us of the *reciprocal causality* or *cyclic causality* where A affects B which then affects A back, etc. (Kelso and EngstrØm 2006, pp. 115,191). We may refer to Statement 15.23 as the "Reciprocal Causality of Mind and Molecules" (RCMM). It may be significant that the source of *control information* and that of *free energy* are located at the two opposite ends of the diagram, reflecting the fact that control information originates in the mind and the energy needed to implement the control instruction can come only from the chemical reactions catalyzed by enzymes.

Table 15.10 characterizes the three branches of coordination dynamics operating within the human body in detail and situates the works of Kelso and mine within the triadic framework of coordination dynamics. As Row 1 indicates, the human body can be viewed as an excellent example of a *renormalizable bionetwork* discussed in Sect. 2.4. That is, the human body is a network of cells, each of which is a network

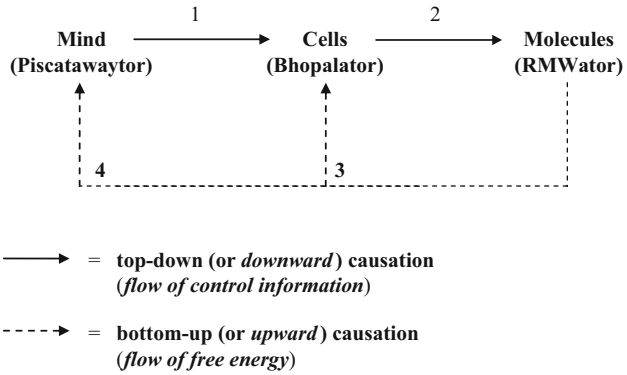


Fig. 15.17 The *Principle of the Reciprocal Causality of Mind and Molecules* (*RCMM*) mediated by *cells,* or more briefly *the Principle of Mind-Molecule Coupling* (*PMMC*). Step **1** represents the action of mind on cells, as when I decide to lift a cup by activating neurons in my motor cortex which in turn activate the muscle cells in my arm and fingers. Step **2** represents the action potential–triggered activation of the myosin ATPase molecules in muscle cells that catalyze the hydrolysis of ATP, the source of free energy. The free energy released from ATP hydrolysis in muscles and the brain powers all the motions in muscle cells (Step **3**) and neurons in the body which constitute the mind (or the brain) (Step **4**). *It will be shown in Footnote 26 below that this figure embodies what is referred to as the First Law of Coordination Dynamics* (*FLCD*). *Mind* (viewed as a part of the human body), *cells*, and *enzyme molecules* in action are examples of dissipative structures (or *dissipatons*) and hence can be named as X-ators, where X is the name of the city where the most important research is done on a particular "ator." The acronym RMW stands for Richland, Minneapolis, and Waltham (see Footnote 27 in Table 15.10)

Table 15.10 Coordination dynamics at three distance scales

		Coordination dynamics at three scales		
		Macroscopic (~1 m)	Mesoscopic (~10^{-5} m)	Microscopic (~10^{-10} m)
1. Renormalizable bionetwork[a]	Node	Cells	Biopolymers	Atoms
	Edge	Intercellular messenger-mediated cell–cell interactions[b]	Noncovalent interactions[c]	Covalent interactions[d]
	Bio-network	Human body	Cells	Biopolymers
2. Experimental data	Kelso	e.g., lip and jaw movement in speech production		
	Ji	(a) Human anatomy[e]	(a) Metabolic Pathways[g]	(a) DNA supercoils[i]
		(b) Pain pathways[f]	(b) Genome-wide microarray data[h]	(b) Single-molecule enzymology[j]
		(c) Brain reward system[f]		
3. Methods	Kelso	(a) Biomechanical[k]		
		(b) Nonlinear dynamical[l]		

(continued)

Table 15.10 (continued)

			Coordination dynamics at three scales		
			Macroscopic (~1 m)	Mesoscopic ($\sim 10^{-5}$ m)	Microscopic ($\sim 10^{-10}$ m)
		Ji	(a) Anatomical[e]	(a) Molecular biological[n]	(a) Physical[p]
			(b) Physiological[e]	(b) Cell biological[o]	(b) Chemical[q]
			(c) Pharmacological[m]		(c) Singe-molecule enzymological[r]
4.	Key concepts	Kelso	Synergies[s]	(synergies)[t]	(synergies)[t]
		Ji	Renormalizable bionetworks[a] (dissipatons, SOWAN machines, or gnergons)[u]	IDSs[u] (dissipatons, SOWAN machines, or gnergons)[u]	Conformons[v] (dissipatons, SOWAN machines, or gnergons)[u]
5.	Models based on PSO[w]	Kelso	BocaRatonator[x]		
		Ji	Piscatawaytor[y]	Bhopalator[z]	RMWator[aa]

of biopolymers, and biopolymers are networks of atoms. It is interesting to note that each bionetwork is characterized by a unique mechanism of interactions among its nodes – short-range *covalent interactions* among atoms to form biopolymers; medium-range *noncovalent interactions* among biopolymers to form cells; and long-range *messenger-mediated interactions* among cells to form the human body. Extensive footnotes are attached to most of the items appearing in Table 15.10, often with their own tables and figures (reminiscent of nested networks of self-similarity).

[a]Biological networks where a node can become a new network at a higher resolution and a network can become a node of another network at a lower resolution (see Sect. 2.4). For example, at the microscopic level, atoms (e.g., H, O, C, N, deoxyribonucleotides) are the nodes of a network known as a biopolymer (e.g., DNA); at the mesoscopic scale, biopolymers are the nodes of a network known as the cell; and at the macroscopic scale, cells constitute the nodes of a networks known as the human body.

[b]This type of interactions make it possible for long-distance interactions or communications between cells, over distances ranging from 0 (e.g., contact inhibition) to meters (e.g., hormone-mediated or axon-mediated connections).

[c]Relatively weak and ATP-independent interactions or bonds requiring only about 5 kcal/mol to break.

[d]Relatively strong, enzyme-catalyzed, interactions or bonds requiring 50–100 kcal/mol to break (Moore 1963, p. 57).

[e]According to the triadic definition of function (Sect. 6.2.11), *structures* (including anatomy; see Figs. 15.19 and 15.20) are as important as *processes* (including physiology) and *mechanisms* to account for functions.

[f]Much is known about the neuroanatomy and neurophysiology underlying the effects of pain and pleasure on human body motions.

[g]Metabolic pathways encoded in a cellular genome are akin to the keys on a piano keyboard (*equilibrons*) and metabolic activities observed in living cells are comparable to the melodies (*dissipatons*) that a pianist produces by striking a select set of keys obeying the instructions given in a sheet music.

[h]The DNA microarray technology allows us to measure (hear) the dynamic changes (audio music) in RNA levels (or waves) occurring within a living cell in response to environmental perturbations. Microarrays make it possible to visualize the coordinated interactions among select RNA molecules in a living cell under a given environmental condition (see Figs. 12.1 and 12.2).

[i]Visual evidence for the concept of conformons (see Sect. 8.3).

[j]Dynamic evidence for the concept of conformons (see Sect. 11.4.1).

[k]For example, the continuous monitoring of the thumb movement in both hands (Kelso 1984).

[l]According to Kelso and Engstrøm (2006, pp. 90–91),

> Coordination dynamics, the science of coordination, is a set of context-dependent laws or rules that describe, explain, and predict how patterns of coordination form, adapt, persist, and change in natural systems. . . . Coordination dynamics aims to characterize the nature of the functional coupling in all of the following: (1) within a part of a system, as in the firing of cells in the heart or neurons in a part of the brain; (2) between different parts of the same system, such as between different organs of the body like the kidney and the liver, or between different parts of the same organ, like between the cortex and the cerebellum in the brain, or between audience members clapping at a performance; and (3) between different kinds of things, as in organism ~ environment, predator ~ prey, perception ~ action, etc. . . . (15.24)

Coordination dynamics at the macroscopic level can be studied using the powerful tools and concepts provided by the mathematics of *nonlinear dynamics* (van Gelder and Port 1995, Scott 2005). A *coordination law* that has been found useful in analyzing real-life biological systems can be expressed as in Eq. (15.25) (Kelso and EngstrØm 2006, pp. 156–157):

$$\mathrm{d(cv)/dt} \;=\; \mathrm{f(cv,\ cp,\ fl)} \tag{15.25}$$

where d(cv)/dt is the rate of change of the *coordination variable* cv whose numerical value changes with the state of the system under investigation, cp is one or more *coordination parameters* that can affect the state of the system but are not affected by it, and fl is the noisy or thermal fluctuations experienced by the system.

It should be pointed out that a given mathematical idea or principle such as Eq. (15.25) can be represented in many equivalent ways. Some examples are shown below:

$$\mathrm{dx/dt} \;=\; \mathrm{f(x,\ P,\ fl)} \tag{15.26}$$

where x = cv, and P = cp in Eq. (15.25), or

$$dx/dt = f(cv,\ cp,\ fl),\ \text{or} \tag{15.27}$$

"(rate of change in x) is a function of x, control parameter cp and fluctuation fl" , or most abstractly (15.28)

$$(\_\_\_\_\_)' = f(\_\_\_\_, \_\_\_\_, \_\_\_\_) \tag{15.29}$$

where (_____)' indicates a time derivative of whatever is inside the parenthesis, f is a mathematical function, and the underlines represent "place holders" which can be filled with appropriate variables, numbers, or words. That is, although Eqs. 15.25–15.29 all look different, their meaning is the same, and this is because mathematics employs *signs* and signs are arbitrary (see Sect. 6.1.1).

Equation (15.25) can be integrated with respect to time t, resulting in:

$$cv = F(t,\ cp,\ IC,\ fl) \tag{15.30}$$

where F is a new function different from f, t is time, and IC is the integration constant whose numerical value is determined by initial conditions. According to Eq. (15.30), the so-called trajectories (see 1 below) in *t-cv plots* depend on *initial conditions*.

Some of the basic concepts and principles embodied in the coordination law, Eq. (15.25), can be visualized using the skateboarder as an analogy. The skateboarder moving up and down the walls of the empty swimming pool is a convenient metaphor to illustrate a set of important concepts in nonlinear dynamics:

1. *Coordination variable,* cv: The position of the skateboarder on the *x*-axis which varies with time, increasing (movement from left to right) or decreasing (movement from right to left) as the skateboarder moves up and down the pool surface acted upon by gravity. The plot of cv against time, t, is known as *trajectories*. The shapes of the trajectories differ (i.e., the trajectories evolve in time in different ways) depending on *initial condition* (i.e., the numerical value of cv at t = 0) and the *control parameter* cp, which is in the present case the curvature of the pool surface.
2. *Stable fixed point* also called *attractor*: The skateboarder always returns to the bottom of the pool to minimize its gravitational potential energy.
3. *Unstable fixed point* also called *repeller*: The skateboarder resting on the top of the hill is *unstable* because he/she can be easily pushed off the peak position. If the skateboarder is unperturbed (e.g., by randomly fluctuating directions of wind), he/she can remain at the precarious position forever.
4. *Potential landscape* often designated as the *cv-V plot*: The relation between the gravitational potential energy of skateboarder's body, V, and its position on the *x*-axis which fixes its *z*-axis due to the constraint imposed by the pool surface.

5. *Control parameter* designated as cp: The *curvature* of the wall of the pool, depending on which the skateboarder moves up and down with different speeds
6. *Bifurcation*: One becoming two. For example, the trajectory of the skateboarder at the top of the hill divides into two (if he/she is pushed off) – either toward the right or the left.

[m]The study of the effects of drugs on human bodily motions provides insights into the mechanisms underlying human movement under normal conditions.

[n]Molecular interactions inside the cell are determined not only by *free energy* changes but also by the *evolutionary information* (Sect. 4.9) (Lockless and Ranganathan 1999) encoded in the structures of interacting partners.

[o]The cell is the smallest DNA-based molecular computer (Ji 1999a) and the unit of biological structure and function.

[p]Many physical principles including the Franck–Condon principle (Sect. 2.2), laws of thermodynamics and quantum mechanics provide guidelines for visualizing molecular interactions in the cell.

[q]Life is ultimately driven by chemical reactions and needs the principles of chemistry and chemical reactions to be understood at the fundamental level.

[r]For the first time in the history of science, it has become possible, since the mid-1990s, to observe enzymic reactions and molecular motor actions on the single-molecule level, providing new insights into the workings of biopolymers, including dynamic disorder (Row A, Table 11.10), molecular memory effects (Row C, Table 11.10), and coordinated motions between remote domains.

[s]Kelso (2008) defines a *synergy* as

> a functional grouping of structural elements (molecules, genes, neurons, muscles, etc.) which, together with their supporting metabolic networks, are temporarily constrained to act as a single coherent unit. (15.31)

Thus defined a *synergy* is more or less synonymous with a *SOWAWN machine* (Sect. 2.4) and a *dissipation* (Sect. 3.1.5), both of which being examples of *gnergons* (Sect. 2.3.2). *Hence synergies may be considered as a member of the gnergon class.*

[t]Although the concept of the synergy originated in macroscopic science of human body motions (Bernstein 1967), the concept was subsequently extended to cellular and molecular levels (reviewed in Kelso 2008, 2009).

[u]*Intracellular dissipative structures* were first invoked in the Bhoplator model of the cell (Ji 1985a, b) as the final form of the expression of genes and generalized in the form of *dissipatons* and *SOWAWN machines* that were suggested to be applicable to other levels of biological organizations (Sects. 9.1, 10.1).

[v]Conformons were invoked in (Green and Ji 1972a, b) to account for the molecular mechanism underlying the coupling between respiration and phosphorylation reactions in mitochondria (Sects. 8.1, 8.7) and later generalized to formulate the concept of *gnergons* in (Ji 1991) which was postulated to apply to all levels of organization, both biotic and abiotic (Sect. 2.3.2).

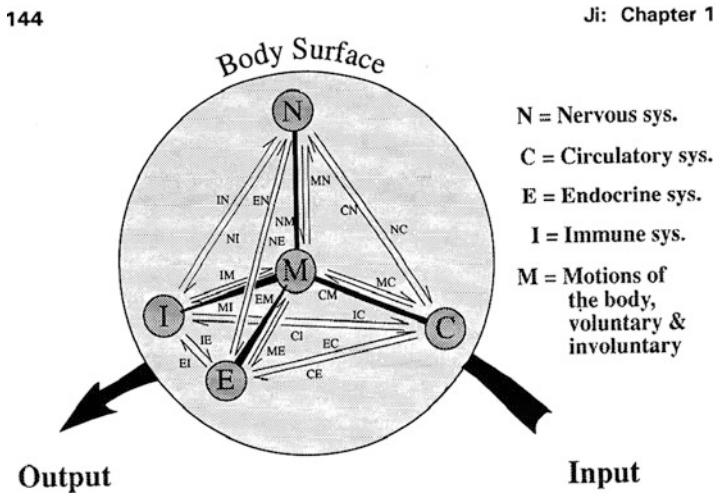


Fig. 15.18 The Piscatawaytor. A theoretical model of the human body based on the principle of self-organization described in Sect. 3.1

[w]The Principle of Self-Organization (Sect. 3.1).

[x]The nonlinear dynamical model of the human body based on the Principle of Self-Organization. The name BocaRatonator is suggested here (as indicated earlier) to acknowledge the contributions that J.A.S. Kelso and his colleagues at the Florida Atlantic University in Boca Raton, Florida, have made in advancing the field of the coordination dynamics of the human body. The Piscatawaytor (see below), in contrast, is best considered as the theoretical model of the human body that integrates, albeit qualitatively, the molecular (micro coordination dynamics), cellular (mesocoordination dynamics), and physiological (macrocoordination dynamics) descriptions of the human body (Figs. 15.16, 15.18).

[y]The theoretical model of the human body comprising five basic compartments (nervous, circulatory, endocrine, immune, and motor systems) dynamically interacting with one another based on the *Principle of Self-Organization* (Ji 1991) (see Fig. 15.18).

As can be seen in Fig. 15.18, the motor system (**M**) is placed at the center of the tetrahedron, the simplex of the 3-dimensional space (Aleksandrov et al. 1984), because motion is thought to constitute the most fundamental aspect of the human body as indicated in the following quotation from Ji (1991, p. 144):

> the fact that the M system must be relegated to the center of the tetrahedron in order to effectuate the simultaneous contacts suggests the possibility that the most important biological function of the human body is voluntary motions, including thought processes (emphasis added). This conclusion places voluntary motions, which we all too readily take for granted, at the center of our biological being. Is it possible that there is some deep philosophical significance to this conclusion? Have we underestimated the fundamental biological and evolutionary significance of our voluntary bodily motions? (15.32)

The idea expressed in this paragraph appears consonant with the dynamical approach to cognitive science advocated in the book entitled *Mind as Motion* edited by Port and van Gelder (1995), which motivates me to suggest that the Piscatawaytor may provide a *biologically realistic* theoretical framework for *cognitive science* of the future that can not only integrate existing paradigms (e.g., computational vs. dynamical approaches) but also open up new possibilities of research.

[z]The Bhopalator model of the cell at the mesoscopic level (see Fig. 2.11) may be essential in linking the microscopic and macroscopic worlds. That is,

> One of the fundamental roles of the living cell in biology is to provide the mechanistic framework for coupling exergonic microscopic processes and endergonic macroscopic processes in the human body. (15.33)

Statement 15.33 is consistent with or supported by Statements 15.34 and 15.35:

> It is impossible for the human body to perform macroscopic movement without driven by microscopic chemical reactions. (15.34)

> The free energy that is required for all macroscopic motions of the body can only be provided by exergonic chemical reactions catalyzed by enzymes at the microscopic level. (15.35)

Statements 15.33–15.35 are also in agreement with the *reciprocal causality of the human body* depicted in Fig. 15.17, according to which the macroscopic events, that is, *mind-initiated body motions*, and the *microscopic events, that is, enzyme-catalyzed chemical reactions*, are coupled through the mediating role of *the living cell*. The fundamental role that the living cell plays in effectuating the bodily motions, therefore, may be more generally stated as a law:

> It is impossible to couple macroscopic bodily motions, either voluntary or involuntary, and microscopic chemical reactions without being mediated by the mesoscopic living cell. (15.36)

For convenience of discussions, Statement 15.36 may be referred to as the "First Law of Coordination Dynamics" (FLCD).

There are two mechanisms of coordinating two positions or points in the human body (and in multicellular organisms):

1. The *static (rigid, equilibrium) coordination mechanism (SCM)* operating between the two ends of a bone, for example, that are connected to each other through a rigid body, and
2. The *dynamic (flexible, dissipative) coordination mechanism (DCM) operating* between two points located in the opposite ends of a muscle, a muscle fiber or in two remote domains within a biopolymer, for example, that are connected through flexible, deformable bodies.

The principles underlying SCM are provided by the *Newtonian mechanics* while those underlying DCM derive from multiple sources including the (1) *Newtonian mechanics*, (2) *thermodynamics*, (3) *quantum mechanics*, (4) *statistical mechanics*, (5) *chemical kinetics*, (6) *control theory*, and (7) *evolutionary biology* which are all implicated, although not always explicitly discussed, in what is known as

coordination dynamics (Bernstein 1967, Kelso 1995, Turvey and Carello 1996, Jirsa and Kelso 2004, Kelso and EnstrØm 2006).

When two objects A and B are coordinated via SCM, they are connected to a rigid body C so that A, B, and C form a mechanically coupled *simple machine* (to be called the *SCM machine*) and the movements of A and B are automatically coordinated. But when A and B are coordinated via DCM, they are connected to a deformable body C (to form what may be called the *DCM machine*) in such a manner that A, B, and C are mechanically coupled system only when appropriate conditions are met. In other words, *the DCM machine is a much more complex and sophisticated than the SCM machine. In addition, the DCM machine is synonymous with the SOAWN machine and the renormalizable network discussed in Sect.* 2.4.

The First Law of Coordination Dynamics (FLCD), Statement 15.36, is a phenomenological law similar to the laws of thermodynamics and does not provide any detailed mechanism as to how the law may be implemented in real life. To the extent that empirical data can be marshaled to formulate realistic mechanisms to implement FLCD, to that extent FLCD will gain legitimacy as a law. Figure 15.17 provides an empirically based mechanistic framework for implementing FLCD and hence can be viewed as a diagrammatic representation of FLCD. According to Fig. 15.17, FLCD consists of two causes – upward causes or mechanisms (Steps 3 and 4) and downward causes or mechanisms (Steps 1 and 2).

The *upward mechanisms* implementing FLCD implicate the hierarchical organization of material components of the muscle from the myosin molecule to the muscle attached to a bone, ranging in linear dimensions from 10^{-10} to 1 m (see Fig. 15.19). Figure 15.19 exposes the essential problem underlying the upward mechanism: *How can myosin molecules move the muscle?* For example, in order for our arm to move a cup of tea or an apple, the arm muscle must generate forces in the range of 1 N acting over distances in the range of 1 m in less than 1 s (Fig. 15.19). But a myosin molecule can generate forces only in the range of 1 pN (picoNewton, or 10^{-12} N) acting over distances in the range of 10^{-8} m. That is,

> In order for our body to move an object powered by chemical reactions, our body must (i) amplify the forces generated by individual myosin molecules from 10^{-12} N to 1 N (an increase by a factor of about 10^{12}), (ii) extend the active distance of the molecular force from 10^{-8} m to 1 m (an increase by a factor of about 10^{8}), and (iii) slow down processes from 10^{-9} s to about 1 s (a factor of about 10^{9}). (15.37)

We may refer to Statement 15.37 as *the FDT amplification requirement* (FDTAR) for the micro–macro coupling in the human body, F, D, and T standing for *force*, *distance*, and *time*, respectively. Now the all-important question from the perspective of coordination dynamics is:

> How is the FDTA requirement met in the human body? (15.38)

As a possible answer to Question 15.38, it is here suggested that there are two key principles to effectuate the FDT amplification in the human body:

1. The Chunk-and-Control (C&C) principle. This principle was discussed in Sect. 2.4.2, according to which the cell controls, for example, the replication of DNA

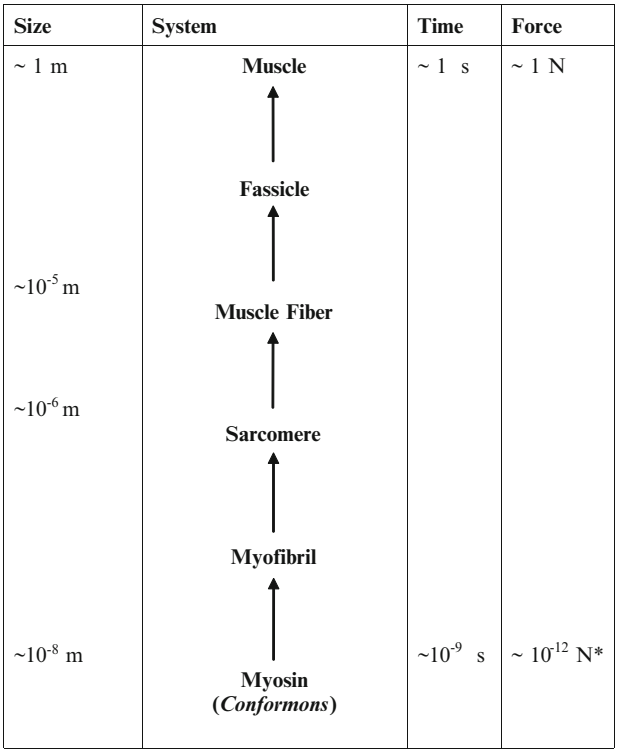


Fig. 15.19 The upward arm of the mind-molecule coupling depicted in Fig. 15.17. The macro–micro coupling in the muscle tissue by increasing the effective mass of contractile system. Myosin molecules generate mechanical energy packets known as *conformons* during the hydrolysis of ATP that myosin catalyzes (see Figure Panel d in Fig. 11.34). *Tominaga et al. (2003)

by chunking it into six different structural units (or chunks) ranging in size from 2 to 1,400 nm in diameter (see Fig. 2.9). Similarly it is postulated here that the human body effectuates the FDT amplification by *chunking* the contractile system into six hierarchical structure ranging from (1) myosin molecules to (2) myofibrils to (3) sarcomeres to (4) muscle fibers (or muscle cell) to (5) fassicles, and to (6) skeletal muscle (Fig. 15.19).

Chunks are dissipative structures (or dissipatons) requiring continuous dissipation of free energy in order to maintain their functions. The chunks depicted in Figs. 2.9 and 15.19 are the shadows of the functional chunks of DNA and the contractile system, respectively, that are projected onto the 3-dimensional space. Cells or the human body forms their functional chunks so that they can more efficiently control the motions of DNA or the skeletal muscle, perhaps not unlike the human brain *chunking* symbols into *phonemes* (units of sound), *morphems* (units of meaning), *words* (units of denotation), *sentences* (units of judgment), *paragraphs* (units of reasoning ?), and *texts* (units of theory building?) to control the language.

2. The Principle of Synchronization (PS) through the generalized Franck–Condon mechanism (Sect. 7.2.2). The synchronization of the actions of protein domains within an enzyme is thought to be needed for effectuating catalysis (see, for example, the synchronization of the amino acid residues 1–4 at the transition state in Fig. 7.5). Synchronization is a nonrandom process and hence requires dissipation of free energy to be effectuated in order not to violate the laws of thermodynamics (see Sect. 2.1). The free energy required to synchronize amino acid residues in the catalytic cavity of an enzyme is postulated to be derived from substrate binding or the chemical reaction that the enzyme catalyzes. Organizing the catalytic residues at the enzyme active site is a relatively slow process compared to the fast electronic transitions accompanying chemical reactions that provide the needed free energy. To couple these two partial processes, the slow process must precede the fast one, according to the generalized Franck–Condon principle (GFCP) or the Principle of Slow and Fast Processes (PSFP) (Sect. 2.2). Thus, the following generalization logically follows:

   Slow and fast partial processes can be coupled or synchronized if and only if i) the fast process is exergonic and ii) the slow process precedes the fast process. (15.39)

Statement 15.39 may be viewed as a more complete expression of GFCP or PSFP than the previous version given in Statement 2.25 (Ji 1991, p. 53), because it specifies the source of free energy needed to drive the coupling or the synchronization of two partial processes, one slow and the other fast: *The free energy must be supplied by the fast, not the slow, partial process.*

The synchronization phenomenon has also been observed among neuronal firing activities in the brain which is known as *neuronal synchrony* (Woelbern et al. 2002, Anderson et al. 2006, Averbeck and Lee 2004). In analogy, we may refer to the synchrony underlying enzymic catalysis (see Fig. 7.5 in Sect. 7.2.2) as the *protein domain synchrony*. Generalizing further, it is postulated here that the principle of synchrony can be extended to all *chuncked systems* in biology, including the contractile system depicted in Fig. 15.19 and that, just as the *protein domain synchrony* is effectuated through the generalized Franck–Condon mechanism (GFCM) (see Fig. 7.5), so all other *chunk synchronies* depend on GFCM in order not to violate the laws of thermodynamics. The essential role of GFCM in "chunk synchrony" resides in making it possible for the synchronized system to pay for its free energy cost by coupling slow, endergonic processes to fast, exergonic process such as ATP hydrolysis or membrane depolarization triggered by action potentials. Based on these considerations, it appears reasonable to conclude that:

The dynamic actions of the chunks in chunked systems in biology and medicine can be synchronized based on the generalized Franck-Condon mechanisms or the Principle of Fast and Slow Processes. (15.40)

We will refer to Statement 15.40 as the *principle of FDT amplification by increasing mass*, or *the FDTABIM (to be read as "FDT-ah-bim") principle*. On the level of the contractile system of the human body, the FDTABIM principle appears to be satisfied because the size of the chunks increases by a factor of about 10^8 from myosin to muscle and because all the chunks can be activated simultaneously by the

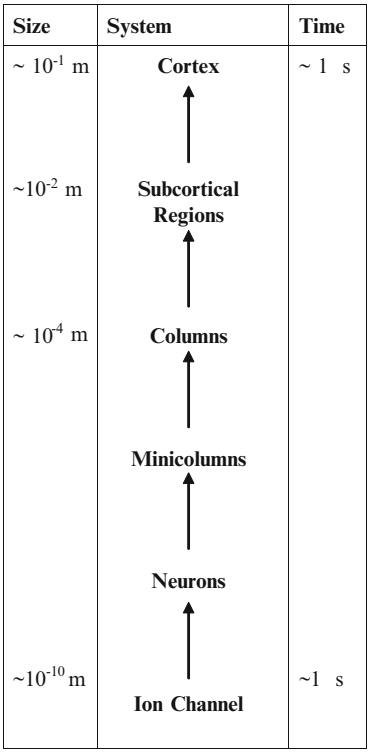


Fig. 15.20 The downward arm of the *reciprocal causation of mind and molecule* depicted in Fig. 15.17. The macro–micro coupling in the brain by increasing the effective mass of computing (or decision-making) system and hence the computational power

synchronous firing of the efferent neurons of the motor cortex (see Fig. 15.20) that innervate the muscle cells. It is interesting to note that the FDTABIM principle is implemented by *nerve impulse* in the contractile system and by *thermal fluctuations* inside cells (Fig. 7.6). We will refer to the former as the "voltage-initiated" FDTABIM mechanism and the latter as the "fluctuation-initiated" FDTABIM mechanism. (Since the *chunk synchronization* is a necessary condition for FDTABIM (see (i) above), we can alternatively refer to these mechanisms as "voltage-initiated" and "fluctuation-initiated" chunk synchrony, respectively.) These two types of FDTABIM mechanisms are not independent of each other but hierarchically linked. Hence, it can be predicted that the action of the skeletal muscle, for example, will depend on both the fluctuation- and voltage-initiated FDTABIM mechanisms, although the details are not yet known.

So far we have been discussing the mechanisms underlying the transmission of force from the myosin molecules to the skeletal muscle given the synchronous activation of the muscle cells involving neuronal synchrony, namely, through the *voltage-initiated FDTABIM mechanism*. That is, we have been focusing on the *upward arm* of the *reciprocal causation* underlying the mind-molecule coupling phenomenon (see Fig. 15.17). We will now discuss the *downward arm* of the reciprocal causation of this mind-molecule coupling. The main idea here is that once the brain decides which muscle cells to activate to produce the desired bodily

motions (a *slow process*), the brain fires the right number of the right neurons in the motor cortex (a *fast process*), innervating the right set of muscle cells that then generate the needed mechanical force to be subsequently amplified through the upward causal mechanism discussed above.

The brain consists of approximately 10^{12} neurons which are organized into functional cortical areas. For example, the motor cortex constitutes 6.3% of the total cortical area of the human brain or about 100 cm^2 (Cook 1986, p. 69). There is experimental evidence (Cook 1986, pp. 61–73) that the neocortex is organized in terms of *column*-like structures arranged in grid-like formation, each consisting of ten to a hundred thousand neurons. The motor cortical column is about 500 μm in diameter and contains 30,000 pyramidal cells, and there are a maximum of 10^6 such columns per cerebral hemisphere (Cook 1986, p. 63). Each cortical column is thought to possess a specific computational function, for example, the processing of the information from a specific whisker in a rat's mustache. Thus, the *cortical column* may be viewed as a *basic computational unit* of the cortex.

The *downward causation* of mind over molecule begins with somatic nerves that originate in the motor cortex and form the neuromuscular junctions (or end plates) on the surface of target muscle cells. Each muscle cell is innervated by one efferent somatic neuron and one such neuron can synapse with tens of thousands of muscle cells, an arrangement that seems ideal for *synchronizing* the activation of many muscle cells for the purpose of amplifying force and distance of myosin action. When activated, these nerves release the neurotransmitter, acetylcholine (Ach), at the neuromuscular junction, causing the depolarization of the postsynaptic muscle cells by opening their Na^{++} and K^{+} ion channels in sequence which in turn leads to the release of intracellular Ca^{++} from the sarcoplasmic reticulum. The rise in the Ca^{++} concentration in muscle cells activates a series of intracellular events, resulting in the generation of mechanical force in myosin molecules coupled to ATP hydrolysis, most likely through the conformon mechanism (see Chap. 8 and Fig. 11.34). The downward arm of the reciprocal causation of mind and molecules (Fig. 15.17) begins in the motor cortex and ends at the level of neuromuscular junction as schematically depicted in Fig. 15.20. Strictly speaking the downward causation does not implicate any molecule directly but only indirectly through depolarized cells and hence should be referred to as mind-cell coupling rather than mind-molecule coupling which should be reserved for the upward causation. In other words, *the motor neurons in the motor cortex do not communicate directly with myosin molecules but only indirectly through muscle cells which control myosin and associated molecules involved in contraction*.

As alluded to above, the downward causation also implicates coupling two partial processes – one *slow* and the other *fast*. It is here postulated that *the slow, endergonic partial process* underlying the downward causation is the thermal fluctuation-induced random and transient contact formation (or assembling) and detachment process (or disassembling) among cortical columns in the motor cortex and *the fast, exergonic partial process* is identifiable with membrane depolarization of assembled columns. *Here it is assumed that cortical columns possess structures (such as specific axon terminals) that can actively explore potential*

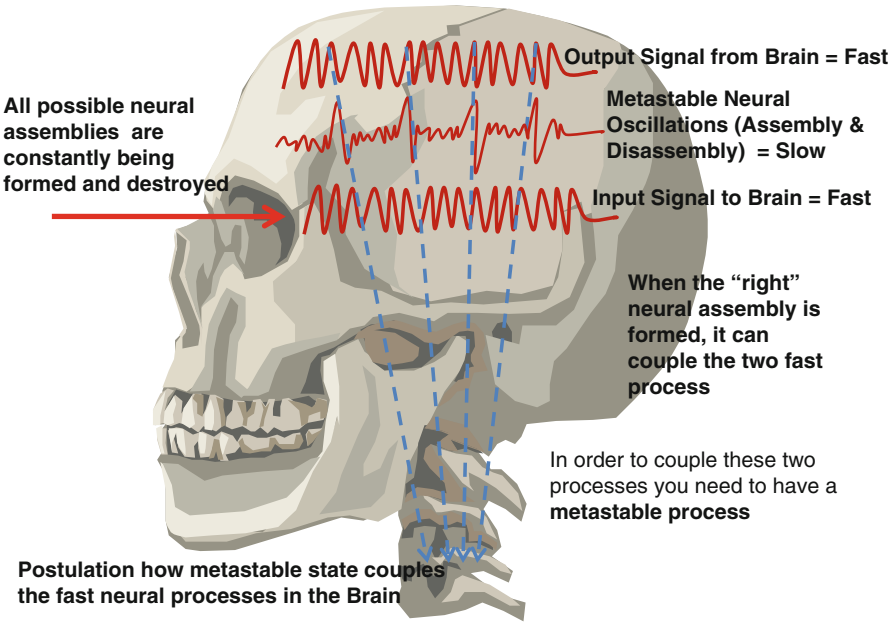


Fig. 15.21 The generalized Franck–Condon principle postulated to underlie the coupling between (1) *the cortical column assembling/disassembling* process essential for mental activities, and (2) *synchronous firings of muscle cells* during the micro–macro coupling accompanying body motions. See text for details (*I thank Julie Bianchini for drawing this figure in December 2008*)

postsynaptic targets in their neighborhood by undergoing random fluctuations or Brownian motions, just as molecules undergo Brownian motions or thermal fluctuations until they find their binding sites. But the "seemingly" random motions postulated to be executed by axon terminals are active (in the sense that depolarized axon terminals are thought to be unable to undergo such explorative motions), while the random motions of molecules are passive since no free energy dissipation is involved. We will therefore refer to the seemingly random motions of axon terminals as "actively random," "quasi-random," or "quasi-Brownian" and the conventional Brownian motions of molecules as "passively random," "truly random," or just "random". Quasi-random processes may be slower than truly random processes.

As indicated above, there are approximately 10^6 cortical columns in the motor cortex per hemisphere (Cook 1986, p. 63). These motor columns may undergo *quasi-random interactions*, exploring all possible patterns of interactions or configurations, and when the right configuration is selected or stabilized by input signal to the brain, that particular set of motor cortical columns is thought to be activated (or depolarized), leading to an almost simultaneous activation of their target muscle cells which results in visual input-specific body motions. This series of postulated events are schematically represented in Fig. 15.21. Using the language

of *coordination dynamics*, we may conveniently describe the transition of the motor cortex from the state where cortical columns are undergoing quasi-random explorative motions to the state where the input signal-induced depolarization of a particular configuration of cortical columns has occurred in terms of the transition from *the metastable state* to *bi-table (or multi-stable) state*. This state transition is suggested to be the result of coupling the slow column rearrangement and the fast axonal depolarization obeying the generalized Franck–Condon principle or the Principle of Slow and Fast Processes (Sect. 2.2.3).

Based on the above mechanisms, it is possible to estimate the force generated in the muscle when one cortical column in the motor cortex is activated as a result of the input of some external stimuli such as visual signals (see Fig. 15.21) through Steps 1–4 described below:

1. The activation of the efferent motor neurons constituting a cortical column in the motor cortex causes an almost simultaneous activation of the muscle cells innervated by the motor neurons.
2. The number of the muscle cells activated by one motor column is equal to nr, where n is the number of motor neurons contained in one motor column (estimated to be 10^4; see below) and r is the number of the muscle cells innervated by one motor neuron which is assumed to be 10^3, leading to $nr = 10^4 \times 10^3 = 10^7$, the number of the muscle cells that can be activated synchronously by one column in the motor cortex.
3. We assume that the number m of the myosin molecules contained in one muscle cell is approximately 10^4. Hence the number of myosin molecules activated by one motor column would be nrm or $(10^7)(10^4) = 10^{11}$.
4. Since one myosin molecule can generate force f in the range of 10^{-12} N (see Fig. 15.21), the force generated by activating one motor column would be $nrmf = (10^{11})(10^{-12}\ \text{N}) = 10^{-1}$ N.
5. The diameter of the cortical column is 5×10^{-6} m and the area of the motor cortex is 6,817 mm^2 (or approximately equal to a circle with 8×10^{-2} m in diameter) (Cook 1986, pp. 63–66). Hence the number of the columns contained in the motor cortex is approximately $[(8 \times 10^{-2})/(5 \times 10^{-6})]^2 = [1.6 \times 10^4] = 3 \times 10^8$.
6. Therefore, the number of the motor columns that needs be activated synchronously to generate 1 N of force in the muscle to lift, say, a cup of tea or an apple (http://en.wikipedia.org/wiki/N) would be $1\ \text{N}/(10^{-1}\ \text{N}) = 10$, which is small compared to the total number of cortical columns present in the motor cortex of the human brain, 3×10^8.

The force (F), distance (D), and time (T) amplification by increasing mass (FDTABIM) is necessary for the upward causation of the mind-molecule coupling (Figs. 15.17, 15.19), ultimately because force originates at the molecular level and the objects to be moved are at the muscle level. But why is the FDTABIM necessary for the downward causation (Figs. 15.17, 15.20)? In other words, why is it necessary to amplify the molecular processes at the ion channel level to the macroscopic electrical activities at the level of cortical regions such as motor cortex (Fig. 15.20)? One possible answer may be suggested as follows:

Just as the FDTABIM is needed for the upward causation because the force originates at the molecular level in muscle cells and is finally needed at the macroscopic skeletal muscle level (Fig. 15.19), so it may be that the FDTABIM is needed for the downward causation because the control information originates at the molecular level in cortical neurons and the final control information is needed at the level of the macroscopic cortical regions (Fig. 15.20). (15.41)

Statement 15.41 seems reasonable in view of the facts (1) that, just as force generation requires free energy, so does decision making (also called *reasoning*, *computation*, or *selecting* between 0 and 1, between *polarization* and *depolarization*), and (2) that free energy is available only from enzyme-catalyzed chemical reactions or membrane depolarization (i.e., collapsing ion gradients) occurring at the ion channel level.

[aa]Enzymes are molecular machines that are driven by chemical reactions that they catalyze. So the operation of an enzyme can be represented as a trajectory in a phase space (van Gelder and Porter 1995, p. 7) which would collapse when free energy supply is blocked. Therefore, an enzyme in action is a dissipative structure or a *dissipation* and hence can be named as an X-ator, X being the name of the city where the most important research has been done to establish the mechanism of action of the dissipative structure under consideration. In the case of enzymology, there are three research groups, in my opinion, that have made major contributions to advancing our knowledge on how enzymes work – (1) S. Xie (2001) and his group then at the Pacific Northwest National Laboratory, *Richland*, WA (by measuring the single-molecule enzymic activity of cholesterol oxidase analyzed in Sect. 11.3), (2) Rufus Lumry (1974, 2009) and his group at the University of Minnesota at *Minneapolis* (for establishing the role of mechanical processes in enzymic catalysis), and (3) William Jencks (1975) at the Brandies University in *Waltham*, MA, for establishing the fundamental role of the substrate binding processes in enzymic catalysis which he referred to as the *Circe effect*. To acknowledge the contributions made by these three groups, enzymes have been named as *RMWators* in this book (see Fig. 15.16).

Chapter 16
What Is Life?

16.1 The Definition of Life

Consistent with Peirce's pragmatic maxim (see Sect. 6.3.6) and triadic metaphysics (Sect. 6.2.2), it is here proposed that

There are three aspects to *life*: Life as *is*, life as *experienced*, and life as *theorized*. (16.1)

In addition to the pragmatic maxim of Peirce, which led to the philosophy of *pragmatism* popularized by William James, Peirce made a major contribution to modern philosophy by formulating his *triadic metaphysical doctrine* that all phenomena in the Universe comprise three fundamental elements or aspects which he referred to as *Firstness*, *Secondness*, and *Thirdness* (Sect. 6.2.2) (Goudge 1969; Hausman 1997; de Waal 2001; Sheriff 1994; Feibleman 1946). It is important to keep in mind that Peircean categories are *ordinal*, not *cardinal* in the sense that *Firstness* can exist all by itself, but *Secondness* cannot exist without *Firstness*, and *Thirdness* cannot exist without *Firstness* and *Secondness*. We may refer to this concept as the *ordinality of the Peircean categories* and represent it diagrammatically as follows:

$$\textbf{Firstness} \rightarrow \textbf{Secondenss} \rightarrow \textbf{Thirdness} \tag{16.2}$$

where the notation "A → B" reads "B cannot exist without A," or "B presupposes A."

Statement 16.1 may be made to connect logically to the Peircean categories, if the following proposition is accepted:

"Life as is" can be identified with *Firstness*; "life as experienced" with *Secondness*; and "life as theorized" with *Thirdness*. (16.3)

By combining Scheme 16.2 and Statement 16.3, it can be inferred that no theory of life (*Thirdness*) is complete without containing elements of *Firstness* (metaphysics such as the philosophy of complementarity; Sect. 2.3.4) and *Secondness* (experimental grounding such as cell biology). The theory of life presented in this book contains all these elements: (1) *Firstness = Life is intrinsic to gnergy* (see Table 2.6), (2) *Secondness = Gnergy can be actualized (or reified) into Energy/Matter*

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_16,

(also called Mattergy) or Information/Life (also called *Liformation*) (see Table 2.6), and (3) *Thirdness = The Universe possesses the cosmolanguage (or Gnergy), which is manifested as material language (including cell language) and mental language (including natural language) as the Universe evolved* (see Sect. 6.2.6). One of the surprising results of the gnergy-based theory of life (see Table 2.5) is that *life* and *information* are inseparably related just as energy and matter are so related in special relativity theory (through $E = mc^2$), leading to the following inference:

Just as matter is considered as a highly condensed form of energy, so life can be viewed as a highly condensed form of information. (16.4)

Or, more briefly,

Just as matter is a highly condensed form of energy, so life is a highly condensed form of information. (16.5)

We may refer to Statements 16.4 and 16.5 as the *information-life identity (ILI) hypothesis* in analogy to $E = mc^2$ which can be viewed as the *energy-matter identity (EMI) principle*.

16.2 Life According to Schrődinger

The first physical theory of life appears to have been formulated in 1945 by Schrödinger (1998) when he published his epoch-making book, *What Is Life?* This book had a major influence in inducing many talented physicists to enter the field of biology after the World War II, ushering in the era of molecular biology (Prigogine 1991), but the book is not without some theoretical inaccuracies as pointed out by Perutz (1987). For example, one of the conclusions that Schrödinger arrived at in his book is that

Organisms feed on negative entropy. (16.6)

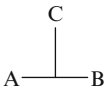
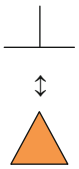
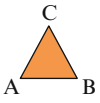
I believe that the term "negative entropy" in Statement 16.6 should be replaced with "negative entropy change," since the Third Law of thermodynamics prohibits "negative entropy" (see the *Schrödinger's Paradox* in Sect. 2.1.5). Statement 16.6 must also be judged inaccurate because organisms, being open systems, feed on *free energy changes* rather than on *entropy changes alone*. Free energy (e.g., Gibbs free energy, G) is a function of both *energy* (E) and *entropy* (S) (see Eq. 2.1). Hence, we can replace Statement 16.6 with Statement 16.7 which is more accurate:

Organisms feed on free energy. (16.7)

16.3 Life According to Bohr

Bohr attempted to characterize the difference between *physics* and *biology* based on the analogy that he drew between *classical physics* (e.g., Newtonian mechanics) and *quantum mechanics*. Although he introduced the two principles,

Table 16.1 The actions of the *principles of supplementarity* and *complementarity* in physics and biology

Principles	Physics	Biology
Supplementarity:  (Classical Mechanics)	1. $E = mc^2$: Principle of *energy-matter equivalence (or mattergy)* resulting from Einstein's special theory of relativity (Shadowitz 1968). A = Matter; B = Energy; C = Matter/Energy or Mattergy	6. Principle of *information-life equivalence* (or *liformation*): As the information density increases in some physical systems as a result of the cosmological e*volution*, life emerges from nonlife. A = Information; B = Energy or Mattergy; C = Gnergy
Correspondence principle:  or Phys ↔ Bio	2. Vertical (or spatial) correspondence principle (?): As the *quantum number increases,* quantum mechanics reduces to Newtonian mechanics	7. Horizontal (or temporal) correspondence principle (?): As the information density of physical systems increases with time, physics is transformed to biology
Complementarity:  (Quantum Mechanics)	3. Wave-particle duality of light (or *quantum objects*) 4. Quantum of action 5. Stability of atoms relative to motions of subatomic particles, ultimately because of the quantum of action	8. Information-energy duality of *gnergons* 9. Conformon as the quantum of life or quantum of purposive action 10. Stability/robustness of processes in cells relative to the thermal motions of intracellular molecules and ions, ultimately because of the conformon, the quantum of life

complementarity and *supplementarity* (see Sect. 2.3.1), he mentioned only the principle of *complementarity* in characterizing the difference between physics and biology. But in effect, he may have utilized the concept of *supplementarity* as well without realizing it. My reading of his writings has led me to conclude that these two principles are important in characterizing the relation between *physics* and *biology* as summarized in Table 16.1. The table lists two examples of the action of the *supplementarity principle* (see Item 1) in Table 16.1 and three examples of the action of the *complementarity principle* (see Items (3)–(5)) in physics (see the first column). In addition, the table contains examples of the action of the principle of correspondence (see Item (2)) (Morrison 1990). For each example, a biological counterpart is suggested in the third column, which is largely self-explanatory.

In Table 16.1, the *correspondence principle* originally formulated by Bohr is referred to as the *vertical correspondence principle* because it connects *Newtonian mechanics* and *quantum mechanics*, which are arranged vertically in the first

column of Table 16.1. In contrast, the newly conceived correspondence principle that connects *physics* and *biology* (which are arranged horizontally in the middle row of Table 16.1) is referred to as the *horizontal correspondence principle*. Since the vertical correspondence principle is formulated in terms of the quantum number (which is associated with *energy* levels) and the horizontal correspondence principle is formulated in terms of *information density* (i.e., the amount of the algorithmic complexity per unit volume of the information carrier), we may also refer to the former as *e-correspondence principle* (*e* standing for energy) and the latter as the *i-correspondence principle* (*i* standing for information), which may be viewed as another instance of the *information-energy dichotomy* found in physics and biology (see Sect. 2.3.2). Since, according to the *information-energy complementarity principle*, information and energy are symmetric with respect to gnergy (in the sense that they are complementary aspects of gnergy), if energy has its correspondence principle, so should information. This may, in part, provide the theoretical rationale for postulating the *i-correspondence principle*. If the *i-correspondence principle* is valid, we can make the following far-reaching inferences:

1. *Physics* and *biology* may be connected via the Darwinian theory of the biological evolution, just as *energy* and *matter* are connected via Einstein's special theory of relativity (Shadowitz 1968), and consequently
2. Life may be viewed as a *highly condensed form of information*, just as matter can be viewed as a *highly condensed form of energy* (see Table 2.5 and Statement 16.5) (Ji 2005a).

In 1932, Niels Bohr (1885–1962) delivered a lecture entitled "Light and Life" in Copenhagen, which was later published in Bohr (1933). In that lecture Bohr suggested that the phenomenon of life may be irreducible to physics and chemistry just as the stability of atoms cannot be accounted for by Newtonian mechanics and that, just as physicists are forced to accept quantum of action as a given, not derivable from any other laws of physics, so biologists might have to accept the phenomenon of life as a given, not derivable from physics nor from chemistry.

He also suggested that the notion of *complementarity* originating from atomic physics may be applicable to biology. As is well known, the idea of complementarity arose from an attempt to reconcile the *wave-particle duality* of light and *Heisenberg uncertainty relations* (Hilgevoord 2006; Plotnitsky 2006). The wave and particle natures of light are mutually exclusive (due to the mutual exclusion of the experimental arrangements needed to measure these contrasting properties of light) and yet both are essential to completely describe the behavior of light (e.g., interference phenomena requiring the wave nature of light and photoelectric effect requiring the particle nature of light). Bohr, in effect, suggested that the *complementarity* concept may apply to the apparent conflict between the *mechanistic* (based on physics and chemistry; synchronic sciences (?); see Sect. 2.6) and *teleological* (unique to biology resulting from the biological evolution; diachronic science (?); see Sect. 2.6) approaches to accounting for life (Bohr 1933).

Max Delbrück (1906–1981) was inspired by Bohr's "Light and Life" lecture and switched his field of research from physics to biology (McKaughan 2005; Stent

1989). By applying the reductionist, physicochemical approach to biology as far as possible (in the process he was so successful as an experimental reductionist as to garner a Nobel Prize for Physiology or Medicine in 1969) until he reached a situation revealing the failure of the reductionist approach, he apparently hoped to uncover a clear example of biological phenomenon where complementarity applied as predicted by Bohr (McKaughan 2005). To the best of my knowledge, Delbrück was not able to discover any new complementary pair in molecular biology beyond the *mechanism-function complementarity* that Bohr had already suggested in 1932.

One possible member of what may be called the *Bohr-Delbrück complementarity class* (i.e., the set of the complementarity-like principles that Bohr and Delbrück looked for in biology) may be suggested as follows:

> The orthogonality of genetic information and free energy, or the idea that genetic information cannot be reduced to free energy or to the laws of physics and chemistry. (16.8)

Statement 16.8 can be diagrammatically represented as shown in Fig. 4.2.

There are many alternative ways of expressing the content of Statement 16.8, just as there are many ways to express the Second Law of thermodynamics, including (1) the genetic information-free energy orthognonality, (2) the genetic information-free energy complementarity, and (3) information-energy complementarity (Sect. 2.3.2).

16.4 Life According to Prigogine

As indicated in Sect. 3.1, Prigogine (1977, 1980) divides structures in the Universe into two fundamental classes – equilibrium and dissipative structures. The former includes tables, chairs, rocks, molecules, etc. that can exist without any dissipation of free energy, and the latter is exemplified by the flame of a candle, the Belousov–Zhabotinsky reaction (Fig. 3.1), the living cell (Fig. 3.2), and social structures of organisms, etc., all of which require continuous dissipation of free energy to maintain their structures.

Prigogine once remarked to me when I was visiting him in Austin in the early 1980s that

> Cells are dissipative structures. (16.9)

As a corollary to Statement 16.9, we may logically attribute the following generalization to Prigogine:

> Organisms are dissipative structures. (16.10)

If we can encapsulate Schrödinger's theory of life with Statement 16.6, so can we express Prigogine's theory of life in terms of Statement 16.10. Whereas the validity of Statement 16.6 is debatable as already indicated (see Sect. 2.1.5), that of Statement 16.10 is beyond doubt. However, it should be pointed out that theoretical

statements about life such as (16.7), (16.9), and (16.10) that are based solely on the laws of physics and chemistry cannot be considered complete (or sufficient), since such statements lack the *Thirdness* (Sect. 6.2.2) aspect of life, namely, the *genetic information* engendered by biological evolution. Thus I am inclined to suggest that:

> No theory of life can be complete without incorporating the irreducible triad of *energy*, *entropy*, and *genetic information*. (16.11)

The theories of life expressed by Schrödinger and Prigogine in Statements 16.6 and 16.9, respectively, are primarily concerned with the energetic and entropic (i.e., thermodynamic and chemical kinetic) aspects of life and offer little or no guidance as to the informational (or evolutionary) aspect of life. But, since the discovery of the DNA double helix by Watson and Crick in 1953, an enormous amount of experimental data has been generated in molecular and cell biology, most of them having to do with genetic information. Any purported theory of life must take this fact into account and provide rational explanations for it. From this perspective, Statements 16.6 and 16.9 above must be deemed necessary but not sufficient to account for life. One of the primary objectives of this book has been to formulate *a molecular theory of life* that is consistent with Statement 16.11, thereby filling the theoretical gaps left behind by Schrödinger and Prigogine.

16.5 Life According to Pattee

By extending the earlier theoretical work of von Neumann on *self-replicating automata* (von Neumann 1966), Pattee (1968, 1995) formulated what he referred to as the *matter-symbol complementarity,* according to which all self-replicating and evolving systems (including organisms) possess two *complementary aspects* – the *physical law-governed material/energetic aspect* and *the evolutionary rule-governed symbolic aspect*. As pointed out by von Neumann, there are in principle two ways of accomplishing self-replication – by *self-inspection* followed by copying and assembling the copied parts, and by *self-description* using symbols (and more generally using signs as defined by Peirce [Sect. 6.2.1]) followed by executing the resulting instructions to self-replicate. Of these two possibilities, von Neumann concluded, without providing any proof, that the *direct copying method* is too inefficient and that the second *symbolic method* was preferred. Pattee developed von Neumann's original idea into his *matter-symbol complementarity*, which may be represented as in Scheme 16.12:

$$\textbf{Matter} + \textbf{Symbol} \rightarrow \textbf{Biological Functions} \qquad (16.12)$$

where biological functions include self-reproduction or self-replication.

Scheme 16.12 is consistent with what is actually found in all living systems, for example, the DNA-based mechanism of self-reproduction. But Pattee and von Neumann did not provide any realistic *molecular mechanisms* for connecting

matter-symbol complementarity to functions such as the concept of the conformon (Chap. 8), the molecular model of the cell (Chap. 10), and the cell language theory (Sect. 6.1.2) presented in this book.

16.6 Life Based on the Information-Energy Complementarity

The theory of life that I have been advocating since the early 1970s is based on the notion of *information-energy complementarity*, according to which all goal-directed, self-organizing chemical reaction-diffusion systems in the Universe, including the Big Bang, the origin of life, and the evolution of living systems, are ultimately driven by a complementary union of *information* and *energy* (see Fig. 4.8). The third entity for which information and energy are the complementary aspects was named *gnergy* in the mid-1980s (Ji 1985a, 1991). Discrete physico-chemical entities carrying *gnergy* are called *gnergons*, which produce heat upon realizing their associated goal-directed processes, that is, functions. Prominent examples of gnergons are *conformons* and IDSs (collectively called *dissipatons*) discussed earlier (see Sects. 3.1.2 and 8.3). Therefore, it would follow that there is a one-to-one correlation between *gnergons* and their conjugate *functions*, as indicated by the double arrow in Scheme 16.13:

$$\textbf{Ergons} \wedge \textbf{Gnons} \equiv \textbf{Gnergons} \longleftrightarrow \textbf{Functions} \tag{16.13}$$

where the symbol ^ is introduced in Eq. 2.32 and indicates the complementary relation between *ergons* carrying energy (energy particle, e.g., mechanical energy) and *gnons* carrying information (information particle, e.g., amino acid sequences of catalytic domains of proteins). The symbol, α, indicates a definition, and the double-headed arrow indicates an *identity relation*. It is evident that Scheme 16.13 is a generalization of the *IDS-Cell Function Identity Hypothesis* presented in Sect. 12.5.

Schemes 16.12 and 16.13 reveal both the similarities and differences between Pattee's theory and the theory of life presented in this book. As already noted, Pattee did not specify any *molecular mechanisms* of coupling *matter-symbol complementarity* to functions. In contrast, Scheme 16.13 invokes the intermediate entity *gnergons* as a means of coupling *information* and *energy* to *functions*. The molecular mechanisms responsible for generating gnergons (e.g., conformons and IDSs) are discussed in depth in Sects. 8.2, 8.4, and 11.4. But it is important to note that, in Scheme 16.13, *gnergons* and *functions* are best viewed as *synonymous* and represent two sides of the same reality: that is., *Genergons* and *functions* exhibit the Möbius relation (see Sect. 6.3.5) and possibly other relations as well, including the principles of closure (Sect. 6.3.2) and recursivity (Sect. 5.2.4).

Biological evolution results from coupling processes on both synchronic (developmental) and diachronic (evolutionary) time scales (see Sect. 15.4 and Fig. 14.3).

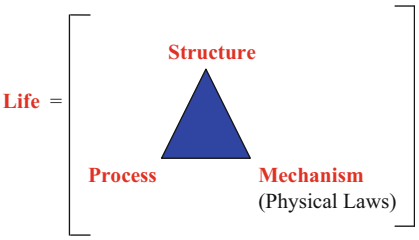


Fig. 16.1 A triadic definition of life: *Structures, processes*, and *mechanisms* implementing the *laws of nature* are irreducible aspects of life. This diagram is consistent with Peirce's triadic Metaphysics (Sects. 6.2.1, 6.2.2)

Thermodynamic and kinetic principles are essential to account for *processes*. *Thermodynamics* determines the direction of changes while *kinetics* determines the speed of changes. The former is path-independent and the latter is path-dependent. Hence, the former does not involve time while the latter does. The relation between kinetics and thermodynamics may be somewhat akin to the relation between processes (i.e., dissipative structures, or dissipatons) and structures (i.e., equilibrium structures or equilibrons): Objects with equilibrium structures (e.g., oxygen and hydrogen molecules) come first and then their interactions to form products, for example, water, comes later. Generalizing, we may say

$$\textbf{Process} > \textbf{Structures} \tag{16.14}$$

where the expression, A > B, symbolizes the original relation in which "A embeds B" or "A presupposes B." In other words, the relation between structures and processes is "ordinal" and "hierarchical" and not "compositional.". That is, life, for example, is not composed of *structures* and *processes* but rather life is selected processes (thereby being associated with information) that embed or enclose structures. This ideas may be diagrammatically represented as in Fig. 16.1.

16.7 Active versus Passive Phase Transitions: Is Life a Critical Phenomenon?

The *hypernetwork* model of the living cell shown in Fig. 9.2 implicates three geometric scales – (1) *microscopic* (or molecular, 0.1–5 nm), (2) *mesoscopic* (or cellular, 5–10^4 nm), and (3) *macroscopic* (or multicellular, greater than 10^5 nm). The individual nodes in the gene, RNA, and protein spaces are on the microscopic scale; their networks within individual spaces operate on the mesoscopic scale; and finally the functions of multicellular systems such as tissues and organs (not shown) operate on the macroscopic scale. Inseparable from the geometric (or spatial) scale is the time (or temporal) scales over which living processes occur, ranging from 10^{-12} to ~10^9 s. These two distinct scales may be coupled in living systems through Brownian (or thermal) motions of biopolymers that play fundamental roles in all

living processes, since the time constants and amplitudes of Brownian (or thermal) motions are mutually dependent and all biopolymer functions are postulated to depend on Brownian motions that are required by the generalized Franck–Condon principle as the prelude to all enzymic catalysis (see Sects. 2.2.3, 15.12 and Ji 1991).

The well-established phenomenon of the p53 mutation-induced tumor genesis (Vogelstein et al. 2000) may be viewed as an example of the *long-range interactions* (characteristic of all *critical phenomena*) that occurs over a distance range varying by a factor of at least 10^5, namely, from 0.1 to 10^4 nm, in the sense that the mutation in p53 at the microscopic level causes (or triggers) the macroscopic tumor formation in the human body in about 50% of all cancer patients (Vogelstein et al. 2000). Another example of long-range interactions in living systems is provided by the familiar phenomenon of weight lifting. Champion weight lifters can raise heavy objects within a matter of seconds, presumably triggered by some subcellular biochemical events such as membrane depolarization (known as mental processes) initially occurring in one or a few neurons located in the motor cortex of their brain, and subsequently propagating throughout their bodies to support the objects often weighing more than their own body weight (Sect. 15.12).

Physicists have been studying *long-range interactions* in abiotic systems for at least one and a half centuries (Domb 1996; Fisher 1998), including the phase transitions occurring between liquid, gas, and solids, which are collectively referred to as *critical phenomena*. The mutation of p53 leading to tumor formation in the human body may be viewed as belonging to the same class of natural processes as the snow crystal formation in which the sixfold symmetry of water molecules dictates (or determines) the sixfold symmetry of all snowflakes visible on the macroscopic scale (see Fig. 5.3 and http://www.its.caltech.edu/~atomic/snowcrystals). To include living phenomena within the physics of critical phenomena, it may be necessary to expand the meaning of *phase transitions* beyond the traditional range, by defining two classes of phase transitions in analogy to the two classes of transport processes, namely, *active* and *passive*. These two kinds of phase transitions can be characterized in a broad framework of statistical mechanics as shown in Table 16.2.

Statistical mechanics deals with random motions of a large number of molecules (in the order of Avogadro number, $N = 6 \times 10^{23}$/mol) belonging to a few classes that underlie macroscopically observable thermodynamic properties of physical systems. In contrast, molecular cell biology deals with both random and nonrandom motions of a small number (much smaller than N) of molecules belonging to a large number (10^3–10^{50} [?]) of classes, leading Elsasser (1998) to refer to biological systems as *finite* and *heterogeneous* in contrast to *infinite* and *homogeneous* physical systems (see the first three rows in Table 16.2). Some examples of phase transitions (which are synonymous with "order–disorder" or "disorder–order" transitions) in physics and biology are given in Row 4.

Enzymic catalysis may be viewed as *phase transition* in the sense that catalysis involves the transition of the random thermal fluctuations of an enzyme molecule to

Table 16.2 *Active* and *passive phase transitions* in physics and biology. N = Avogadro number

	Physics	Biology
1. System	Physical	Biological (e.g., cells)
2. Homogeneity	Homogeneous	Heterogeneous
3. Observables averaged over n	n ~ N	n << N
4. Examples	Freezing of water to ice Magnetization Liquid crystals	Enzyme catalysis Activated metabolic pathways Lifting of weights powered by ATP hydrolysis
5. Intensive variable	Temperature Pressure Mass density	Information density (?)
6. Order parameter	Translational degree of freedom Magnetization	Patterns of distributions of RNA trajectories (see Figs. 12.1 and 12.2a)
7. Correlation	Spatial	Temporal
8. Mode	Passive (i.e., approach to equilibrium)	Active (i.e., driven away from equilibrium by chemical reactions)
9. Key variables	Gibbs free energy	Gibbs free energy and genetic information (see Sect. 4.3)
10. Mechanisms	Self-assembly (equilibrium structures or *equilibrons*)	Self-organization (dissipative structures or *dissipatons*)

its transient state of orderly motions required by the catalytic act, paid for by the free energy of the reaction it catalyzes. Hence, we can consider enzymic catalysis as an example of a phase transition where the *correlations among events (in contrast to structures) occur not only along the spatial dimensions as in physics but also along the time dimensions*. In other words, the essence of enzymic catalysis may be the "freezing out" of the transient, thermally activated conformations of the enzyme needed for catalysis for the time durations much longer than are allowed for by the second law of thermodynamics *by utilizing conformational energy (or conformons) stored in enzymes*. This is why we can view catalysis as an "active" form of phase transition in contrast to the traditional phase transitions studied in physics which are viewed here as "passive" phase transitions. The fundamental difference between *passive* and *active phase transitions* may be that physical phase transitions are driven by free energy (a function of energy and entropy), whereas biological phase transitions are driven by *both* free energy *and* genetic information resulting from the selection inherent in biological evolution, thus justifying the neologism, "info-statistical mechanics" discussed in Sect. 4.9.

The intensive variables in the physics of critical phenomena, that is, *passive phase transitions*, are temperature, mass density, and pressure. The intensive variable for *active phase transitions* is proposed here to be the *biological (or genetic) information* encoded in the structures of biopolymers that allows biopolymers to undergo long-range interactions mediated by stereospecific ligands (e.g., see the garage-door mechanism described in Table 11.12). The order parameter in passive phase transitions captures the order–disorder properties of *intermolecular* interactions. In contrast,

the order parameter in active phase transitions may be identified with the degree of coupling between two or more dynamic processes or dissipative structures, exemplified by the coupling of the RNA trajectories shown in Table 12.12 and the positively and negatively correlated trajectories of the glycolytic and oxidative phosphorylation RNAs observed in budding yeast during glucose–galactose shift (see panel **a** in Fig. 12.2). In general, any *pattern* of distributions of RNA trajectories as visualized on a two-dimensional principal grid produced by the ViDaExpert program or its equivalent may be viewed as an order parameter of active phase transitions (see Sect. 12.8.2).

Chapter 17
Why Is the Cell So Complex?

It is useful to compare the complexity of the living cell with that of the atom. If the complexity of a physical system is expressed in terms of the algorithmic information content (defined as the number of words or bits needed to describe a system; see Sect. 4.3) and if we assume that the algorithmic information content of a system is approximately proportional to its volume, the complexity of the average cell would be about 10^{15} times that of the hydrogen atom (see Table 10.3). Think of the number of the articles (and the words or symbols in them) that have been published describing the essential features of the hydrogen atom, which can be easily in the hundreds. Then the number of the papers that would be needed to describe the essential features of the living cell could well reach 10^{17}, a number equivalent to about a million papers written per person now living on this planet! This is probably why there are so many biological papers published every week in *Science*, prompting nonbiological scientists (such as one of my professors in chemistry at the University of Minnesota, Duluth, in the mid-1960s) to complain in effect that there are too many biological articles in *Science*. The situation is far worse now than it was a half century ago. As will become evident below, one simple answer to the title suggested by the *Law of Requisite Variety* (Sect. 5.3) is that *the internal structure of the cell has to be complex in order to survive the environment that is at least as complex.*

Before we consider the complexity of the living cell, it may be necessary to have an overview of the problem of classifying physical entities of the Universe in general. As pointed out in Sect. 3.1, the *dissipative structure theory* of Prigogine (1977, 1980, 1991) posits that all structures in the Universe can be classified into *equilibrium structures* (or *equilibrons*) and *dissipative structures* (or *dissipatons*). Prigogine's division of structures into *equilibrons* and *dissipatons* is primarily based on the nonequilibrium thermodynamics perspective. But there are aspects to physical entities other than thermodynamic ones. Thus, we can divide each of the two classes of the structures proposed by Prigogine into three further classes based on the *size* of the physical entities, namely, micro-, meso-, and macro-entities, and each of these, in turn, into two classes based on *viability*, that is, whether or not the entities

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_17,

Table 17.1 Examples of the classification scheme based on the triple criteria of (1) energy (1 = equilibrial, 2 = dissipative), (2) size (A = microscopic, B = mesoscopic, C = macroscopic), and (3) viability (a = living, b = nonliving)

		Energy	
		1. Equilibrium	2. Dissipative
Size	(A) Micro (atoms, molecules)	(a) Thermal fluctuations of enzymes	(a) Enzyme catalysis
		(b) Thermal motions of molecules	(b) Electronic excited states, vibrational excited states
	(B) Meso (cells, nanoparticles)	(a) Cell membrane	(a) Membrane potentials, chemotaxis, morphogenesis
		(b) Brownian motions of nanoparticles	(b) Bernard convection cells
	(C) Macro (humans, stars)	(a) Skeletons	(a) Body motions, thinking
		(b) Rocks, continents, planets	(b) Belousov-Zhabotinsky reaction, tornadoes, stars

involved are alive. Thus, according to *this triple criteria scheme*, there are a total of 12 distinct classes of physical entities that we can recognize in the Universe as shown in Table 17.1. For example, the morphology of rivers would belong to Class 2Cb, the moon to Class 1Cb, stars to Class 2Cb, the cell to Class 2Ba, etc. This way of classifying physical entities is not free of ambiguities. In order for the cell to exist, its dissipative structures must be supported by equilibrium structures at both the micro- and mesoscopic levels. In other words, Class 2Aa structures cannot exist alone but must be supported by Class 1Aa and 1Ba structures.

The living cell exhibits two broad categories of complexities – the *structural* (i.e., Class 1Aa and 1Ba entities) and *dynamic* (i.e., Class 2Aa and 2Ba entities). When trying to distinguish between *equilibrons* and *dissipatons*, it is important to keep in mind that the distinction critically depends on the size of the time window (TW) employed, that is, the time range (minutes, hours, days, years, etc.) within which observations or measurements are made. For example, although entity A is classified as an equilibron with a TW in the minutes range, A may appear as a component of dissipation when the TW is increased to days, if the half-life (HL) of A (i.e., the time it takes for A to undergo 50% of its maximal change) is in hours. In other words, the concepts of *equilibrons* and *dissipatons* are not absolute but relative to the size of the ratio, TW/HL. If TW/HL is greater than say 10^2, an entity A may appear as a dissipaton, but when TW/HL is one or less, A may appear as an equilibron. Thus, it may be justified to make the following general statement to be referred to as the Principle of the Relativity of Equilibrons and Dissipatons (PRED):

> The concepts of equilibrons and dissipatons are relative and depend on the magnitude of the ratio of the time window over the half life of the physical entity under observation. (17.1)

It is interesting to point out that *Heraclitus* thought that everything changes constantly (and hence is a dissipation in my idiom), while *Parmenides* thought the opposite, namely, that the ultimate reality is unchanging and eternal (and hence is an

equilibron in the modern terminology). However, according to PRED, Statement 17.1, the question of whether the ultimate reality is an equilibron or a dissipation cannot be decided unless and until the TW of the observer and the HL of the observed objects are known. Thus, the world views of Heraclitus and Parmenides may reflect the two extremes of PRED.

Before we attempt to explain in greater details why the living cell is so complex (probably the most complex structure per unit mass in the Universe!), it would be helpful to briefly summarize the *equilibrons* and *dissipatons* that constitute the living cell, equilibrons and dissipatons being defined in accordance with PRED. That is, any physical entities of the living cell that remain constant within the time window of minutes or hours will be considered to constitute "structures," "things," or "equilibrons," whereas any entities lasting only for times shorter than about seconds or minutes upon removing free energy will be referred to as "processes" or "dissipatons."

17.1 The Structural Complexity of the Living Cell

The complexity of any entity or object, including the living cell, in principle, can be expressed (as alluded to above) in terms of the algorithmic information (also called the Kolmogorov–Chaitin complexity) equal in quantity to the number of symbols or signs (e.g., numbers, words, equations, graphs, and pictures) in the shortest symbol string that is required to characterize/describe the entity under consideration (Sect. 4.3). Thus, the longer the symbol string needed to describe an entity, the more algorithmic information that entity carries (Klir 1993), and hence the more complex is the entity. For example, the complexity of the mitochondrion can be equated with the number of symbols needed to describe all the scientific knowledge that has accumulated on this organelle as of, say, December 31, 2010. Even without performing any exhaustive data mining, we can reasonably conclude that the mitochondrion is more complex than the endoplasmic reticulum, which is in turn more complex than the lysosome, which is more complex than the peroxisome, since it would take successively longer strings of symbols to describe these organelles as we know them. The structural and functional characteristics of the major components of the living cell are briefly summarized in Table 17.2.

Applying the Law of Requisite Variety (Sect. 5.3.2) to these organelles, it may be concluded that

> The relative algorithmic complexities of the structures of organelles reflect the relative complexities of their intracellular functions. (17.2)

Statement 17.2 seems reasonable since the mitochondrion, along with the nucleus, is one of the most complex organelles, since it provides the energy for all of the hundreds of metabolic processes that are driven either directly or indirectly by ATP hydrolysis. It is important to keep in mind that mitochondria not only synthesize ATP but also most likely communicate with other organelles,

Table 17.2 The major structural components of the living cell and their functions

	Cell component	Function
1	Cell membrane	To prevent cellular components from being lost by diffusion and to protect the cell interior from the harmful influence of its environment. Proteins embedded in (or spanning) the membrane act as selective pathways for material movement and information transfer in and out of the cell. These proteins undergo *thermal fluctuations* leading to their conformational, rotational, and translational diffusions within the membrane. Cholesterol molecules alter the fluidity of the membrane, lowering their levels in the membrane having the same effects as raising local temperature. Therefore, in principle, individual cells can control their "local membrane temperature" by controlling the expression of the genes coding for the enzymes catalyzing the cholesterol biosynthesis.
2	Cytoskeleton	To provide the mechanical framework to organize intracellular components in space and time, utilizing the free energy of hydrolysis of GTP and ATP. The cytoskeleton determines the cell shape, cell motility, cell cycle, and the organization of organelles and vesicles in the cytosol. The eukaryotic cytoskeleton consists of actin filaments, microtubules and intermediate filaments. The network of the filamentous elements are dynamic and deformable, providing the flexible mechanical framework for organizing subcellular components and their movements in space driven by nucleotide triphosphate hydrolysis catalyzed by the cytoskeletal components themselves.
3	Nucleus	To separate chromosomes from the cytoplasm in eukaryotes in order to control their structure and function better without being interfered by cytoplasmic elements.
4	Nuclear envelope	To control the trafficking of materials between the nucleus and the cytoplasm and to help organize chromosomes and their dynamics.
5	Chromosomes	To store genetic information of the cell for transmission from one cell generation to the next in an orderly manner. They are formed from the DNA double helix wrapped around the histone complex to form *nucleosomes*, which in turn form higher-order helical chains known as *chromatins*, *chromatids*, and the *chromosome* (Fig. 2.9).
6	Nucleolus	To transcribe and assemble ribosomal RNA for export to the cytosol
7	Centrosome	The controsome consists of two centrioles, each having ninefold symmetry due to the nine triplets of microtubules. Centrioles are self-replicating organelles found only in animal cells. They help organize cell division but are not essential for it (Doxsey 2001).
8	Mitochondria	(a) To serve as the power house of the cell, providing the free energy needed to drive all endergonic physical and chemical processes in the cell. (b) According to the *chemiosmotic theory* (Mitchell 1961), the mitochondrial inner membrane is for storing osmotic energy to produce ATP (Sect. 11.6).

(continued)

Table 17.2 (continued)

	Cell component	Function
		However, the *conformon theory* of molecular machines (Sect. 11.5) maintains that ATP production is driven mainly by conformational energy of proteins (i.e., *conformons*) confined within the inner membrane that can be produced without the membrane acting as an osmotic barrier and the transmembrane proton gradient is there to serve as the communication channel between mitochondria and the rest of the cell (Ji 1979, 1991).
9	Ribosome	Consists of approximately 60% RNA and 40% proteins. Acts as molecular machine to synthesize polypeptides from amino acids using mRNA as templates.
10	Endoplasmic reticulum (ER)	A network of sacs that produce, process, and transport molecules to be used inside and outside of the cell. It is connected to the nuclear envelope and serves as a link between the nucleus and the cytoplasm.
11	Golgi apparatus	To distribute and export the products of the cell to its external environment. The Gogi apparatus modifies proteins and fats produced in ER and prepares them for export to the outside of the cell via secretory vesicles.
12	Proteosome	To control the intracellular level of proteins by regulated degradation of unneeded or damaged proteins in communication/coordination with protein-producing ribosomes. The proteosome is a large protein complex found in eukaryotes, archea, and some bacteria. It is a barrel-shaped protein complex with internal channel and consists of the core (20 S) and two adaptors (19 S) attached to the ends of the core. The 19 S adaptors or caps recognize the ubiquitinated target proteins for degradation and the 20 S core carries out the task of protein degradation through its proteinase activity localized in its interior.
13	Lysosome	To help digest foods and to degrade cellular waste products and debris from the intracellular and extracellular spaces for recycling. Lysosomes are spherical organelles containing acid hydrolases (optimally active at pH 4.5) for digesting endogenous or exogenous proteins and particles. The lysosomal membrane protects the cytosol from undesired attack of cellular components by lysosomal enzymes. Lysosomes are also called "garbage disposal system" of the cell that keeps the interior of the cell free of unneeded materials (Ciechanover 2005).
14	Peroxisome	To oxidize fatty acids and other metabolites and to detoxify hydrogen peroxides. Peroxisomes are a single membrane-bound organelles that contain enzymes able to remove peroxides and catalyze the β-oxidation of very long chain fatty acids
15	Cilia	For unicellular eukaryotes to move around. In multicellular organisms, cilia are used to move fluid or materials past an immobile cell. Cilia protrude from the cell anchored on the basal body and encased in the cell membrane. The filaments within a cilium carries out forward and backward stroke motions using free energy of ATP hydrolysis.

including the nucleus, to constantly monitor their energy needs so that mitochondria can provide ATP *whenever* and *wherever* it is needed (Ji 1979). To accomplish such a cell-wide function of timely supplying ATP to endergonic (free energy-consuming) processes in the cell, it was postulated that mitochondria utilize the *proton-motive* force (which is *global* in its influence) of Mitchell (1961, 1968) as the means for communicating with the rest of the cell and utilize *conformons* (which is *local* in its influence) for the purpose of synthesizing ATP (see Deconstructing the Chemiosmotic Hypothesis in Sect. 11.6).

The cell is composed of three categories of microscopic objects – (1) macromolecules (e.g., DNA, RNA, proteins), (2) what may be conveniently referred to as *micromolecules* (e.g., glucose, NADH, FAD, ATP, pyruvate) in contrast to *macromolecules*, and (3) metal ions (e.g., K^+, Na^+, Ca^{++}). These components are not distributed randomly inside the cell but organized into what may be called the *unit cell volume* (UCV) in analogy to the unit volume of the *phase space* in statistical mechanics (Sect. 4.9), which in turn may be organized into familiar subcellular compartments. If the linear dimension of UCV is about 10 Å (or 10^{-9} m), there may be $(10^{-5}\ \text{m}/10^{-9}\ \text{m})^3 = 10^{12}$ UCVs in a typical cell with a diameter of 10^{-5} m. If one CUV stores at least n bits of information, the minimum possible algorithmic information content of the cell would be $n \times 10^{12}$ bits. If n is comparable to the number of bits of the algorithmic information stored in the hydrogen atom, the cell would store 10^{12} times the amount of the algorithmic information content of the hydrogen atom. It took physicists several decades to elucidate the structure of the hydrogen atom, publishing at least 100 fundamental papers, including those establishing the quantum theory of the atom. Based on this comparison, it may be predicted that

1. It will take 10^{14} fundamental papers to completely elucidate the structure and function of the living cell, a number equivalent to approximately 10,000 papers written for every person alive on the this planet at present.
2. It may be beyond the human capacity to completely characterize the structure and function of the living cell, and
3. Despite the avalanche of experimental data being published in life sciences in general and cell biology in particular in recent decades, post-Internet, *Homo sapiens* may be glimpsing only the tip of the biological iceberg.

For convenience, item (2) may be referred to as the *Infinite Complexity Postulate of the Living Cell* (ICPLC).

17.2 The Dynamic Complexity of the Living Cell

There are structures in the cell that disappear within the time window (TW) of seconds to minutes upon blocking the free energy supply to the cell, for example, membrane potentials, the concentration gradients of many metabolites in the cell including ATP, RNA, and glucose. That is, the living cell *contains dissipatons*.

The dynamic complexity of the cell refers to the complexity of the *interactions* among the molecular and macromolecular components of the cell organized in space and time (constituting various *dissipatons*). In 1999, Bernard Jacq and his colleagues coined the term "interactome" to represent the whole set of *molecular interactions* in cells (see Sect. 9.3). There are two (and only two) kinds of interactions in the cell – (1) covalent (e.g., the phosphoryl group transfer from ATP to a protein catalyzed by a kinase) and (2) noncovalent interactions (e.g., hormone binding to its receptor, electrostatic interactions among charged molecules) (Sect. 3.2). In general, the interaction energies of the former are about 20 times those of the latter, that is, 50–100 kcal/mol versus 2–5 kcal/mol.

The metabolic maps or metabolism charts summarize all the biochemical reactions occurring inside the cell, and the arrows in these charts symbolize covalent interactions each catalyzed by at least one enzyme, supported by noncovalent interactions such as substrate and product binding to enzymes. The complexity of the metabolic map is evident in the large numbers of the biochemicals (represented by nodes numbering 500–600) and the chemical reactions (represented by directed edges or arrows). Some nodes such as acetyl Co-A has a dozen edges connected to them. One way to estimate the complexity of the metabolic map would be to count all the nodes and the edges in it and all the symbols needed to describe each node and edge.

Unlike the metabolic maps (or networks) whose nodes are *biochemicals* and the enzymes catalyzing their transformations are hidden, the signal transduction pathways focus on the intracellular *proteins* that interact either *covalently* (mostly through phosphoryl transfer) or *noncovalently* (through electrostatic, hydrophobic, and/or hydrogen-bonding interactions).

Since the living cell can be viewed as an organized system of the four key molecular components – DNA (d), RNA (r), proteins (p), and biochemicals (b) (see Fig. 10.2) and, since the existence of the d–d, p–p, and b–b interactomes is well established (see Table 9.6), with the last interactome being identified with the traditional metabolic pathways, it seems logical to raise the question: *Is there any experimental evidence for the existence of the r–r (or RNA-RNA) interactome?* The answer to this question will critically depend on how the r–r interaction or correlation, both linear and nonlinear, is defined (see Table 12.12). Just as the d–d interactome is based on defining the *d–d interaction* as the "digenic lethal relation," or the relation between two genes whose simultaneous mutations leading to a lethal phenotype of the cell (Costanzo et al. 2010), so one way to define the *r–r interaction* is in terms of the similarity of the RNA trajectories (i.e., *ribons*) between two or more RNA molecules as measured with microarrays (Sects. 12.2 and 12.8). One way to describe the similarity among ribons in cells is to utilize *ribonoscopy* as explained in Sect. 12.8.3. Based on the ribonic spectra such as shown in Fig. 12.12, it is possible to identify those RNA molecules whose trajectories (i.e., ribons or RNA waves) have the same node numbers. Thus, 1 RNA molecule from the glycolytic pathway, 4 from the protein folding pathway, 5 from the secretion pathway, 4 from the transcription pathway, 5 from the protein synthesis pathway, 3 from the sterol metabolic pathway, and about 65 from the group of 294 RNA molecules with unknown functions all have the same node number 20, indicating that they exhibit a similar kinetic behavior or

Table 17.3 The correlation between the interactome size of various species and the extent of their noncoding DNA regions. The interactome size is defined as the number of the edges in the whole interactome, estimated from the number of edges in the partial interactomes using Eq. 8 in Stumpf et al. (2008). *IS* interactome size, *NTR* the noncoding DNA over the total genomic DNA ratio, *ncDNA* noncoding DNA, *tgDNA* total genomic DNA

Species	Interactome size (IS)	ncDNA/tgDNA ratio (NTR)
1. *Saccharomyces cerevisiae*	25,229	0.30
2. *Drosophila melanogaster*	74,336	0.75
3. *Caenorhabditis elegans*	240,544	0.87
4. *Homo sapiens*	672,918	0.97

cluster close to one another in the six-dimensional concentration space (Sect. 12.8.2). In contrast, the six RNA molecules belonging to the oxidative phosphorylation pathway with node number 3 have no interaction with any of the over 250 RNA molecules belonging to the seven well-known metabolic pathways in Fig. 12.12. This method of defining the r–r interaction may be referred to as the "*ribonic correlation method* (RCM)." The r–r interactome constructed with the RCM will depend not only on the cell type but also on the perturbations imposed on the cell system by its environment (see the *ribonic matrix* in Table 12.6). Thus, the *r–r interactome* of budding yeast underlying glucose–galactose shift may differ from the *r–r interactome* of budding yeast undergoing a nitrogen stress (Mendes-Ferreira et al. 2007), for example. All such information on the *r–r interactome* can be displayed in what is referred to as the "ribonic matrix" in Table 12.6. According to the hypothetical numerical values given in the interior of the *ribonic matrix*, it can be concluded that RNA molecules, R_4 and $R_{11,}$ exhibit node number $n_{7,}$ and hence are correlated or interacting with each other.

Stumpf et al. (2008) developed a mathematical procedure for estimating the size of the whole p–p interactomes of various species based on the experimental data on their subnetworks. The results are displayed in the second column of Table 17.3, which indicates that the interactome size (IS) increases progressively from about 25,000 in *Saccharomyces cerevisiae* to about 6,700,000 in *Homo sapiens*. A similar trend was observed in the ratio of the noncoding DNA over the total genomic DNA in various species (Mattick 2004) as shown in the third column of Table 17.3 which was abstracted from Fig. 15.15.

When the logarithms of the IS values in Table 17.3 are plotted against the corresponding NTR values of the four species, a nonlinear plot was obtained as shown in Fig. 17.1. The following features of this plot are noteworthy:

1. The multicellular organisms (i.e., the points labeled 2–4) lie close to a straight line passing through the origin. The slope, w, of the line is 14.3, leading to the conclusion that these organisms obey Eq. 17.3:

$$\begin{aligned} \ln\,(\mathrm{IS}) &= \mathrm{w}(\mathrm{NTR}) \\ &= 14.3(\mathrm{NTR}) \end{aligned} \tag{17.3}$$

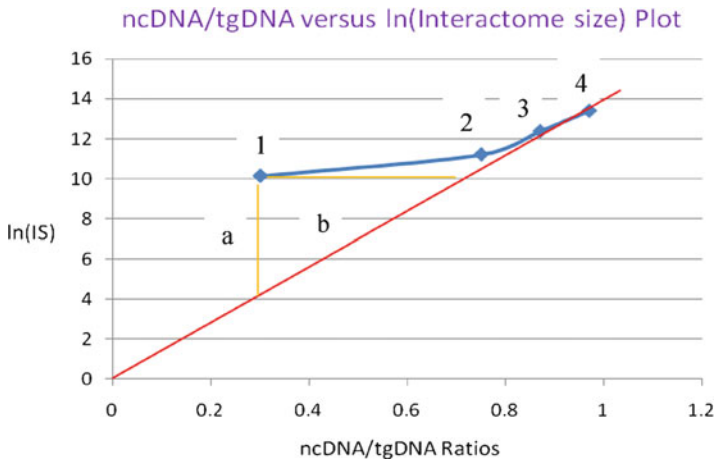


Fig. 17.1 A semi-logarithmic relation between the protein–protein interactome size (IS) and the extent of noncoding regions of DNA in four species (Data from Stumpf et al. 2008 and Mattick 2004). *1 = Saccharomyces cerevisiae*; *2 = Drosophila melanogaster*; *3 = Caenorhabditis elegans*; *4 = Homo sapiens*

Or

$$\begin{aligned} \text{IS} &= e^{14.3(\text{NTR})} \\ &= (e^{14.3})^{(\text{NTR})} \\ &= (1.6 \times 10^6)^{(\text{NTR})} \end{aligned} \tag{17.4}$$

2. According to Eq. 17.4, the interactome size of multicellular species is an exponential function of their NTR's. Since NTR cannot be greater than 1, the maximum size of the p–p interactomes in multicellular species is predicted to be less than 1.6×10^6. Since there are about 20,000 genes in the human genome,

   The maximum number of the gene-gene interactions that can be encoded in the human genome would be $1.6 \times 10^6/2 \times 10^4 = 80$ per gene. (17.5)

   Statement 17.5 may be referred to as the Principle of the Maximum Interactome Size of the human genome (PMISHG), or simply the Principle of the Maximum Human Interactome (PMHI).
3. The deviation of *S. cerevisiae* from the straight line in Fig. 17.1 by a = 6 units (or by a factor of $e^6 = 403$) along the *y*-axis and b = 0.4 units (or 40%) along the *x*-axis may not be due to experimental errors but has a biological significance. The anomaly here is that the budding yeast appears to have a much more complex p–p interactome relative to the noncoding portions of its genome. The noncoding potion of the yeast genome, that is, 0.3 or 30%, should be worth about e^4 55 edges but its number estimated, based on empirical measurements (Stumpf et al. 2008), is about 25,000 (see Table 17.3). One possible rationale for this discrepancy can

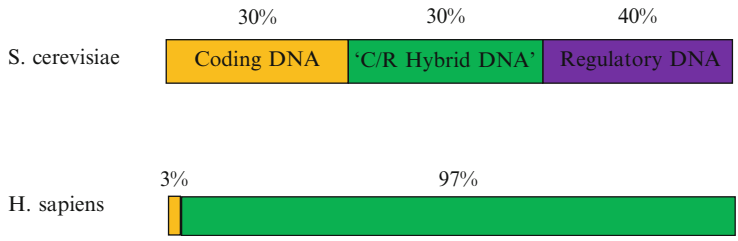


Fig. 17.2 A schematic representation of the hypothesis that 40% of the budding yeast genome is both *protein-coding* and *transcription-regulatory DNA*, or the *self-transcribing* DNA. C = coding; R = regulatory; C/R = coding/regulatory hybrid

be provided if we assume that about 40% of the yeast genome has a dual role, that is, protein-coding and transcription-regulatory (see Fig. 17.2). We may refer to this assumption as the "Coding/Regulatory Hybrid DNA (CRHD) hypothesis" or the "Self-Transcribing Structural Genes (STSG)" hypothesis, since "self-transcribing" would require a structural gene to *both* encode RNA *and* control its transcription level. The concept of the "structural genes regulating their own transcript levels" (Sect. 12.9) was invoked in (Ji et al. 2009c) based on the microarray evidence that nucleotide sequences of structural genes co-regulate (with other regulatory regions of DNA) the intracellular levels of their transcripts probably through Steps 4 and 5 in Fig. 12.22. According to this view, the yeast genome is 30% coding, 30% regulatory, and 40% both coding and self-regulating (Fig. 17.2). In contrast, the human genome is 3% protein-coding and 97% regulatory and coding, since the latter, although not coding for proteins, does code for DNA for self-replication. Hence, most of the genomic DNA in humans can be viewed as coding/regulatory hybrid regions.

17.3 The Fourfold Complexities in Physics and Biology

In Sect. 2.3.5, we discussed two distinct types of complementarities in physics as suggested by Murdoch (1987, p. 80). This idea is represented in the row labeled Physics in Table 17.4. The wave-particle complementarity is thought to belong to ontology (the study of being) while the kinematics-dynamics complementarity belongs to epistemology (the study of knowledge). These dual complementary relations are thought to reflect the well-known dual dichotomies of *discontinuity* versus *continuity* and *global* versus *local* that contribute to the complexity of material systems in physics. It is suggested here that the same set of dichotomous or complementary categories contribute to the complexity of living systems. Examples belonging to these four categories of classification are given below the last row in Table 17.4.

Table 17.4 The fourfold complexity in physics and biology is suggested by the two kinds of complementarities, i.e., matter-wave and dynamics-kinematics complementarities. *Mattergy stands for matter-energy, and liformation stands for life-information* (See Table 2.6)

	Ontology		Epistemology	
	I (discontinuity)	II (continuity)	III (global)	IV (local)
Physics (secondness)	Particle	Wave	Kinematics	Dynamics
	Photoelectric effects	Interference effects	Planetary motions	Particle collisions
	Wave-particle complementarity		Kinematics-dynamics complementarity	
Biology (thirdness)	Organized chemical reactions	Random chemical reactions	Metabolic pathways	Mechanisms
	Chemical reactions in the cell	Chemical reactions in test tubes	Metabolism chart	Single-molecule mechanics
	Liformation-mattergy complementarity			

17.4 The Law of Requisite Variety and Biocomplexity

If forced to choose one principle that best accounts for the complexity of living systems, I would not hesitate to select the *Law of Requisite Variety* (LRV) as the most powerful candidate of all the laws and principles of biology discussed in this book. LRV (Sect. 5.3.2), when combined with the Second Law of thermodynamics (also called the Law of Maximum Entropy) (Sect. 2.1.4), can logically lead to the *Principle of Maximum Complexity* (LMC) (Sect. 14.3), according to which "*The active complexity of living systems increases toward a maximum,"* Statement 14.15, where "active complexity" is defined as the *"complexity created by living systems utilizing free energy in order to survive under complex environment."* Simply put, the reason surviving organisms increase the complexity of their internal states is because the complexity of their environment is constantly increasing due to the Second Law of thermodynamics and no simple organisms can survive complex environment, Statements 5.10 and 14.8.

17.5 Cybernetics-Thermodynamics Complementarity

Since cybernetics mainly deals with *control information* and thermodynamics with *free energy,* both of which being necessary and sufficient for producing complex living processes, it appears logical to conclude that *cybernetics* (including *informatics*) and *thermodynamics* (including *energetics*) are complementary sciences essential for a complete description of life and hence can be viewed as a complementary pair obeying the Principle of *Information-Energy Complementarity*

or, more accurately, the *Liformation-Mattergy Complementarity* (Sect. 2.3.1). Just as the early twentieth-century physics saw heated debates between the supporters of the particle- versus the wave-views of light, which remains incompletely resolved (Plotnitsky 2006; Bacciagaluppi and Valenti 2009), I predict that biology, as it matures as a science, will experience similarly heated controversies surrounding the definition of life between two complementary views – the *cybernetic*/*informatic* (e.g., gene-centric) view of life and the *thermodynamic*/*energetic* (e.g., process-centric) view. Again just as the wave-view of light was dominant throughout the modern history of physics until the particle-view gained support from Einstein's theory of photoelectric effect published in 1905, the *gene-centric view* of life has been dominating molecular biology for over half a century now (since the discovery of the DNA double helix in 1953) with little or no attention given to the alternative *process-centric view*. The characteristics of the gene-centric view of biology is that most, if not all, biological phenomena can be satisfactorily accounted for in terms of genes, static nucleotide sequences in DNA (Sect. 11.2). In contrast, the process-centric approach to biology (e.g., see Sect. 10.2) maintains that *genes are necessary but not sufficient* to account for life and that genes and their RNA and protein products must be coupled to exergonic chemical reactions (processes) through thermal excitations (Sect. 12.12) and the Franck–Condon mechanisms (Sect. 2.2.3) before living phenomena can be completely explained (see Fig. 14.7).

One example of the conflict between the *gene-centric* and *process-centric* views in biology is provided by the field of microarray data interpretation:

> Most biologists believe that RNA levels in cells measured with microarrays can be used to identify the genes of interest. But careful analyses (Ji et al. 2009a) have revealed that these changes in RNA levels cannot be used to identify the genes of interest but reflect the different ways in which transcription and transcript degradation processes are coupled or interact in the cell. (17.6)

Statement 17.6 is reminiscent of the famous *wave-particle debate or paradox* in physics in the early decades of the twentieth century and hence may be viewed as a species of what may be referred to as the "structure-process paradox in biology" (SPPB) or the "structure-process conflation in biology" (SPCB). My students at Rutgers and I have examined over 100 prominent papers reporting the results of DNA microarray experiments and found that over 90% of these papers have committed SPCB, that is, the authors conflated *transcripts* (structures) and *transcription* (processes) rates (Sect. 12.6). The structure-process conflation may be related to the quality–quantity duality discussed in Sect. 17.7 below.

17.6 The Universal Law of Thermal Excitations and Biocomplexity

In Sect. 12.12, evidence was presented indicating that thermal excitations of biopolymers are implicated in single-molecule enzymology, whole-cell metabolism, and protein stability, thus establishing the fundamental role that *thermal motions*

(also called Brownian motions or thermal fluctuations) play in living systems. But thermally excited states of biopolymers can last only briefly, in the order of 10^{-12}–10^{-13} s, and hence very difficult to study unlike stable structures or ground-state structures or conformations (see nodes B and C in Fig. 14.7). The transition from the ground-state conformation of a biopolymer to its excited state requires thermal excitation which corresponds to Step 2 in Fig. 14.7. According to the generalized Franck–Condon principle (GFCP) (Sect. 2.2.3), the thermally excited states of proteins are necessary for catalyzing exergonic chemical reactions (Step 3 in Fig. 14.7), which must release heat rapidly enough to pay back, within the lifetime of the excited states, the thermal energy "borrowed" by enzymes from their environment to reach excited states. When a sufficient number of thermally excited enzymic processes are coupled properly in space and time, self-organized processes are thought to emerge called Intracellular Dissipative Structures (IDSs) or dissipatons, capable of carrying out specific intracellular functions (Step 4 in Fig. 14.7). One of the major sources of *biocomplexity* can be identified with the many-to-one mappings between the lower nodes and their higher counterparts in Fig. 14.7. For example, many different amino acid sequences of proteins (node A) are known to fold into similar three-dimensional conformations (node B), leading to what is known as the "designability of a structure," defined as the number of sequences folding into the same structure (Zeldovich and Shakhnovich 2008). There are almost infinite number of amino acid sequences for a finitely sized protein (e.g., $20^{100} = 1.27 \times 10^{107}$ different sequences of proteins with 100 amino acid residues), but there are only several thousand known protein folds. The single-molecule enzymological data provided by Lu et al. (1998) and analyzed in Sect. 11.3.3 indicate that many ground-state conformations of cholesterol oxidase are thermally excited to a common transition state designated as $C^{\ddagger}$ in Fig. 11.27.

The mapping between thermally excited states of enzymes (node C) and exergonic chemical reactions (node D) may be one-to-one due to the fact that these two nodes are *coupled* through the mechanism constrained by the generalized Franck–Condon principle (Sect. 2.2.3).

It is here suggested that the mapping between exergonic chemical reactions (node D) and IDSs (node E) (see Step 4 in Fig. 14.7) is similar to the mapping between ground-state conformations of proteins (node B) and their excited states (node C), since both these mappings involve thermal excitations as discussed in Sect. 12.12. In other words, it is here postulated (1) that there are more exergonic chemical reactions (each catalyzed by an enzyme) than there are cell functions and (2) that two or more different sets of exergonic chemical reactions can support an identical *intracellular function* or an *intracellular dissipaton*.

17.7 The Quality–Quantity Duality and Biocomplexity

The duality of *quality* versus *quantity* is a well-established topic in philosophy. Spirkin (1983) states that the quality of an object is "the sum-total of its properties" and that the quantity of an object "is expressed by numbers." Table 17.5 lists some examples of the quantity–quality dualities that occur in molecular and cell biology.

Table 17.5 The quality–quantity dualities found in biology

	Quality	Quantity
Proteins	Amino acid sequences	Concentrations or copy number
RNA	Ribonucleotide sequences	Copy numbers
Genes	Deoxyribonucleotide sequences	Copy numbers
Ribonoscopy	RNA sequences	RNA trajectories (or *waves*); i.e., n(t), where n is the copy number and t is time

When biologists think about proteins, RNAs, or genes in the living cell, they tend to think more about the qualitative aspects of these objects, that is, their sequences and three-dimensional shapes than their quantitative aspects, such as the changes in their concentrations (or copy numbers) inside the cell as a function of time. Qualitative aspects appear to be more closely related to *equilibrium structures* or *equilibrons*, while quantitative aspects are related to *dissipative structures* or *dissipatons* (Sect. 3.1.5). We may refer to this phenomenon as the "quality over quantity bias" in biology. This bias is prevalent in the field of microarray experiments where practically every measurement is interpreted in terms of *genes* (quality) underestimating the importance of their *concentration changes* in time or trajectories (quantity), leading to false positive (Type I) or false negative (Type II) errors (Sect. 12.6) (Ji et al. 2009a).

Chapter 18
Ribonoscopy and Personalized Medicine

As pointed out in Sect. 12.6, microarrays can be used to measure either DNA or RNA from cell samples (see Fig. 12.5). Hence, it may be useful to coin two words, *ribonoscopy* and *deoxy-ribonoscopy* to distinguish between these two types of measurements. Conflating these two different measurements can lead to logical errors in interpreting microarray data (Ji et al. 2009a). The term "ribonoscopy" is composed of two stems – "ribo-" meaning *ribonucleic acid* or *RNA*, and "-scope" meaning *to look carefully* or *to see* – and hence "ribonoscopy" literally means "to carefully look at RNAs" (rather than genes or DNA) with respect to the changes in both their *sequences* (or kinds, quality) and abundances (also called levels or concentrations, quantity). More formally *ribonoscopy* can be defined as

> The study of the genome-wide RNA sequences and concentrations inside the cell measured with cDNA microarrays and visualized as spectra (called ribonic spectra) with the *y*-axis registering RNA levels and the *x*-axis recording time, structure, or other related variables. (18.1)

It is often useful to distinguish between the raw, unprocessed microarray data and the results of the analysis of the raw data using software such as hierarchical clustering (Eisen et al. 1998) and ViDaExpert (Gorban and Zinovyev 2004, 2005). The former (i.e., RNA trajectories) is referred to as "ribons" (see Sects. 12.8.2 and 12.8.3) and the latter (i.e., 2- or 3-D displays of the results of analysing microarray data) as "ribonic spectra" or "ribospectra." The relation among ribons, computer-assisted analytical tools, and ribonic spectra can be illustrated using an analogy between *optical spectra* in physics and *ribonic spectra* as shown in Fig. 18.1. Thus *ribons* are akin to light, computer *softwares* are analogous to a prism, and *ribonic spectra* are comparable to optical spectra.

The content of *ribonoscopy* is explained in a greater detail in Table 18.1. There are two major types of ribons – (1) the *t-ribons*, namely, *time series* as exemplified by RNA trajectories (e.g., Fig. 9.1) and (2) what is here referred to as the *s-ribons,* or *structure series* (see Table 9.1 and Figs. 19.2 and 19.3) in analogy to "time series." These two types of ribons are the inputs to ribonoscopy as indicated in the first column of Table 18.1. The raw data from microarray measurements on n RNAs

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_18,

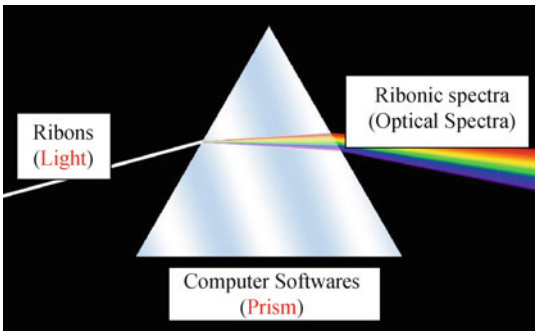


Fig. 18.1 An analogy between the optical spectra and "ribonic spectra." The prism and optical spectra have been reproduced from http://wimminwiselpts.wordpress.com

can be represented as a set of n points in an N-dimensional mathematical space (to be called the "ribonic space" or "RNA concentration space"), where N is either the time points of measurements or the number of different samples analyzed. The ribonic space is depicted in the top figure in the second column of Table 18.1, where the undulating membrane indicates a principal manifold onto which the nearest points are projected by the ViDaExpert program (Sect. 2.8.1). The ViDaExpert software is based on several well-established mathematical and computational frameworks. Each of the n point in the N-dimensional concentration space represents a *ribon* with N coordinate values which is the main reason for referring to the mathematical space as the *ribonic space*. In the case of a *t-ribon* (e.g., see the upper figure in the first column of Table 18.1), its coordinate values are the levels (or copy numbers) of an RNA measured at N different time points. In the case of an s-ribon (e.g., see the lower figure in the first column of Table 18.1), its coordinate values represent the levels or copy numbers of an RNA measured in N different samples.

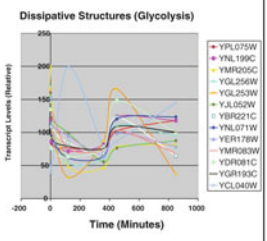
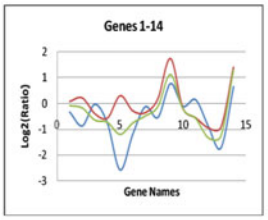
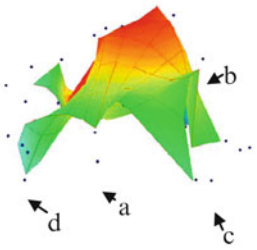
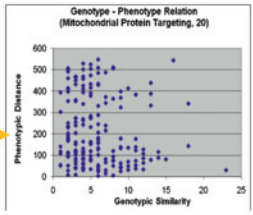
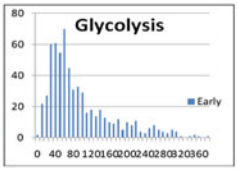
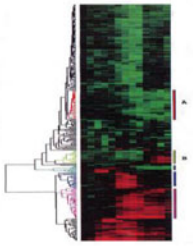
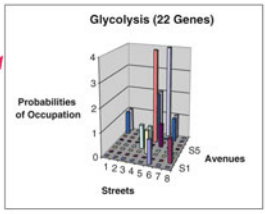
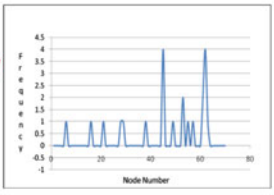
The raw data of microarray measurements can also be represented as a "distance matrix" (see the table in the second column of Table 18.1) where the Euclidean distances between all possible pairs of the points (i.e., ribons) in the N-dimensional concentration space have been calculated based on the Pythagorean formula. It should be noted that

> All the information contained in the raw RNA data measured with microarrays is encoded in the distance matrix which is symmetric with respect to its diagonal because the distance between a and b is the same as that between b and a. (18.2)

The distance matrix defined in Statement 18.2 may be referred to as the "ribonic matrix," since the first row and the first column of the matrix are composed of the names of the ribons measured by microarrays.

It is possible to analyze the raw data, that is, both t- and s-ribons, in the forms of ribonic matrices, without relying on any specialized analytical soft wares such as hierarchical clustering or ViDaExpert. The top two figures in the third column of Table 18.1 represent significant results of analyzing ribonic matrices without utilizing any computational softwares (Ji et al. 2009b, c). The third figure in the

Table 18.1 Various forms of inputs, methods of analysis, and outputs underlying ribonoscopy, the study of RNA molecules with respect to their sequences and copy numbers in the living cell

Input (RNA raw data or "Ribons")	Computer-aided analysis	Output (ribonic spectra)
Time-Series Data (e.g., ***RNA trajectories***)  **Structure Series Data** (e.g., ***Gene expression profiles***) 	1. N-dimensional *Ribonic space*  2. *Ribonic matrix*	
		
		
		
3. Genotype-phenotype correlation analysis		
4. Histograms		
5. Clustering		
6. ViDaExpert		 

third column of Table 18.1 is the result of clustering the ribonic matrices measured from human breast tissues and tumors (Perou et al. 2000). The fourth and fifth figures in the third column of the same table are the 3-D and 2-D visualizations of the ViDaExpert-analyzed results of the t-ribons measured from budding yeast undergoing glucose–galactose shift (Sects. 12.8.2 and 12.8.3).

One of the major assumptions of this section is that, to apply *ribonoscopy* to personalized medicine, it is necessary to utilize the *molecular theory of the living cell* such as the one developed in this book, especially the concept of *dissipative structures* in general and *intracellular (ic) dissipative structures* (IDSs or *ic-dissipatons*) in particular (Sect. 3.1.2). Ribonoscopy is one of the few experimental methods now available that allows IDSs or ic-dissipatons to be measured genome-wide. Personalized medicine differs from traditional medicine in that it tailors health care (through the triad of *diagnosis*, *prognosis*, and *therapy*) to best fit individual patients taking into account their unique genetic (i.e., nucleotide sequence-dependent) and epigenetic (i.e., non-nucleotide sequence-dependent) characteristics. The roles that *ribonoscopy* and the *molecular theory of the living cell* (*MTLC*) developed in this book play in *personalized medicine* are schematically represented in Fig. 18.2. Since the cell is the building block of the human body, it is logical to anticipate that cell biology will play a fundamental role in personalized medicine (see the top node and the bottom three nodes in Fig. 18.2). Ribonoscopy consists of two parts – (1) the microarray data acquisition (Step 1) using cDNA microarray technology (Sect. 12.8), and (2) the dimensional reduction and visualization of high-dimensional microarray data (Step 2) in the form of what is referred to as *ribonic spectra* (see Fig. 12.17) using ViDaExpert or similar computer softwares. It is here assumed that, in order to analyze ribonic spectra correctly and identify the ribonic spectral characteristics reflective of a diseased cell, it is necessary to apply a comprehensive *MTLC* (Step 3). In other words, it is thought to be *impossible to identify a biomarker from ribonic spectra without applying a comprehensive molecular model of the living cell, just as it is impossible to interpret molecular spectra without quantum mechanics, the theory of the atom.* Once a correct biomarker (or a disease-related cell-state, or *biomarker ribonic spectrum*) is identified, it can be utilized for developing *companion diagnostics* (i.e., the diagnostic tools that identify the patients most likely to benefit from a drug) (Step 4), *drug target discovery* (Step 5), or *personalized drug therapy* (or pharmacotherapy) (Step 6).

There is an interesting analogy to be drawn between *the nuclear power industry* and *drug industry* on several levels as indicated in Table 18.2.

The final product of a power plant is *electricity*; the final product of a drug manufacturing plant is safe and efficient *drugs*. Both kinds of plant activities inevitably produce wastes that contribute to environmental pollution – the *external environmental pollution* by the nuclear power industry (e.g., the Cherbonyl, Three Mile Island, and Fukushima disasters) and the *internal environmental pollution* by drug industry (e.g., the Vioxx fiasco). Nuclear reactor engineering that emerged in the 1940s as a spinoff from the atomic bomb production in the USA and the then-USSR is based on the theory of the atom, that is, quantum mechanics that was

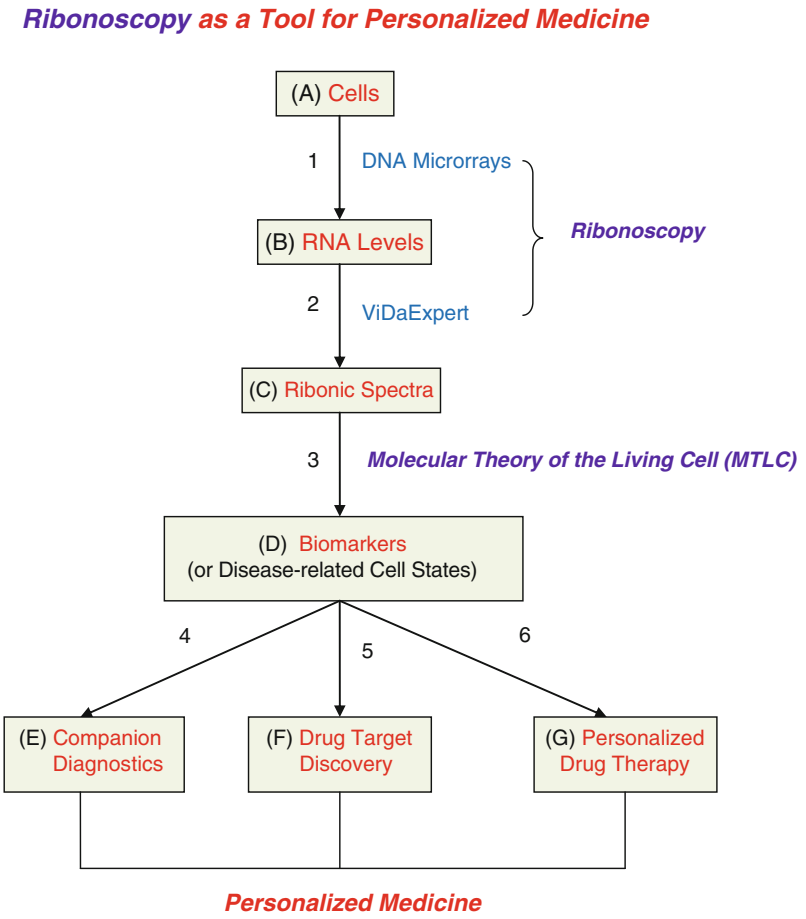
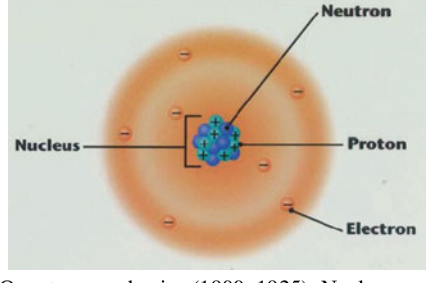
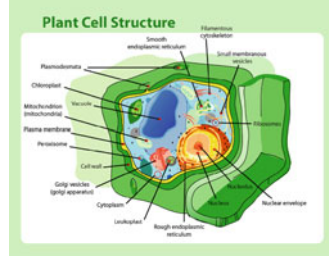


Fig. 18.2 A schematic representation of the roles that *ribonoscopy* and *the molecular theory of the cell (MTLC)* play in personalized medicine

firmly established between 1900 and 1925. In stark contrast, the theory of the cell, the building block of the human body, is still lacking. The molecular theory of the living cell developed in this book may represent one of the first, if not the first, *comprehensive molecular theories of the living cell* (MTLC), to the best of my knowledge. The *ribonoscopy* described in this book for the first time combined with MTLC may turn out to be to drug industry what nuclear reactor engineering has been to nuclear power industry (see the last row in Table 18.2). Based on this comparison, it may be asserted that:

> Trying to develop safe and efficacious drugs without a comprehensive molecular theory of the living cell is akin to trying to construct a safe and efficient nuclear power plant without quantum mechanics. (18.3)

Table 18.2 An analogy between nuclear power industry and pharmaceutical industry

Plant		
Final product	Electricity	Drugs
By products	Harmful radiation and heat	Thousands of chemicals synthesized and discarded for every drug reaching the market; besides, only 50% of the approved drugs work
Object		
Microscopic theory	Quantum mechanics (1900–1925), Nuclear reactor engineering (1940s)	Molecular theory of the living cell (1985–2010), Ribonoscopy (2010)

The emergence of personalized medicine over the past decade or so has been strongly motivated by the revolutionary developments in the so-called *omics* in basic biological sciences throughout the second half of the twentieth century and the first decade of the twenty-first century. The development of personalized medicine is now officially endorsed by the Obama Administration. Early in 2010, Dr. M. Hamburg, FDA Commissioner, "announced a new partnership with the National Institutes of Health that is designed to more quickly get scientific and medical breakthroughs in personalized medicine, among other fields, into clinical practice" (*Personalized Medicine Coalition Newsletter*, Spring, 2010, p. 8).

Omics is defined as the genome-wide studies of genes (*genomics*), transcripts (*transcriptomics*), proteins (*proteomics*), and metabolites (*metabolomics*). Transcriptomics, the study of genome-wide alterations of RNA levels inside the cell, is often omitted in defining personalized medicine, but I predict that transcriptomics will play a major role in drug discovery research and personalized medicine because RNA molecules can serve as convenient *intracellular reporter molecules* whose behaviors can be easily monitored using *ribonoscopy* (Sect. 12.8.2). Another component not included in the current definition of personalized medicine is intracellular (ic) *dissipative structures* or *ic-dissipatons* (Sect. 12.5) such as the patterns of the changes in RNA levels and RNA sequences that can be used to differentiate subtypes of cancer cells (for a recent review, see van't Veer and Bernards 2008). As can be seen in the Bhopalator models of the living cell (Fig. 2.11) and biological evolution (Fig. 14.7), all intracellular processes involving genes, RNAs, proteins, and metabolic pathways eventually converge to generate various *ic-dissipatons*, which are postulated to be synonymous with cell functions (see Sect. 10.2). For convenience, the study of genome-wide *ic-dissipatons* may, therefore, be referred to as *ic-dissipatonics,* in analogy to "electronics," the study of electrons. The molecular theory of the living cell developed in this book can provide the theoretical framework for developing *personalized medicine* as defined in Fig. 18.3.

The other side of the *personalized-health* coin is *personalized pathology*, and according to Fig. 18.3, *personalized pathology* can arise in five distinct ways – due to the failure of any one of the cellular components belonging to *genomics* (G), *transcriptomics* (T), *proteomics* (P), *metabolomics* (M), or *ic-dissipatomics* (D), whichever happens to be the *weakest link*, W, in the complex network of molecular interactions constituting the living cell under a particular environmental condition. If we express the stability of the weakest ic-dissipatons in diseased cells as P(D) (the more stable the ic-dissipatons, the higher would be the probability of finding that dissipations), where P(D) is determined by the probability of the weakest G, T, P, or M, depending on the health condition of the patient, we can express the *death rate*, d, of individuals from the disease under consideration as in Eq. 18.4 in analogy to the *death-rate equation* discussed in the context of the MTLC-based model of evolution, Eq. 14.40:

$$d = d_0[1 - P(D)] \tag{18.4}$$

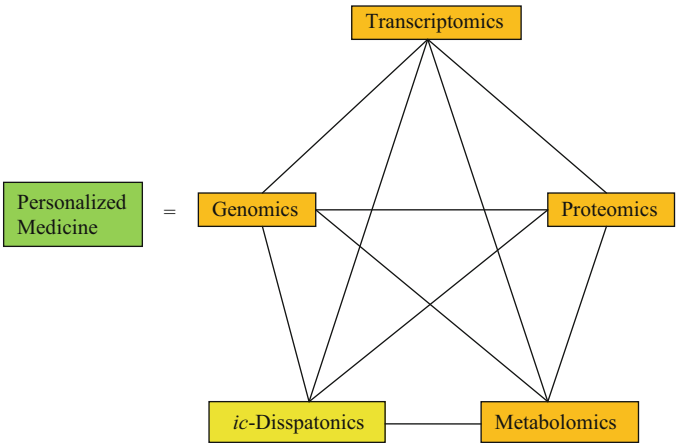


Fig. 18.3 A network representation of *personalized medicine* consisting of five nodes and their inter-relations suggested by the *molecular theory of the living cell* developed in this book. The node labeled *ic-dissipatonics* is unique because it is the node closest to cell functions, in fact, so close as to make it indistinguishable from cell functions (see Node E in Fig. 14.7)

where d_0 is the death rate without any therapy. In other words, diseased cells treated with drugs will have higher P(D) values than diseased cells without drug treatment and hence will have lower death rate. It should be pointed out that D in Eq. 18.4 is synonymous with Node E in Fig. 14.7. Furthermore, replacing P(D) with $P_{nat}^{(i)}$ in Eq. 18.1 leads to the *Zeldovich-Shakhnovich model* of evolution, Eq. 14.32. $P_{nat}^{(i)}$ is the probability of the native conformation of the protein that serves as the weakest link under the i^{th} environmental condition (Sect. 14.7). It is quite surprising and unexpected to find that the basic mathematical equation developed to account for biological evolution from the molecular perspective, namely, the Zeldovich-Shakhnovich model, Eq. 14.32, can be applied to describe the effect of drug therapy on the death rate of human patients.

Chapter 19
Ribonoscopy and "Theragnostics"

The combined field of researches in drug therapy, diagnostics, and prognostics may be referred to as "theragnostics." Some investigators have already coined the word "theranostics" to refer to the same but I prefer theragnostics over theranostics because the second stem in the latter word, "nostics," has no etymological basis. The main purpose of this section is to propose that ribonoscopy will find important applications in *theragnostics*.

According to Bain and Company (2007), the cost of developing a new drug is estimated to be $1.7 billion and it takes 12–16 years to complete a drug development process from the compound discovery stage to marketing. The overall attrition rate for developing a drug is calculated to be 10,000:1. According to another survey, the USA invested a total of $25 billion in 2000 on the research and development for pharmaceuticals and produced only 11 new drugs on the market in that year, costing the US pharmaceutical industry $2.3 billion per new drug.

In addition, once a drug is approved by FDA, the success rate of drug treatment is only 30–60% (Ingleman-Sundberg 2010). In other words, only about 50% of the patients treated with drugs respond favorably. The success rate (R_{suc}) of a drug is calculated as the percentage of the number of responders (N_{res}) over the total number (N_{tot}) of the patients treated with a drug as explained in Fig. 19.1.

There are two ways to improve the success rate of drug therapy – (1) to improve the efficacy of drugs so that more patients respond to them, and (2) to develop the *companion diagnostics* and *prognostic tools* to identify those patients who are most likely to respond to drugs, thereby lowering the number of nonresponders in clinical trials. When these two approaches are combined into one package, we have the example of what has been referred to as "theragnostics" or "theranostics" defined by Wikipedia as the combination of diagnostics and therapy in order to test patients "for possible reaction to taking a new medication and to tailor a treatment for them based on the test results" (Wikipedia 2010).

The use of *ribonoscopy* as a theragnostic tool is illustrated in Table 19.1, where the top panel depicts a hypothetical set of three RNA trajectories (i.e., t-ribons) each corresponding to one of the three cell types – normal (A), diseased and drug resistant (B), and diseased and drug responding (C). The *x*-axis records time in

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_19,

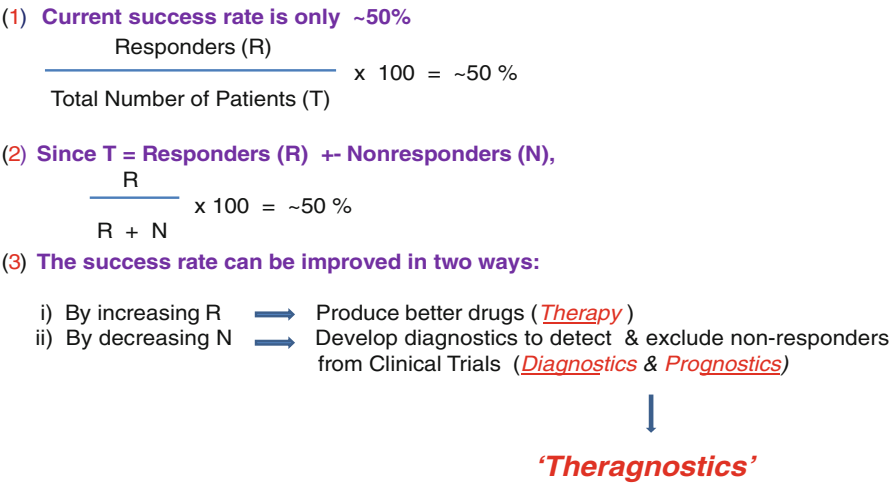


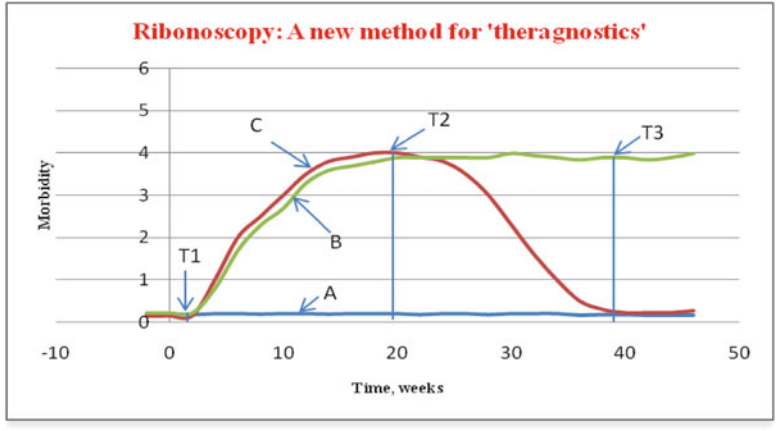
Fig. 19.1 How to improve the success rate of drug therapy, and the need for developing *theragnostics* (also called *theranostics*) as a combined field of *therapy*, *diagnostics*, and *prognostics*

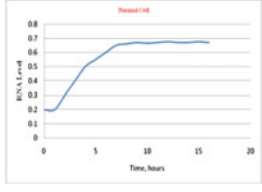
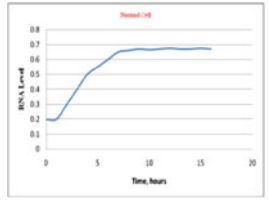
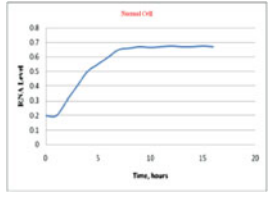
two scales – the "chronic" timescale of weeks to months and the "acute" timescale of minutes to hours, and the *y*-axis registers some quantitative index of the morbidity under consideration, for example, breast tumor. Two types of raw data can be employed for theragnostics, both providing two independent information and hence, when used together, increasing the confidence level of theragnostic determinations.

The nine panels of t-ribons shown in the rows labeled Time Series A, B, and C are hypothetical levels of the RNA molecules belonging to one or more specific metabolic pathways (such as glycolysis, oxidative phosphorylation, and fatty acid catabolism). At "chronic" times of T1, T2, and T3 (which can range from weeks to months), cell samples were obtained and their RNA levels were measured at acute times (ranging from minutes to hours after applying a common perturbation such as glucose–galactose shift). These nine t-ribons divide into three groups – (1) Group I consisting of the t-ribons located at boxes A-T1, A-T2, and A-T3 that represent the biomarkers of normal cells, (2) Group II consisting of the t-ribons at B-T1, B-T3, and C-T1, and (3) Group III consisting of the t-ribons at B-T2, C-T2, and C-T3. Group I t-ribons, Group II t-ribons represent the biomarkers of disease-susceptible cells, and Group III t-ribons are the biomarkers of the diseased cells. From the pattern of distribution of these three groups of t-ribons, we can conclude that Type A cells are normal, Type B cells are disease-susceptible but favorably respond to drug therapy, and Type C cells are disease-susceptible and resistant to drug therapy.

It is predicted that the same theragnostic results can be obtained from the same set of cell types if s-ribons, rather than t-ribons, are measured with microarrays as illustrated in the nine s-ribons shown in the lower three rows of Table 19.1. The s-ribons shown in these panels are the result of microarray measurement made on

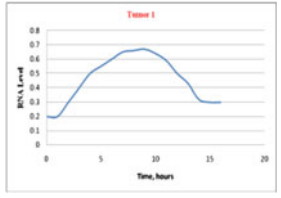
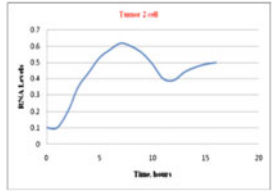
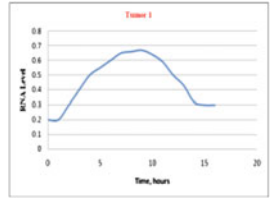
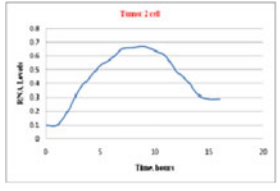
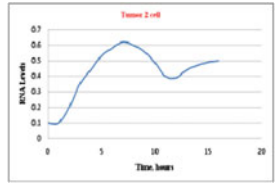
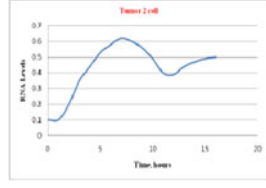
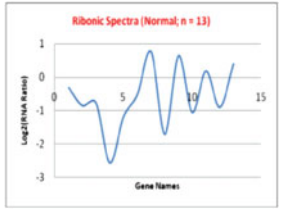
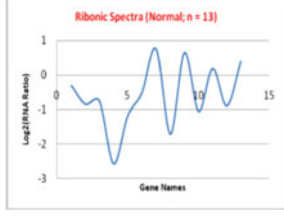
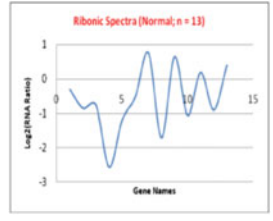
Table 19.1 A diagrammatic representation of ribonoscopy and its application to "theragnostics." The *time series plots* are hypothetical simulations, while the *structure series plots* are constructed utilizing the experimental data reported by Perou et al. (2000). For the definitions of the t- and s-ribons, see Table 18.1

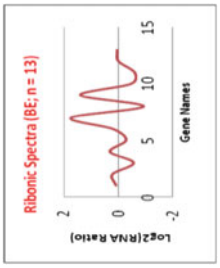


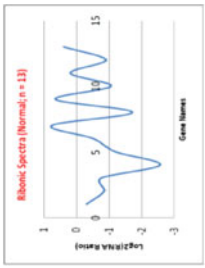
RNA data type	Cell type	T1 = $t_{11} + t_{12} + t_{13} + \ldots$	T2 = $t_{21} + t_{22} + t_{23} + \ldots$	T3 = $t_{31} + t_{32} + t_{33} + \ldots$
Time series (*t-ribons*)	A (type I)			

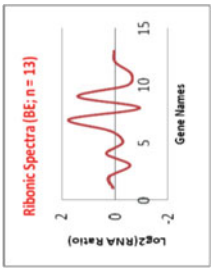
(continued)

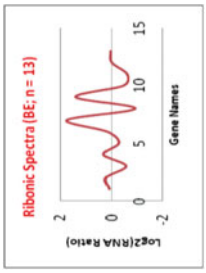
Table 19.1 (continued)

RNA data type	Cell type	T1 = $t_{11} + t_{12} + t_{13} + \ldots$	T2 = $t_{21} + t_{22} + t_{23} + \ldots$	T3 = $t_{31} + t_{32} + t_{33} + \ldots$
	B (type II)			
	C (type III)			
Structure series (*s-ribons*)	A			

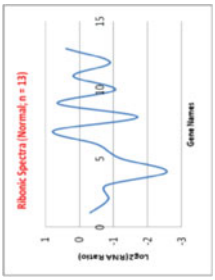

Ribonic Spectra (BE; n = 13)
Log2(RNA Ratio)
Gene Names


Ribonic Spectra (Normal; n = 13)
Log2(RNA Ratio)
Gene Names

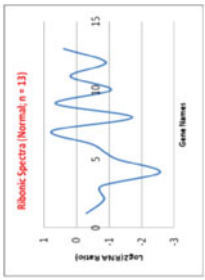

Ribonic Spectra (BE; n = 13)
Log2(RNA Ratio)
Gene Names


Ribonic Spectra (BE; n = 13)
Log2(RNA Ratio)
Gene Names

B


Ribonic Spectra (Normal; n = 13)
Log2(RNA Ratio)
Gene Names

C


Ribonic Spectra (Normal; n = 13)
Log2(RNA Ratio)
Gene Names

the cells isolated from human breast tissues and tumors (Perou et al. 2000). The s-ribons at AT1, AT2, A-T3 are the "gene expression profile" of 13 RNAs selected by Perou et al. (2000) as biomarkers of the *normal* human breast tissue. The s-ribons at B-T2, B-T3, and C-T2 (labeled BE, i.e., "before treating with doxorubicin") are the levels of the 13 RNAs serving as the biomarkers for human breast *tumors*. The distribution of these different types of s-ribons is consistent with the conclusion that Type A cells are normal, Type B cells are tumor cells resistant to drug therapy, and Type C cells are tumors that are completely restored to the normal cell type by drug therapy.

Perou et al. (2000) applied the hierarchical clustering method to the three human breast tissues – (1) normal, (2) tumor before (BE) treating with doxorubicin, and (3) tumor after (AF) the drug therapy. The tumor samples were obtained from 65 surgical specimens of human breast tumors. They measured the RNA levels using microarrays representing 8,102 human genes. Twenty tumors were sampled twice before (BE) and after (AF) treating with doxorubicin for ~16 weeks. The Cy5 dye was used to label the cDNA synthesized from the mRNA isolated from experimental samples, and the Cy3 dye was used to label the cDNA synthesis from the mRNA isolated from different cultured cell lines which served as the common reference samples. A total of 84 cDNA microarray experiments were performed, and 1,753 RNAs (which is 22% of 8,102 RNAs) were analyzed, whose levels varied by at least fourfold from their median level in this sample set in at least three of the samples. Out of the 65 tissue samples analyzed, a subset of 496 RNAs (termed "intrinsic gene subset") was selected that showed significantly greater variations in abundances between different tumors than between paired samples from the same tumors.

Perou et al. (2000) found that eight clusters of RNAs, numbering 134 in total, reflected variations in specific cell types in tumors. These RNAs can be viewed as "breast cancer-related" RNAs since their levels varied more between different tumors than within each tumor sample. Since these RNA have been selected out of 1,753 RNAs, the fraction of the RNAs that is related to cancer may be estimated to be $(134/1{,}753) \times 100 = 8\%$.

From the microarray data on 8,102 RNAs isolated from human breast tissues and tumors published by Perou et al. (2000), 54 RNAs specializing in energy metabolism (i.e., glycolysis, Krebs cycle, oxidative phosphorylation, and fatty acid catabolism) were selected and their "gene expression profiles" (i.e., s-ribons) in three different tissue samples, that is, *normal*, and *tumors* before and *after* treating with doxorubicin, were plotted as shown in Fig. 19.2. As evident in the four panels in this figure, all of the 54 s-ribons showed distinct patterns for the three samples with little overlap, except for RNAs 9, 13, 23, 25, 33, 34, and 51 (whose peaks coincide). These constitute about 10% of the total number of RNAs. Therefore, we can conclude that, about 90% of the time, s-ribons participating in energy metabolism serve as unique biomarkers for the different states of the cells constituting the three human breast tissues. This is consistent with the following hypothesis:

> The structural ribons of energy metabolizing RNAs (and most likely other RNAs as well) can be employed as reliable cell-state biomarkers for breast cancer theragnostics. (19.1)

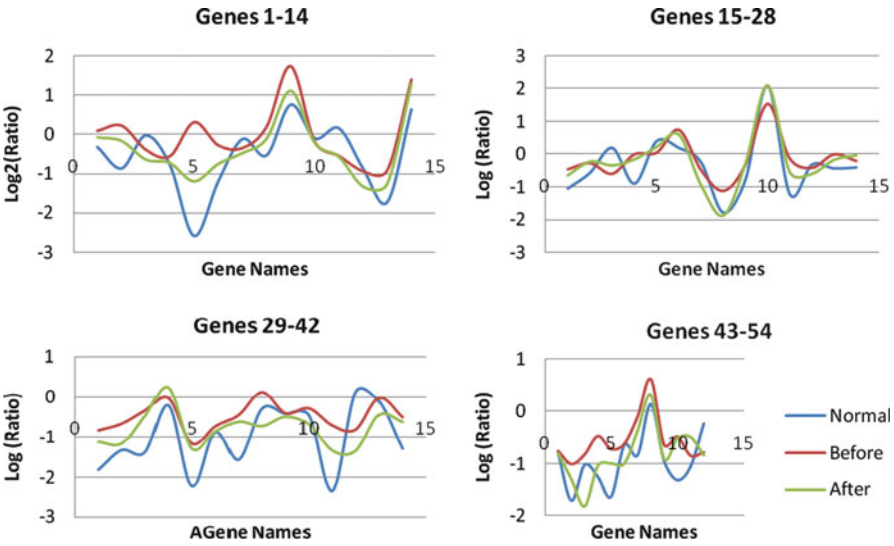


Fig. 19.2 Ribonic spectra of normal human cancer cells, and cancer cells isolated from human breast tissues "before" or "after" treating with doxorubicin for ~16 weeks (n = 54) (Perou et al. 2000) (I thank Drs. J.K. Lee and J.K. Eom for their assistance in producing these graphs)

Table 19.2 The definitions of the cancer-related and drug-responding RNAs

RNA levels			
Cancer-related		Drug-responding	
Positively	Negatively	Positively	Negatively
BE > NO	BE < NO	BE > AF > NO	e.g., AF > BE > NO
		BE < AF < NO	e.g., BE < NO < AF

We may refer to this statement as the "ribons-as-cell-state-biomarkers" (RACSB) hypothesis, which is evidently consistent with the more general *IDS-Cell Function Identity Hypothesis* discussed in Sect. 10.2.

As indicated in Fig. 19.2, the 90% of the 54 energy-metabolizing RNAs exhibited concentration levels that are different for each one of the three human breast tissues – Normal, BE, and AF. Based on the "ribons-as-cell-state-biomarkers" hypothesis, it should be possible to identify those RNA molecules whose levels are affected by tumors before or after drug therapy. We will arbitrarily define the RNA "positively cancer-related" as the RNAs whose levels in tumor before drug therapy (BE) is higher than in normal tissues (NO), i.e., BE > NO (see the first column in Table 19.2). Any RNA molecules whose levels are lower in tumors than in normal tissues are then defined as "negatively cancer-related" (see the second column in Table 19.2). We can recognize two kinds of drug-responding RNAs – (1) positively drug-responding RNAs, if their levels in tumor after (AF) drug therapy are "sandwiched" between their levels in normal (NO) and tumor

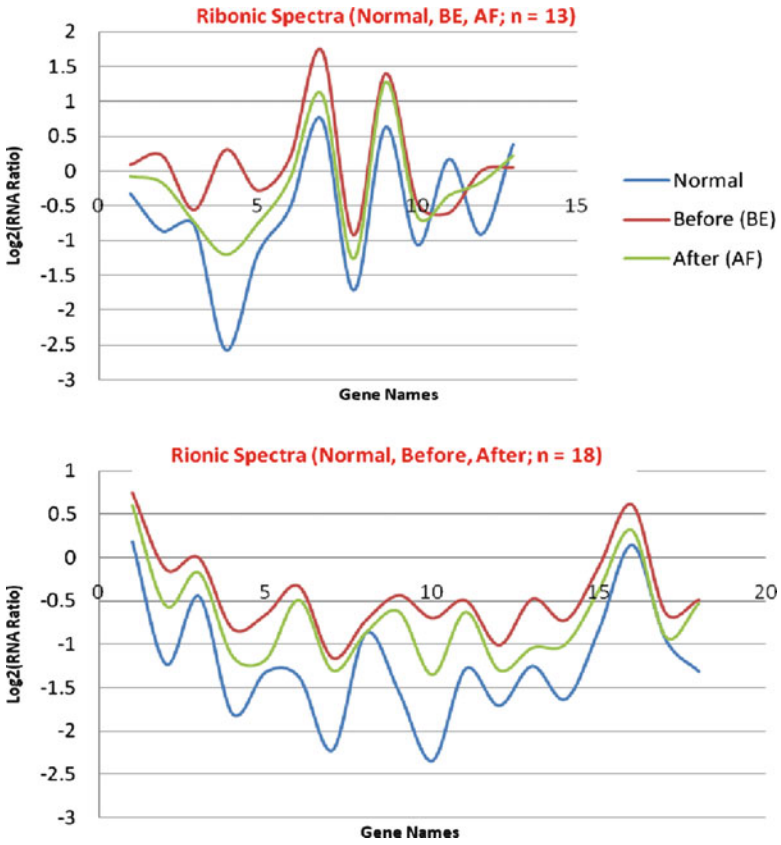


Fig. 19.3 Ribonic spectra of the same sample as in Fig. 19.2. Only those RNAs are selected whose levels meet the quantitative requirement that NO < AF < BE, where NO – normal, AF = tumors after drug treatment, and BE = tumors before drug treatment

tissues before (BE) drug therapy (see the third column in Table 19.2). All other cases, including the two cases shown in the fourth column of Table 19.2, then represent *negatively drug-responding RNAs*.

From the s-ribons shown in Fig. 19.2, it was relatively easy to select, out of the 54 energy-metabolizing RNAs, the 31 "positively drug-responding RNAs" whose s-ribons are shown in Fig. 19.3.

The ribonoscopic analysis of microarray data presented above has been based on raw data without any clustering. But the same principle of *sandwiching* the AF sample between the NO and BE samples (which may be referred to as the Principle of "sandwiching AF between NO and BE," or the "sandwiching AF between NO and BE principle") can be applied to microarray data after clustering with ViDaExpert as schematically illustrated in Fig. 19.4. Panel a shows a typical ribonic spectrum (see Sect. 12.8.3) of a set of 156 functionally related RNA molecules (such as glycolytic, respiratory, or protein synthesis related) of a normal cell type.

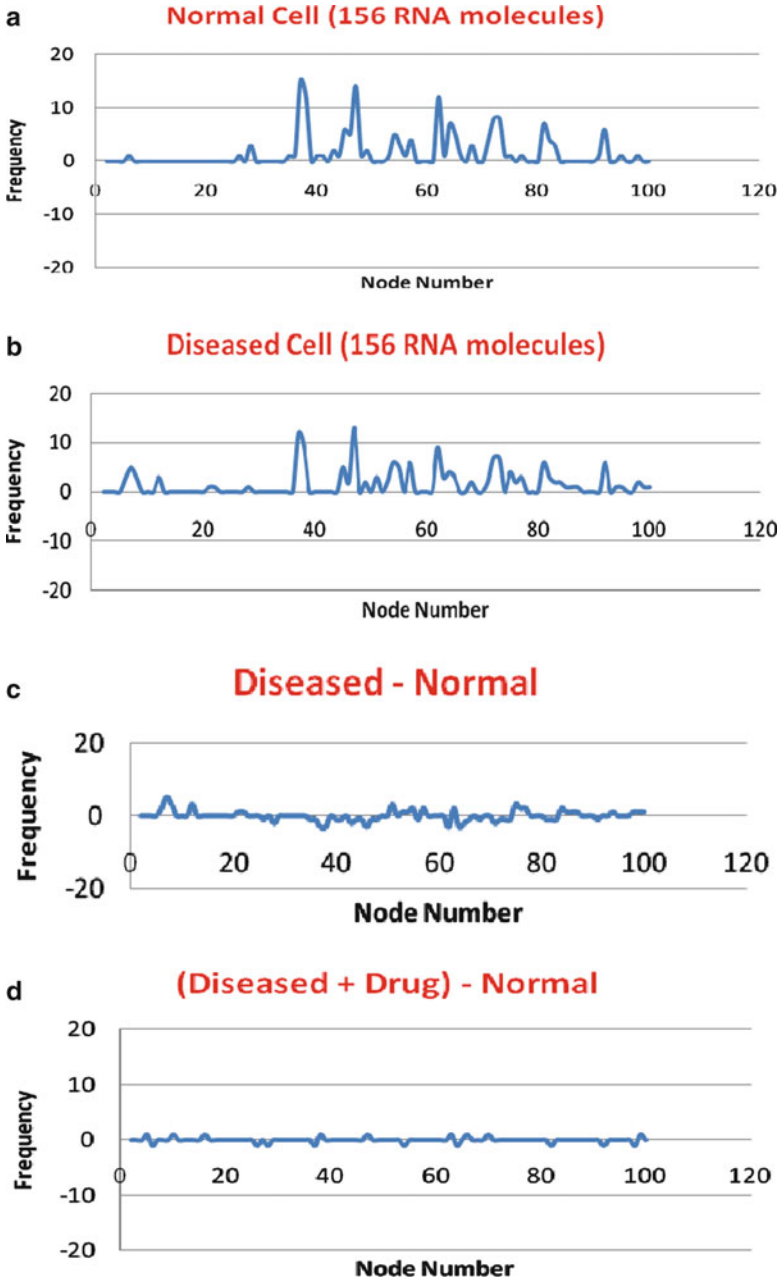


Fig. 19.4 A simulation of the predicted results of the ribonoscopic analysis of microarray data after clustering with ViDaExpert. For the two-dimensional display of ViDaExpert-clustered microarray data, see Sect. 12.8.3

(Please note that the number of RNA molecules being analyzed is thought not to affect the conclusions to be drawn as long as they are greater than about a dozen.) Panel b is a simulated ribonic spectrum of the same set of RNA molecules as Panel a but of the cells in a diseased state measured with the same microarray used in measuring the ribonic spectrum of the normal cell type. When the ribonic spectrum of the normal cell is subtracted from the ribonic spectrum of the diseased cell, a *difference ribonic spectrum* (DRS) is obtained as shown in Panel c. It is predicted that different diseases will exhibit different *difference ribonic spectra*. If proven correct, DRS can be employed as "disease-related biomarkers." The DRS can also be employed to characterize the disease-related cell states. Any drug candidate (pure or composition unknown) that has the ability to "flatten" or "abolish" the difference spectrum (see Panel d) can be selected as the drug candidate for the disease under investigation.

It is important to keep in mind the following features of the ViDaExpert program:

The ribonic space on which the ViDaExpert program acts must contain the microarray data (i.e., ribons in Table 18.1) measured from *all three samples*, that is, the *normal*, and the *diseased before* and *after drug therapy*, since the topology and hence the node number assigned to each ribon in a ribonic spectrum is the function of the number of ribons in the ribonic space. In other words, it is not allowed to apply the ViDaExpert program to the three samples mentioned above individually and then try to obtain the difference ribonic spectrum by subtracting the normal ribonic spectrum from the diseased ribonic spectrum.

Since the frequency distribution of ribons over node numbers sensitively depends on the number of the points (or ribons) in the ribonic space, the stretching coefficient and bending coefficient (Eq. 12.20), at least a part of the "flattening effect" of drug on the difference spectra (i.e., the transition from Panel c to Panel d) can be accidental. Such accidental or random effects can be detected and removed by running the ViDaExpert program on the ribonic space of three samples as many times as is needed to correct for random changes.

The difference spectrum, Panel c, can be used as a *companion diagnostic tool* to identify the patient who can benefit from a drug and who cannot by observing whether the drug "flattens" a patient's difference spectrum. Those patients whose difference ribonic spectra are not flattened by the drug under investigation can be excluded from clinical trials, which will decrease N in the equation shown in Fig. 19.1, thereby increasing the success rate of a drug for FDA approval.

The drugs discovered by the ribonoscopic method described here can be named as "dissipative structure-targeting drugs (DSTDs)" or "dissipaton-targeting drugs (DTDs)," since they are identified through their effects on either ribons (Figs. 19.1, 19.2, 19.3) or difference ribonic spectra (Fig. 19.4) which are all examples of Prigogine's dissipative structures or *dissipatons* (i.e., no ribonic difference spectra can be obtained when the cell system involved dissipates no free energy).

Although it is generally accepted that microarrays, as commonly used, measure RNA levels in cells indirectly by measuring the cDNA synthesized from the RNAs isolated from cells (see Fig. 12.5), there are important differences between the

Table 19.3 A theoretical comparison between the current and the new methods for analyzing microarray data

	Methods and theories underlying microarray data analysis	
Categories of comparison	Currently fashionable	*Ribonoscopic*
1. Objects measured with microarrays	Changes in *RNA levels* in *time (time series),* or across individual *sequences* at a given time (*structure series*)	Changes in *RNA levels* in time *(time series),* or across individual *sequences* at a given time (*structure series*)
2. Changes are interpreted in terms of	Genes	The whole cell under the influence of its environment
3. Assumption: the level of an RNA molecule inside the cell is determined by	Its structural gene	Its structural gene plus dozens of proteins coded by other structural genes and regulatory DNA regions
4. Role of RNA degradation	Not taken into account	Taken into account
5. The "structural gene: RNA ratio"	1:1	1:N, where N = 10–10^4 due to alternative splicing
6. The goal of analysis	To discover sets of genes responsible for phenotypes	To discover the ribons (i.e., the patterns of RNA level changes) responsible for phenotypes
7. The category to which the sought-after object belong	Static, stable structures (equilibrium structures or equilibrons)	Dynamic, transient structures (dissipative structures or dissipatons)

ribonoscopic approach to microarray data analysis being advocated here and the approach widely adopted by contemporary investigators in microarray technology as summarized in Table 19.3. One of the main differences is that, whereas ribonoscopy is centered on RNA levels (as its name indicates) as regulated by the whole cell, the currently widely used approach is centered on DNA or genes, that is, on discovering the genes responsible for the phenotypes under investigation (see Rows 2, 3, and 6 in Table 19.3). The following excerpts from a leading journal article are good examples of what is here referred to as the *gene-centric approach*:

> This study was undertaken to indentify genes that could predict response to doxorubicin-based primary chemotherapy in breast cancer patients . . . (Folgueira et al. 2005, p. 7434)
>
> . . . A set of three gene, *PRSS11, MTSS1, and CLPTM1,* could correctly classify 95% of the samples . . . (Folgueira et al. 2005, p. 7442)

The gene-centric approach to microarray data analysis is untenable for two main reasons:

1. Since the level of an RNA molecule inside the cell is determined by two opposing processes, *transcription* and *transcript degradation* (see Row 4 in Table 19.3 and Steps 4 and 5 in Fig. 12.22 and Steps 2 and 3 in Fig. 12.27), each of which is catalyzed by a set of enzymes numbering up to several dozens, it is erroneous to

attribute the changes in the level of an RNA level as resulting only from the structural gene encoding it.

2. In multicellular organisms, one gene can code for up to 38,016 mRNAs through alternative splicing (Schmucker et al. 2000) (see Row 5 in Table 19.3). Thus, it is highly unlikely that all of the proteins encoded in a given gene contribute to only one phenotype and hence it would be impossible to infer the gene responsible for a phenotype (such as breast tumor) from observing that an RNA molecule is associated with that phenotype.

Finally, the object of discovery by the currently fashionable approach in microarray data analysis, that is, genes, are equilibrium structures (*equilibrons*), whereas the objects sought after by ribonoscopy is ribons, which are dissipative structures (*dissipatons*) (see Row 7 in Table 19.3). As pointed out in Sect. 3.1.5, *equilibrons* and *dissipatons* belong to the two different categories of structures.

As is clear from the above discussions, the ribonoscopic strategy for discovering drug targets being advanced here is based on the idea that *dissipative structures* (or *dissipatons*) (Sect. 3.1) are the ultimate targets of drugs in contrast to the traditional view which regards *equilibrium structures* (equilibrons) as drug targets. The new idea can be expressed in several equivalent ways:

> The ultimate targets of all drugs are the dissipative structures of the living cell or ic-dissipatons. (19.2)

> No therapeutic nor toxic effects can be exerted by any agent without affecting cell functions or ic-dissipatons. (19.3)

> It is impossible for an agent to be therapeutically effective unless it can affect cell functions, i.e., ic-dissipatons. (19.4)

We may refer to any of Statements 19.2–19.4 as the *First Law of Theragnostics*.

According to *Bloomberg Business Week* (as reported in *Personalized Medicine Coalition Members Newsletter*, spring 2010, p. 12), FDA Commissioner Dr. Margaret Hamburg said in February, 2010 that

> . . .diagnostic tests based on biomarkers will make it possible for drug companies to salvage data from unsuccessful clinical trials by resubmitting drugs for approval for smaller subsets of patients. (19.5)

Statement 19.5 by Dr. Hamburg encourages the development of *biomarker-based diagnostic tools* for which ribonoscopy, armed with a comprehensive molecular theory of the living cell, may play an essential role in the coming decades.

The ribonoscopic method of drug target discovery is different from the traditional method at several levels (in addition to the differences listed in Table 19.3). The ribonoscopic method allows discovering both pure compounds and mixtures of compounds as potential drug candidates, since, in principle, both types of substances can "flatten" the difference ribonic spectra (see Panels c and d, Fig. 19.4). In other words,

> Unlike the traditional method of drug discovery which is limited to pure compounds, the ribonoscopic method can identify both pure compounds as well as compounds consisting of two or more known or unknown chemicals as drug candidates. (19.6)

Statement 19.6, therefore, entails classifying drugs into at least two groups – (1) drugs composed of pure chemicals to be called "Type I drugs," and (2) drugs composed of two or more compounds of known or unknown structures to be referred to as "Type II drugs." Using these new terms, Statement 19.6 may be more succinctly expressed as follows:

> Unlike the traditional method of drug discovery which is limited to finding Type I drugs, the ribonoscopic method can identify both Type I and Type II drugs. (19.7)

It should be noted that, according to the *First Law of Theragnostics*, Statements 19.2–19.4,

> Both Type I and Type II drugs produce their therapeutic effects by affecting intracellular dissipative structures or ic-dissipatons. (19.8)

For convenience, Statement 19.8 may be referred to as the *Second Law of Theragnostics*.

The formulation of the *Second Law of Theragnostics* was greatly stimulated by the informative lecture that Carl P. Decicco of Bristol-Myers Squibb delivered at the Chemistry Department at Rutgers in May 2010. I take the liberty of reproducing the email below that I sent to Dr. Decicco about a week after his lecture. This email discusses dividing drugs into two groups referred to as the "first-order" or "linear drugs" and "n^{th}-order" or "nonlinear drugs," which correspond, respectively, to Type I and Type II drugs in Statement 19.8.

Dear Dr. Decicco,

. . .

I am the one who asked the question after your talk about whether or not your group at BMS tried to develop a set of chemicals acting as a unit to prevent blood clotting, rather than focusing exclusively on discovering a single chemical agent such as *Apixaban* as an anticoagulant.

The reason I asked that question is to challenge the efficacy of the traditional one-molecule-based approach to drug discovery which, from the perspective of theoretical cell biology (TCB), seems antiquated. The emerging TCB perspective (described in Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications, Springer, New York, to appear in 2010–2011) suggests that the real biological/pathological processes are often too complex to be affected by any single chemical agent and hence a more realistic approach may be to try to identify a set of (instead of single) chemicals that act as the effective therapeutic unit. For convenience, we may refer to this idea as the "one-to-many paradigm shift in drug discovery" or "1-to-many PSDD" for short. As you pointed out, such approaches have already been proven effective in some combination therapies worked out in BMS and elsewhere. But the traditional combination therapeutic agents, as far as I know, are composed of already FDA-approved drugs.

(continued)

(continued)

But the "1-to-many PSDD" would support the drug-discovery approach wherein any chemical agents, regardless of whether or not approved by FDA, can qualify as the components of a new, "higher-order" drug.

It would be necessary therefore to distinguish two classes of drugs – (1) the traditional, single-agent based drugs to be referred to as the "first-order" or "linear" drugs, and (2) the "nth-order drugs" composed of n chemical components where n can be 2, 3, 4, etc., which may be referred to as the "nonlinear" drugs. I firmly believe that there is no scientific basis for FDA restricting drug-discovery activities to "first-order drugs" and that FDA may have to relax its regulations to accommodate high-order drugs in order to improve the efficiency (and competitiveness) of developing new drugs in the coming decades.

As I indicated after your talk, I think the traditional chemistry-based drug discovery approach may be too *precise* for the complex nature of living processes, just as mathematics are often *too precise* for physics, prompting Einstein to make the following remark:

> As far as the laws of mathematics refer to reality, they are not certain; and as far as they are certain, they do not refer to reality. (1)

Analogously, it may be stated that

> As far as the laws of chemistry refer to pharmacology, they are not certain; and as far as they are certain, they do not refer to pharmacology. (2)

For example, Statement 2 would predict that, although careful molecular designing can decrease the K_i values of a serine protease inhibitor by a factor of 10^4 or 10^5, this would not necessarily translate into a similar increase in the associated therapeutic index for anticoagulant activities.

In fact, Statement 2 suggests that serine protease inhibitors with high K_i values (that would routinely have been discarded as ineffective agents in the early stages of drug discovery process) can serve as better components of high-order drugs for anticoagulant activities than their counterparts with low K_i values.

If Statement 2 proves useful in drug discovery and other pharmacological researches, we may be justified to refer to it as the "Pharmacological Uncertainty Principle (PUP)" in analogy to the Heisenberg Uncertainty Principle (HUP) in physics. It was suggested elsewhere that PUP and HUP may be instances of a more general uncertainty principle operative in the Universe referred to as the Universal Uncertainty Principle (UUP) (Molecular Theory of the Living Cell, cited above, pp. 151–152).

Chapter 20
The Knowledge Uncertainty Principle in Biomedical Sciences

According to the Knowledge Uncertainty Principle described in Sect. 5.2.7, all knowledge is uncertain (including physical, chemical, biological, mathematical, pharmacological, toxicological, medical, and philosophical knowledge), which agrees with the views expressed by many thinkers throughout the ages (Sect. 5.2.5). What is new in this book is the idea of quantitating the degree of uncertainty of a knowledge using what is referred to as *the Kosko entropy* or S_K in Sect. 5.2.7. A knowledge with $S_K = 1$ is least certain and that with $S_K = 0$ is 100% certain, which is thought to be beyond human capacity as indicated by Inequality 5.26. A knowledge has been defined as *the ability to answer a question or solve a problem* (Sect. 5.2.7). These ideas will be illustrated using the Nrf2 signaling pathway in toxicology as an example.

20.1 The Toxicological Uncertainty Principle (TUP)

Many drugs (e.g., acetaminophen or Tylenol®), dietary components (e.g., 6-(methylsulfinyl)-hexyl isothiocyanate or 6-HITC from Japanese horseradish *wasabi*), and environmental chemicals and radiations (e.g., ozone, UV light) can generate reactive oxygen and nitrogen species inside the cell. When cells are exposed to such pro-oxidants, they respond to counteract the effects of the resulting oxidative stress by activating *self-defense mechanisms*, including the Nrf2 signaling pathway shown n Fig. 20.1. The mechanism of the Nrf2-mediated self-defense has been well worked out in recent years (Surh 2003; Nguyen et al. 2009; Kundu and Suhr 2010).

The Nrf2 (nuclear factor erythroid-2-related factor-2) (see nodes 8 and 10 in Fig. 20.1) is a transcription factor that plays a major role in regulating the expression of the genes encoding many cytoprotective enzymes (see nodes 20–24) in response to oxidative stress. It is normally bound to the Kelch-like-ECH-associated protein 1 (Keap1) (see nodes 7 and 9) which confines Nrf2 to the cytosol and prevents it from being translocated to the nucleus. Keap1 contains many cysteine residues (see SH on

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_20,

node 9) that can be oxidized or covalently modified (see SR on node 7) in other ways by pro-oxidants, resulting in the dissociation of Nrf2 from its grip (see the separation of the 9–10 complex into nodes 7 and 8). The dissociation of Nrf2 and Keap1 is also facilitated by the phosphorylation of Nrf2 at serine (S) and threonine (T) residues by phosphotidylinositol-3-kinase (PI_3K) (node 1), by protein kinase C (PKC) (node 2), c-Jun NH2-terminal kinase (JNK) (node 3) and extracellular-signal-regulated kinase (ERK) (see node 2). Once translocated into the nucleus, Nrf2 heterodimerizes with MAF and binds to *antioxidant response element* (ARE) (see nodes 15, 16, and 19), thereby activating the transcription of genes encoding many Phase II enzymes (see nodes 20–24) that detoxify foreign chemicals or xenobiotics and reactive oxygen species (ROS) and reactive nitrogen species (RNS). In short, chemical stress activates the Nrf2 signaling pathway to induce enzymes that can remove the stressful compounds, which may be regarded as an analog of *the Le Chatelier Principle* on the intracellular metabolic level. As is well known in chemistry, the Le Chatelier Principle states that, if a system in chemical equilibrium is disturbed, it tends to change in such a way as to counter this disturbance. In another sense, the Nrf2 signaling pathway may be viewed as an intracellular version of *self-defense mechanisms* that have been postulated to operate in the human body as a whole and local tissue levels (Ji 1991, pp. 186–199). Frustrating any of the many processes constituting self-defense mechanisms has been postulated to underlie all diseases, including cancer. According to this so-called "frustrated self-defense mechanisms (FSDM)" hypothesis of chemical carcinogenesis (Ji 1991, pp. 195–199), many cancers may originate by frustrating some of the biochemical and cellular processes underlying inflammation (including the cellular proliferation step in wound healing). The FSDM hypothesis appears to have been amply supported by recent findings (e.g., see Fig. 1 in Kundu and Suhr 2010).

The Nrf2 interaction network shown in Fig. 20.1 can be represented as an interaction matrix (Table 20.1). Although there are some ambiguities in assigning node numbers (e.g., nodes 7 and 9 or nodes 8 and 10 may be combined into one entity each), the matrix representation is sufficiently accurate in capturing the key information embodied in the Nrf2 signaling network. The interaction matrix combined with the diagram of the original signaling network allows us to identify all the theoretically possible pathways that may be realized in the Nrf2 signaling network in the cell under a given condition.

For example, any agent (e.g., diacylglycerol or intracellular Ca^{2+}) that activates PKC (node 2) can lead to the production of any one of the Phase II enzymes (nodes 20–24) passing through nodes 8, 15, and 19, or may get stuck in the middle of any one of these pathways, thus generating a set of eight possible pathways that can be engaged by the activation of node 2:

2-8-15-19-20, 2-8-15-19, 2-8-15, 2-8
2-8-15-19-21
2-8-15-19-22
2-8-15-19-23
2-8-15-19-24

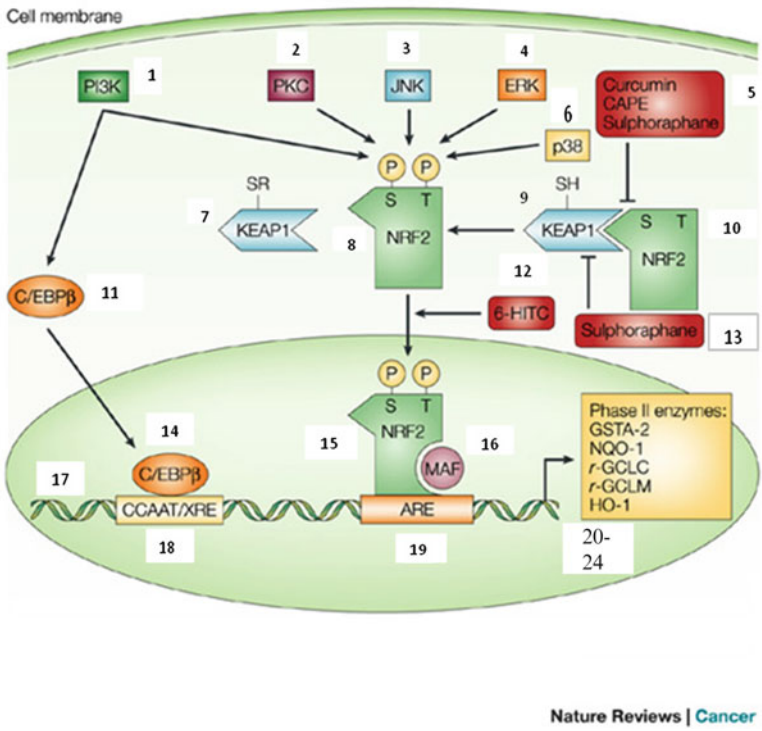


Fig. 20.1 The Nrf2 signal transduction pathway as schematically represented by Surh (2003). The numbers are my additions (The figure was reproduced from http://www.nature.com/nrc/journal/v3/n10/fig_tab/nrc1189_F4.html)

Similar sets of signal transduction pathways can be engaged by the activation of nodes 1, 3, 4, 5, and possibly others, leading to the final set of Nrf2 signal transduction pathways numbering at least 40. For each one of these 40 possible pathways, one can raise a binary question. For example, "Is pathway 3 activated under the given experimental condition?" The answer to this question can be expressed in the unit of fits, that is, any number between 0 (no) and 1 (yes), including decimals such as 0.3 (i.e., the degree of the yes answer being correct is 30%), or 0.9 (i.e., the degree of the yes answer being correct is 90%), etc., depending on the certainty of the relevant experimental data. Or these numbers may be viewed as the *probabilities* of the occurrence of the pathway being considered under the experimental condition. Table 20.2 lists all the possible answers to the binary questions elicited by experiments (i.e., the "apparatus-elicited answers" discussed in (6) of 13) in Sect. 5.2.7. These "apparatus-elicited answers" can also be viewed as the possible "mechanisms" of the actions of the agents that interact with the Nrf2 signaling pathway. For example, under experimental condition 1 (see the row labeled 1 in Table 20.2), the probabilities of the occurrence

Table 20.1 The *interaction matrix* of the Nrf2 signaling pathway constructed from Fig. 20.1 (or Fig. 4 of Surh 2003). The interaction between the ith and jth nodes is positive (+1, i.e., enhanced), negative (−1, i.e., inhibited), or nonexistent (0, i.e., has no effect). Out of the $24 \times 24 = 576$ possible interactions, only 25 directed interactions have been found experimentally, thus the Nrf2 signaling pathway carries $\log_2(576/25) = 4.5$ bits of Shannon/Hartely information (see Sect. 4.3 for the definition of the Shannon and Hartley informations). Please note that some of the assignments of +1, −1 or 0 (especially involving nodes 7, 8, 9, and 10) are ambiguous and admit other possibilities

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1	0	0	0	0	0	0	0	+1	0	0	+1	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	+1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	+1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	+1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	−1	−1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	+1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+1	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	+1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	+1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0	0	+1	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+1	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	–	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+1	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+1	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+1	0	0	0	+1	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0	0	+1	0	0	0	+1	+1	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0	0	+1	0	0	+1	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+1	0	+1	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

of the Nrf2 pathways 1, 2, 3,4, 5, 6, …, 39, and 40 are, respectively, 0.3, 0, 0.4, 0, 0.1 0.2, …, 0, 0, and 0. The corresponding probabilities under experimental condition 2 are 1, 0, 0, 0, 0, 0, …, 0, and 0, meaning that only pathway 1 is activated under this condition.

Once the *question-and-answer matrix* is determined, all the apparatus-elicited answers can be mapped onto the 2^{40}-dimensional hypercube discussed in Sect. 5.2.7. The uncertainty of each answer measured in term of the so-called *Kosko entropy* can be estimated using the coordinate values of each answer and Eq. 5.23. These entropies were calculated for the rows labeled 1, 2, and 3 in Table 20.2. As can be seen, Apparatus-elicited answer 1 is least certain, while apparatus-elicited answers 2 and 2^{40} are both much more certain than Answers 1 and 3.

The above method of calculating the Kosko entropy associated with any toxicological statement or knowledge can be summarized as shown in Table 20.3.

Table 20.2 The question-and-answer matrix for the Nrf2 signaling pathway, each cell being filled with the fit (i.e., fuzzy bit) or the probability values (ranging from 0 to 1) derived from the experimental data on the Nrf2 signaling pathway depicted in Fig. 20.1. Each question requires an answer consisting of 40 fits ranging from 0 (= No) to 1 (= Yes), inclusive. The elements of the matrix not explicitly shown and symbolized as dots can be assumed to be zero

	Possible binary questions										
Apparatus-elicited answers	1	2	3	4	5	6	.	.	.	39	40	Kosko entropy, S_K
1	0.3	0	0.4	0	0.1	0.2	.	.	.	0	0	0.872
2	0.9	0	0	0	0	0.1	.	.	.	0	0	0.00262
3	0.4	0	0.1	0.2	0	0.2	.	.	.	0	0.1	0.816
.												
.												
.												
$2^{40} = 1.10 \times 10^{12}$	0	0	0	0	0.9	0				0.1	0	0.00262

Table 20.3 The five-step procedure for calculating the Kosko entropy as a measure of the *uncertainty* associated with a toxicological knowledge, statement, or mechanism

Step	Procedure
1	*Summarize the preexisting knowledge of interest in the form of a pathway such as the Nrf2 signaling pathway (Fig. 20.1)*
2	*Construct the interaction matrix (e.g., Table 20.1) based on that pathway*
3	*Construct the question-and-answer matrix (e.g., Table 20.2)*
4	*Fill in the appropriate boxes in the question-and-answer matrix based on the experimental observations (also called the apparatus-elicited answers) available*
5	*Calculate the Kosko entropies for all apparatus-elicited answers (also called mechanisms) based on the numerical coordinates given in the question-and-answer matrix, using the Pythagorean equation, Eq. 5.23*

This five-step procedure for calculating the *Kosko entropy* associated with any toxicological statement represents or defines the content of the *Toxicological Uncertainty Principle*. As such, the same procedure can be applied to any toxicological statement, including those concerning the mechanisms underlying the liver toxicity of acetaminophen (also called paracetamol or Tylenol®), for example.

Over the past four decades, we have accumulated a massive amount of information about how *Tylenol®* in excessive doses can injure the liver (Ryder and Beckingham 2001; Larson et al. 2005) and how chronic and acute alcohol ingestions may aggravate or protect against, respectively, the drug toxicity (McClain et al. 1980; Prescott 2000). Acetaminophen is the most widely used over-the-counter analgesic and found in nearly 200 medications such as *Excedrin*, *Midol*, *NyQuil*, and *Sudafed*. Despite the long history of research, both basic and clinical, on the mechanisms responsible for acetaminophen hepatotoxicity, our knowledge about these mechanisms is still uncertain and may remain so even if much more detailed investigations are to be carried out in the future in this field. Parallel to further research along the traditional line, it may be helpful for the further progress in acetaminophen toxicology to introduce the Toxicological Uncertainty Principle as embodied in the Kosko entropy (see Table 20.2). That is, it may be necessary to

calculate the Kosko entropies for all the *competing statements* about how acetaminophen injures the liver in order to evaluate the degree of certainty of their claims. To accomplish this task, it is necessary to summarize relevant existing knowledge in the form of various mechanistic schemes or pathways, two of which are discussed below.

In the early 1980s when I first entered the field of toxicology, one of the most intensely studied toxicant was acetaminopen. Although, when taken in pharmacological doses, acetaminophen is safe, it can injure the liver when taken in toxicological (or suicidal) doses (Black 1984). Many toxicologists believed in the hypothesis that the mechanism of the toxic action of this drug involved following key steps:

1. The metabolic activation of acetaminophen into its reactive intermediate catalyzed by cytochromes P-450 and other pro-oxidant enzymes (Kocsis et al. 1986), later found to be N-acetyl-p-benzoquinone imine (NAPQI) (Dahlin et al. 1984),
2. The depletion of the intracellular antioxidant, glutathione, GSH, and
3. The covalent-binding of NAPQI to essential nucleophiles including proteins and DNA when the GSH store is depleted below a critical level (James et al. 2003).

Because of the highly reactive nature of NAPQI, it can bind nondiscriminately to all electron-rich atoms, making it difficult to pinpoint the critical macromolecule leading to cell injury. The experimental data available in the late 1980s indicated to me that the molecular mechanisms underlying acetaminophen hepatotoxicity may not be as simple (i.e., certain) as then widely believed, prompting me to propose what I called the "multiple metabolite-multiple target" (MMMT) hypothesis of chemical toxicity reproduced below:

***The Toxicologist* 9(1):161 (1989)**

"MULTIPLE METABOLITE-MULTIPLE TARGET" HYPOTHESIS AS APPLIED TO BENZENE AND ACETAMINOPHEN TOXICITY.
S. Ji, Dept. of Pharmacol. and Toxicology, Rutgers University, Piscataway, N.J.

Existing experimental data on benzene (BZ) and acetaminophen (AA) toxicity support the general concept that the toxicological consequences of these compounds are derived not from one but many reactive or stable molecular species related to them and that these toxic species interact with not one but multiple molecular targets ("toxicological receptors"). In addition, the kinetics of the interactions between toxic metabolites and their respective targets is critical in the expression of the toxic potential of these xenobiotics. There are at least six possible toxic benzene metabolites (phenol, hydroquinone, p-benzoquinone, catechol, trihydroxybenzene and muconaldehyde), two target cell groups in bone marrow (stroma and stem cell), and two kinds of kinetics (one fast enough to effectuate toxic manifestations and the other too slow to do so), so that there are at least $6 \times 2 \times 2 = 24$ possible mechanisms for

(continued)

(continued)

benzene toxicity. Similarly, there are at least two toxic species for AA (AA itself, N-acetyl-p-benzoquinoneimine), three target sites (hepatocellular membrane, mitochondria, Kupffer cells), and two types of kinetics (effective and ineffective), thus giving rise to $2 \times 3 \times 2 = 12$ possible mechanisms of AA toxicity. Such multiple mechanistic possibilities for AA and BZ toxicity are not surprising in view of the complex living systems with which they interact

A mechanism of chemical toxicity published in (Ji 1989) that is consistent with the *Toxicological Uncertainty Principle* described in this section

My students and I demonstrated in the isolated perfused rat live system that acetaminophen and its metabolite, NAPQI, can inhibit mitochondrial respiration both reversibly and irreversibly (Cheng and Ji 1984; Esterline et al. 1989), potentially weakening various intracellular self-defense mechanisms driven by ATP (Ji 1987) (see Steps 8, 9, and 10 in Fig. 20.2).

Using the same experimental system as in Fig. 20.2 and isolated granulocytes and hepatocytes from the rat, we also demonstrated that the irreversible inhibition of mitochondrial respiration was

1. Not blocked by 500 μM metyrapone, indicating that NAPI was not generated from cytochrome P-450.
2. Accompanied by lactate dehydrogenase release.
3. Blocked by 10 mM mannitol, a hydroxyl radical scavenger.
4. Required Ca^{++} in the perfusate.
5. Abolished in the liver isolated from hypophysectomized rats.
6. Abolished in the liver isolated from thyroidectomized rats, and
7. Enhanced in the liver isolated from adrenalectomized rats.
   In addition we found that
8. Isolated granulocytes (also called neutrophils) caused the covalent binding of tritiated acetaminophen (^{3}H-AA) to granulocyte proteins when stimulated with phorbol myristate acetate.
9. Synthesized NAPQI irreversibly inhibited the respiration of isolated rat liver mitochondria, and
10. The acute administration of alcohol to rat increased the liver content of granulocytes by threefold.

To account for these varied experimental observations, we were led to propose the 14-step mechanism for the alcohol-potentiated acetaminophen hepatotoxicity shown in Fig. 20.3. In a separate series of experiments performed in collaboration with D. Laskin and her group at Rutgers, we discovered that acetaminophen hepatotoxicity is in part mediated by macrophages (Laskin et al. 1986), which could be readily accommodated by including liver macrophages (also called

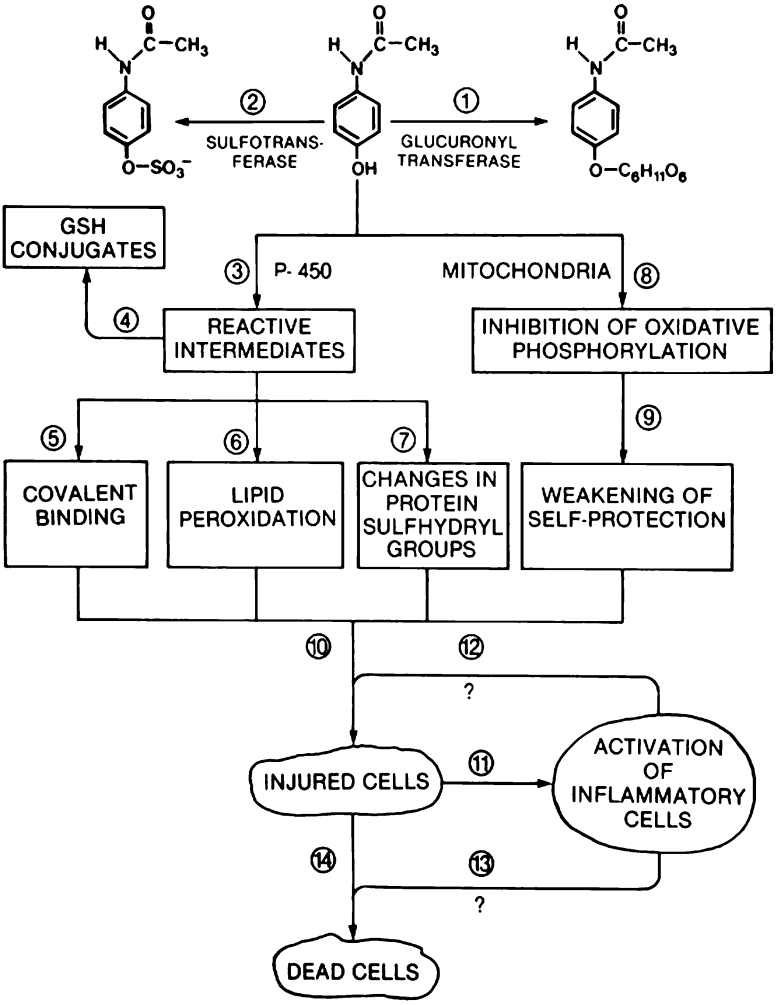


Fig. 20.2 A 14-step mechanism of acetaminophen hepatotoxicity proposed in Ji (1987)

Kupffer cells) in the same node where neutrophils appear in Fig. 20.3. To accommodate the most recent finding that reactive nitrogen species (RNS) are also implicated in acetaminophen-induced mitochondrial damage (Burke et al. 2010), it is only necessary to include RNS in the same node where reactive oxygen species (ROS), that is, superoxide anion, hydrogen peroxide, and hydroxyl radicals, are located in Fig. 20.3.

There is a considerable amount of overlap between the two mechanistic schemes or pathways shown in Figs. 20.2 and 20.3. Therefore, it should be possible to combine these two pathways into a new one with less than the sum of the steps involved in the two separate pathways, that is, less than 28 steps. This new pathway can then serve as the starting point (i.e., Step 1 in Table 20.3) for applying the Toxicological

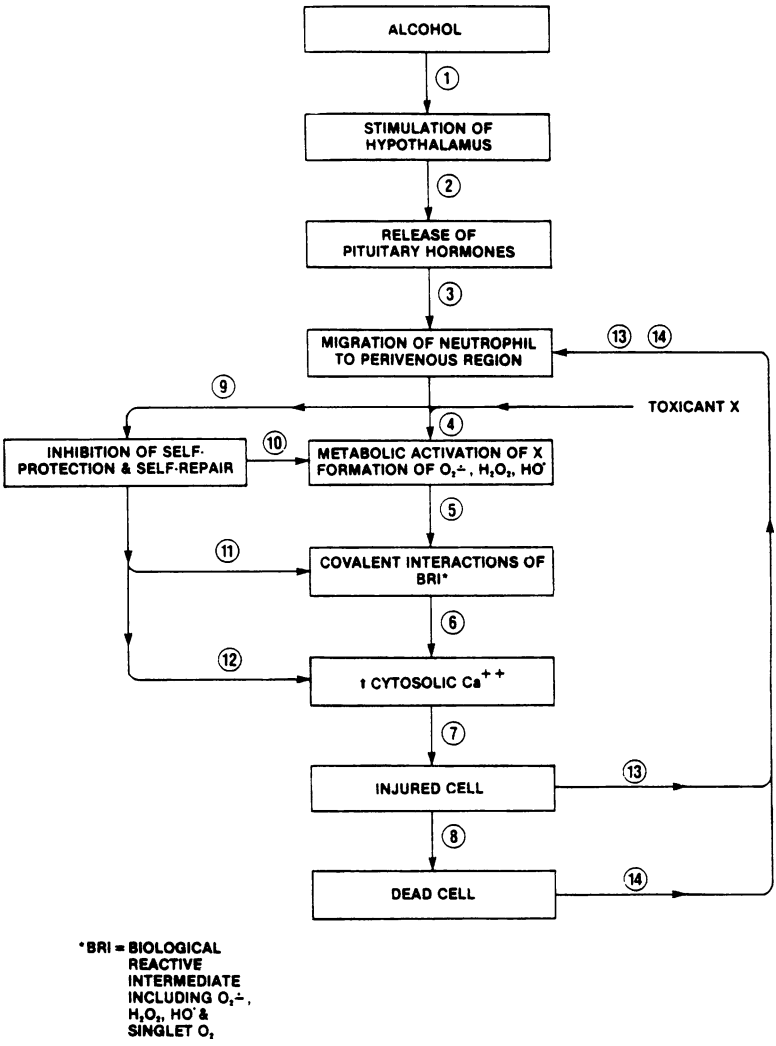


Fig. 20.3 A 14-step mechanism of the alcohol-potentiated acetaminophen hepatotoxicity. This figure was constructed around 1987 on the basis of the experimental observations reported in Ji et al. (1988)

Uncertainty Principle to estimate the uncertainties (i.e., Kosko entropies) associated with all of the mechanistic statements published so far about the acetaminophen hepatotoxicity in humans based on animal experimental data and epidemiology.

Finally, in a qualitative sense, the *Toxicological Uncertainty Principle* may be formulated by extending *Einstein's Uncertainty Thesis* (see Statement 5.38 in Sect. 5.2.7) from physics to toxicology, leading to the following statement:

> As far as the laws of chemistry and molecular biology refer to chemical toxicity, they are not certain; and as far as they are certain, they do not refer to chemical toxicity. (20.1)

20.2 The Pharmacological Uncertainty Principle (PUP)

According to the Knowledge Uncertainty Principle (Sect. 5.2.7), all our knowledge about how drugs work in the human body are uncertain, which may be referred to as the Pharmacological Uncertainty Principle (PUP). PUP has two aspects – quantitative and qualitative. The quantitative aspect of PUP can be expressed in terms of the Kosko entropy, S_K, which can be estimated using the five-step procedures presented in Table 20.3 in the previous section. One way to formulate the qualitative aspect of PUP using Einstein's Uncertainty Thesis (Sect. 5.2.7) would be as follows:

> As far as the laws of molecular mechanisms refer to drug actions, they are not certain; and as far as they are certain, they do not refer to drug actions. (20.2)

20.3 The Medical Uncertainty Principle (MUP)

Although not discussed explicitly among medical professionals, the fact that all our knowledge about human diseases, despite decades of intense research, are fraught with uncertainties is probably widely recognized. Similar to the Toxicological and Pharmacological Uncertainty Principles described in Sects. 20.1 and 20.2, the Medical Uncertainty Principle (MUP) can be formulated, both quantitatively following the five-step procedures for estimating the associated Kosko entropies and qualitatively using Einsteins' Uncertainty Thesis as a template. One possible formulation of the qualitative aspect of MUP is given below:

> As far as the laws of molecular biology refer to diseases, they are not certain; and as far they are certain, they do not refer to diseases. (20.3)

If TUP, PUP, and MUP turn out to be true, they are predicted to have important practical consequences in the fields of risk assessment, drug development, and medicine, particularly in the emerging field of personalized medicine.

Table 20.4 The Universal Uncertainty Principle (as a type) and its various manifestations (as tokens)

Fields	X	Y
1. Einstein's Uncertainty Thesis (Statement 5.38)	Laws of mathematics	Reality
2. Knowledge Uncertainty Principle (Statements 5.33–5.37)	Laws of crisp logic	Reality
3. Cellular Uncertainty Principle (Statement 5.51)	Laws of energy	Reality
	Laws of information	Reality
4. Toxicological Uncertainty Principle (Statement 20.1)	Laws of chemistry	Toxicology
5. Pharmacological Uncertainty Principle (Statement 20.2)	Laws of molecular biology	Pharmacology
6. Medical Uncertainty Principle (Statement 20.3)	Laws of molecular biology	Medicine

20.4 The U-Category: The Universal Uncertainty Principle as a Category

It is clear that the Einstein's Uncertainty Thesis (EUT) introduced in Sect. 5.2.7 (see Statement 5.38) can serve as a convenient and veridical "logical template" (or a category) to express the action of the Universal Uncertainty Principle (UUP) (Sect. 5.2.8) in many fields of inquiries. I therefore suggest here that the combination of EUT and UUP can logically lead to the following general statement which may be viewed as a category in the sense defined in Statements 15.51 and 15.52 and hence referred to as the *Uncertainty Category* (U-category or UC):

> As far as X refers to Y, X is not certain; and as far as X is certain, X does not refer to Y. (20.4)

The examples of X and Y that have appeared in this book are listed in Table 20.4.

Chapter 21
Towards a Category Theory of Everything (cTOE)

The purpose of this last chapter is i) to compare the molecular theory of life presented in this book with some of the theories of life proposed by others and ii) to propose an incipient theory of everything that attempts to integrate, based on category theory, the biological theory described here with the major ideas and theories formulated by numerous investigators in other fields, including physics, *informatics* and *philosophy*.

In 1943, Schrödinger (1998) attempted to answer the question "What Is Life?" in his historic book with the same title which contained about 90 pages. Six decades later, in this book, I needed more than 700 pages to try to answer the same question. The eightfold increase in the number of pages in this book relative to that of Schrödinger probably does not do justice to the enormous increase in our experimental knowledge about living systems that has occurred since 1943 (e.g., see Table 11.1). In his book, Schrödinger proposed three main ideas:

1. The gene is a molecule that encodes heritable traits and contains "the means of putting it into operation" (Schrödinger 1943, p. 68).
2. The gene is "the aperiodic solid" (Schrödinger 1943, p. 60).
3. "The living organism feeds on *negative entropy*." (Schrödinger 1943, p. 70)

It is not the purpose here to analyze in detail these well-known claims of Schrödinger, except to point out that the first of these ideas has largely been validated by experimental findings since Schrödinger's time, the second idea has been invalidated since genes (whether viewed as DNA segments as in the contemporary sense or chromosomes as Schrödinger thought) are not solids that *resist thermal fluctuations* but rather *deformable bodies* that actively utilize *thermal fluctuations* for their biological functions (see Sect. 12.12), and the last idea must also be judged as invalid, since it violates the Third Law of Thermodynamics (see Sect. 2.1.5).

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8_21,

Table 21.1 A comparison among different theories of life

	Self-reproducing system	Molecular machine	Genetic information	Chemical reaction	Generalized Franck–Condon principle
1. Schrödinger (1943)	+	−	+	−	−
2. Prigogine (1977)	+	−	−	+	−
3. Blumenfeld and Tikhonov (1994)	+	+	+	+	−
4. Alberts (1998)	+	+	−	−	−
5. This book (2011)	+	+	+	+	+

The meaning of the symbols: + = "is included at least implicitly," − = "is not included explicitly or implicitly"

If I had to summarize my own answer to the question "What Is Life?" in one sentence, I would suggest that the following is one possibility:

> Life is the property of self-reproducing systems composed of molecular machines driven by chemical reactions under the control of genetic information. (21.1)

There are five key concepts in Statement 21.1, i.e., (i) *self-reproduction*, (ii) *molecular machines* (Alberts 1998), (iii) *chemical reactions* (Prigogine 1977, 1980, 1991), (iv) *genetic information*, and (v) one fundamental principle, the *generalized Franck–Condon principle*, which enables molecular machines to utilize the free energy supplied by chemical reactions (see Sect. 2.2). Not all of these five items appear in any of the contemporary theories of life listed in Table 21.1, to the best of my knowledge.

The theory of life presented in this book contains all of the five items in Table 21.1 and the theory proposed by Blumenfeld and Tikhonov (1994) contains four of the five items. One difference between the theory of Blumenfeld and Tokhonov and that proposed in this book is the generalized Franck-Condon principle (GFCP) with the discussion of which this book began (see Sect. 2.2). Please recall that it is this principle that enables proteins to transduce chemical energy into mechanical energy of enzymes, called *conformons* (Chap. 8) which then drive all the functions of molecular machines including DNAs and RNAs (see Sects. 11.3, 11.4, 11.5).

In the following excerpt, Blumenfeld and Tikhonov (1994) point out that, to explain the functioning of molecular machines (Alberts 1998), it is necessary to apply principles other than those of classical statistical physics, although the authors did not indicate the nature of such new principles.

> . . .It has become fashionable today to speak of the machine-like behavior of enzymes, intracellular particles (e.g., ribosomes), etc., during their functioning. The phrases "a protein is a machine", "an enzyme is a machine" are now trivial clichés, and at the same time remain vague. The main reason for this is the very approach used by the majority of scientists in the treatment of the chemical properties of biopolymers. In spite of speculation regarding the "machineness" of proteins, they apply, as a rule, to the conventional approaches of chemical thermodynamics and chemical kinetics that have been developed for the reactions of low-molecular (weight; my addition) compounds in gaseous phases and dilute solutions.

> These approaches are based essentially on the classical statistical physics of ergodic systems, i.e., on the assumption that the systems under consideration have only statistical, thermal degrees of freedom fast enough to exchange energy for each other. However, if biological constructions (beginning at the level of macromolecules) are machines, in the course of their functioning there might be excited specific, mechanical degrees of freedom which exchange slowly with the thermal ones. This requires an essentially different approach to their description (different from the classical statistical physics; my addition).

With due humility, I suggest that the approach described in this book, i.e., the *conformon* approach based on *GFCP* (Sects. 2.2, 8), provides one plausible mechanisms by which molecular machines actually work, *the ultimate cause of life*.

Having provided a comprehensive molecular theory of cell biology in this book, it appears natural to ask the question: How does the proposed biological theory relate to the fields of human knowledge beyond biology? For example, how does the new biological theory relate to what Popper (1978) refers to as *world 1* (the physical world, both living and nonliving), *world 2* (the mental world), and *world 3* (the world of the products of the human mind, including mathematics, philosophy, art, literature, and engineering)? Or how is the proposed new theory of biology related to what Rosen (1991) calls the *natural* (N) and *formal* (F) systems? Finally, how does the new theory of biology relate to the *mind-body problem* or the problem of *consciousness* recently reviewed by Pinker (2003, 2011)? Possible answers to these questions appear to emerge when it is attempted to correlate and integrate the following four hybrid words, *mattergy*, *gnergy*, *liformation*, and *infoknowledge using category theory*. The first three of these terms have already appeared in this book (see Table 2.6 and Sects. 2.3.1 through 2.3.5) and the last one was coined just recently (Ji 2011) based on the suggestion by Burgin (2004, 2011a, 2012) that the relation between *information* and *knowledge* is akin to the relation between *energy* and *matter*. For convenience, we may refer to this suggestion as the *Burgin's analogy*.

The principles of *complementarity* and *supplementarity* described in Sect. 2.3.1 will play key roles in integrating the four hybrid terms and their associated theories and philosophies. Supplementarity is an additive principle, i.e., A + B = C, and complementarity is nonadditive, i.e., A^B = C, where the symbol ^ indicates that A and B are complementary aspects of a third entity C. These principles led to the coining of the terms *gnergy* and *liformation*, respectively (see Table 2.6, Sect. 3.2.2). My initial attempt to integrate the four hybrid terms started with the diagram shown in Fig. 21.1.

Burgin's suggestion that the relation between *information* and *knowledge* is akin to that between *energy* and *matter* is depicted at the center of Fig. 21.1 (see Arrows 1 and 4 in this figure and Table 21.2). Since *energy* and *matter* are related to each other through $E = mc^2$, which can be viewed as a *supplementary relation*, and since the combination of *energy* and *matter* is conserved according to the First Law of thermodynamics, it is natural to combine these two terms into one word, *matter-energy* or *mattergy*, more briefly. Analogously, it may be convenient to coin a new word to represent the combination of *information* and *knowledge*, namely, *information-knowledge* or *infoknowledge*, more briefly (see Arrows 4/5 relative to Arrows 1/8 in Fig. 21.1 and Table 21.2).

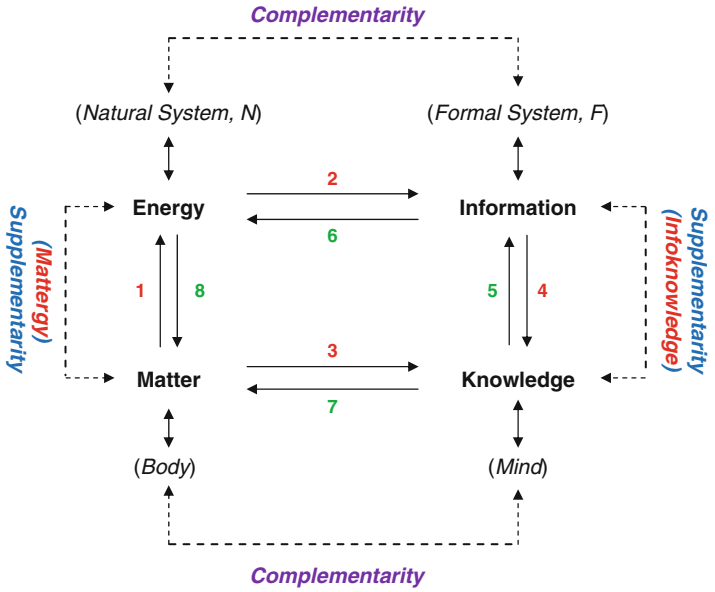


Fig. 21.1 The suggested qualitative (or *complementary*) and quantitative (or *supplementary)* relations among *energy*, *matter*, *information*, and *knowledge*. The meanings of the numbered arrows are explained in Table 21.2. *Mattergy* – the combination of matter and energy that is conserved in the Universe, according to the First Law of thermodynamics. *Infoknowledge* – a new term coined by combining *information* and *knowledge* in analogy to mattergy. Unlike mattergy which is conserved, *infoknowledge* may increase with time

Table 21.2 The integration of the ideas of Rosen (1991), Burgin (2004), Polanyi (1958/62), and Stenmark (2001) within the framework of the postulated "mattergy-infoknowledge complementarity" depicted in Fig. 21.1. The various symbols appearing in this table are E = energy; m = mass; c = speed of light; H = Shannon entropy; $p(x)$ = the probability of the occurrence of event x; S = thermodynamic entropy; k = Boltzmann constant; W = the variety of molecular configurations compatible with thermodynamic constraints; C = channel capacity of a communication system; B = bandwidth of the communication channel; P = power of the message source; N = noise of the communication channel

Authors	Arrows and nodes in Fig. 21.1	Meaning or referent
M. Burgin (2004, 2011a)	1	"Contains"
	4	"Contains"
	2, 6	"Similar"
	3, 7	"Similar"
	1, 2, 3 and 4	The "fundamental unit of knowledge," with the following identification of the *nodes* in Scheme 3 in Burgin (2004, 2011a) and those in Fig. 21.1
	Matter	"U" or objects of knowledge
	Energy	"W" or intrinsic properties of objects

(continued)

Table 21.2 (continued)

Authors	Arrows and nodes in Fig. 21.1	Meaning or referent
	Knowledge	"C" or names of objects
	Information	"L" or ascribed properties of objects
M. Polanyi (1958/62)	Information	"Explicit knowledge"
	Knowledge	"Tacit knowledge"
Stenmark (2009)	4, 5	"Information" = Information; "knowledge" = Knowledge
R. Rosen (1991)	1, 8	"Causality" governing the processes occurring in the natural system, N
	4, 5	"Inference," or "implication" governing the processes occurring in the formal system, F
	3	"Encoding" of N in F
	2, 7	"Decoding" of F to infer N
S. Ji (2011)	1	$E = mc^2$, and $S = k \ln W$, chemical reactions, quantum mechanics. It is assumed that *Energy* in Fig. 21.1 includes free energy which is a function of both matter-energy obeying the First Law and entropy obeying the Second Law of thermodynamics
	2	Big Bang cosmology and biological evolution or measurements by *Homo sapiens*
	3	Biological evolution, phylogenesis, ontogenesis (speculative)
	4	$H(X) = -\sum p(x) \log p(x)$, where X is a set of messages or events, x is its members, and p(x) is the probability of the occurrence of event x (Shannon and Weaver 1949). Communication, languages. It is interesting to note that the Boltzmann equation, $S = k \ln W$, is postulated to be associated with Arrow 1, whereas Shannon equation is postulated to be associated with Arrow 4. In other words, S and H are thought to be complementary to each other
	5	Cognitive sciences
	6	$C = B \log (1 + P/N)$ indicates that energy dissipation is absolutely necessary for any information transmission, i.e., for any communication (Shannon and Weaver 1949). "Without energy, no communication"
	7	Epistemology, learning, inquiry. Since (1) knowledge is stored in the brain, (2) the brain is made out of cells, and (3) cells are made out of matter, it would follow that "Without matter, no knowledge"
	8	Big Bang cosmology and biological evolution
	4, 5	"Infoknowledge"

As a theoretical cell biologist interested in discovering the molecular mechanisms underlying living processes, I was led to conclude in Ji (1991) that *information* and *energy* are complementary aspects of a third entity called *gnergy*, the complementary union of information (gn-) and energy (-ergy) (Sect. 2.3.2). In addition, I postulated that *gnergy* is the necessary and sufficient condition

for all organizations in the Universe, including life (Sect. 4.13). In Sect. 2.3.1, I hypothesized that the relation between *information* and *life* is akin to that between *energy* and *matter* (see Schemes 21.2 and 21.4), leading to coining the term "liformation," in analogy to mattergy (Scheme 21.4). Thus the *energy-matter relation* has given rise to two hybrid terms, *infoknowledge* (based on Burgin's analogy (2004)) and *liformation*, both embodying the principle of supplementarity of Bohr (1958):

$$\textbf{Matter} \xrightarrow{\ f\ } \textbf{Energy} \qquad (\textit{Mattergy Category}) \tag{21.2}$$

$$\textbf{Knowledge} \xrightarrow{\ g\ } \textbf{Information} \qquad (\textit{Infoknowledge Category}) \tag{21.3}$$

$$\textbf{Life} \xrightarrow{\ h\ } \textbf{Information} \qquad (\textit{Liformation Category}) \tag{21.4}$$

In Sect. 2.3.1, it was suggested that *life* and *information* are quantitatively related, i.e., *liformation* reflects the principle of supplementarity:

Just as matter can be considered as a highly condensed form of energy, so life may be viewed as a highly condensed form of information. (21.5)

The set of the three hybrid terms, mattergy, infoknowledge, and liformation, can be viewed as the names of the associated categories as shown in Schemes 21.2 through 21.4. A category is a mathematical entity consisting of *nodes* and *arrows* (Lawvere and Schanuel 2009; Hilman 1997). A category is a mapping graphically represented as f: A → B, where A and B are, respectively, the *domain* and *codomain* and f is called the *morphism*.

We can recognize at least three hierarchical levels of categories as shown in Table 21.3. Examples of each class of categories are also provided. It is interesting to note that the categories in Schemes 21.3 through 21.4 are line segments, those in Fig. 21.3 are triads, and that in Fig. 21.4 is a square.

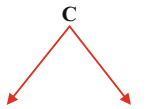
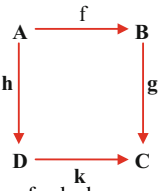
Table 21.4 attempts to capture the common features of the philosophical systems advocated by the four scholars whose thoughts are being integrated in Table 21.3 in relation to the metaphysical and scientific theories described in this book.

Figure 21.3 represents the postulate that liformation, mattergy, and infoknowledge are the complementary aspects of gnergy or that gnergy is ultimately responsible for (or reifies into) liformation, mattergy, or infoknowledge through mechanisms (or laws, rules, etc.) denoted as i, j, or k, respectively. The functor i, j, or k signifies *gives rise to* or *reifies into* and is thought to be associated with the principle of *complementarity*.

Figure 21.4 depicts the Class III category that integrates the four hybrid terms defined in Table 21.3. Most significantly, the diagram in Fig. 21.4 is postulated to embody the commutativity relation given in Eq. 21.6.

$$(\mathrm{i}^{-1}) \times \mathrm{m} = (\mathrm{K}^{-1}) \times \mathrm{n} \tag{21.6}$$

Table 21.3 The category theory of everything (cTOE) integrating Peirce (1839–1914), Popper (1902–1994), Rosen (1934–1998), and Wheeler (1911–2008)

Category class	Nodes	Arrows	Examples
Class I category	Objects	Morphisms[a]	**A** ⟶ **B** AB (arrow) = Matter/energy (conservation of *mattergy*) Life of knowledge/information (conservation of *liformation*[b] ?)
Class II category	Categories	Functor[c]	 **A** . . . . . **B** A = Mattergy B = Liformation or Infoknowledge[d] C = Category of gnergons[e] Functor = the principle of complementarity (?)
Class III category (or the functor category)	Functors	Natural Information[f]	 g∘f = k∘h A = Gnergy[g] (or Natural Law of Rosen ?)

[a]Characcterize the structure of a category

[b]The hybrid term indicating the combination of *life* and *information* in analogy to *mattergy*, the combination of *matter* and *energy*; *see* Scheme (21.4)

[c]A higher-level morphism characterizing the structural relationships between categories

[d]The hybrid term indicating the combination of information and knowledge, in analogy to mattergy; see Scheme (21.3)

[e]The discrete units of gnergy such as conformons, the conformational energy packets localized at sequence-specific sites within biopolymers (see Chap. 8) and dissipatons (Chap. 3.1.5)

[f]"morphisms from functor to functor which preserves the full structure of morphism composition within the categories mapped by functors" (downloaded from Mark C. Chu-Carroll's post dated 6/19/2006)

[g]The hybrid term constructed from information (gn-) and energy (-ergy) that is postulated to represent the material source and the organizational force of our Universe (Ji 1991, 2012)

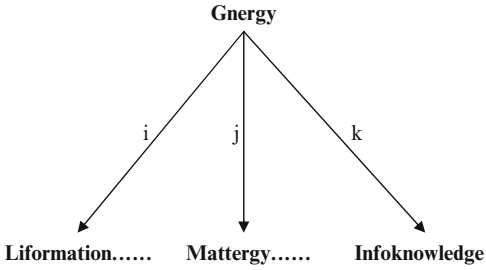


Fig. 21.3 Liformation, mattergy, and infoknowledge as the reification of gnergy

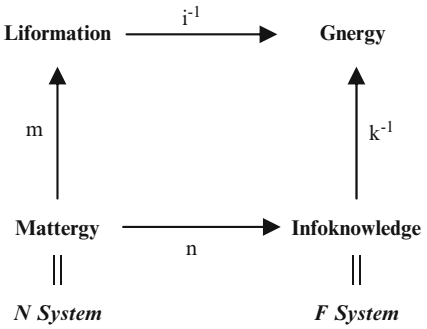


Fig. 21.4 A class III category endowed with the commutativity relation shown in Eq. 21.6

Table 21.4 The three-component philosophical systems of Peirce, Popper, Rosen, and Wheeler. The Arabic numerals in bold refer to those appearing in Rosen's modeling relation shown in Fig. 21.5.

Authors	Component I	Component II	Component III
Rosen	Natural law (**2** and **4**)	Natural system (**1**)	Formal system (**3**)
Peirce	Firstness[a]	Secondness[b]	Thirdness[c]
	Sign[d]	Object[e]	Interpretant[f], or Sign (?)
	Interpretant	Object	
Popper	World 1[g]	World 2[h]	World 3[i]
Wheeler	Participant/observer[j]	It[k]	Bit[l]
Ji	Gnergy	Mattergy	Liformation
	Cosmolanguage[m]	Cell language[n]	Human language[o]

[a]Any entity or process that can exist without anything else, e.g., quality, feelings, possibilities (see Table 6.7)
[b]Any entity or process that exists because of another entity, e.g., facts, actuality, reaction
[c]Any entity or process that exists as the mediator between two other entities or processes, e.g., representation, mediation, thought
[d]Something which stands for something other than itself (see Sect. 6.2.1)
[e]The thing that is referred to by a sign (see Sect. 6.2.1)
[f]The effect that a sign has on the mind of the sign processor
[g]The physical world including the living world
[h]The mental world
[i]The world of the products of the human mind, including poems, arts, and scientific theories
[j]The human as the observer and participant in defining the reality
[k]The reality or the object of measurement
[l]The result of measurements
[m]The language that enables cell and human languages (see Sect. 6.2.6)
[n]The molecular language used by living cells to communicate within and between themselves
[o]The symbolic and iconic languages (see Sect. 6.2.5) used by Homo sapiens to communicate within and between themselves

The precise nature of the functors appearing in Eq. 21.6 is currently unknown. One possible set of the meanings/properties of the functors is suggested below:

m = the origin of life through self-organizing properties of matter and energy (see the Shillongator in Ji 1991, pp. 156–163, 230–237).

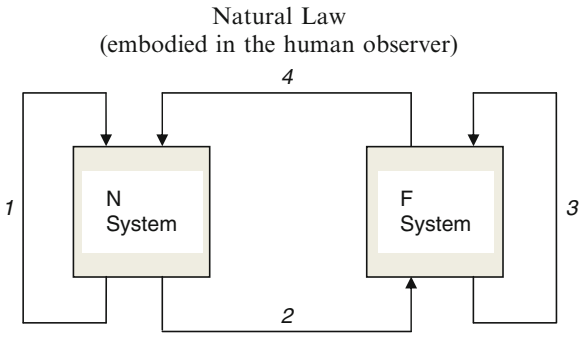


Fig. 21.5 Rosen's modeling relation. N = the natural system, or the part of the Universe exhibiting regularities; F = the formal system; 1 = causal entailment; 2 = encoding; 3 = inferential entailment; 4 = decoding/ actualization

n = the registration or recording of the history of the Universe in the structures of the environment and genomes of organisms

i^{-1} = the inverse of morphism i in Fig. 21.3; cell language (Sect. 6.1.2) (?), and

k^{-1} = the inverse of morphism k in Fig. 21.3; cognition (?)

If Eq. 21.6 turns out to be correct, and if the commutative diagram in Fig. 21.4 can be divided into two halves, each denoted as the natural (N) system and the formal system (F) system, following Rosen (1991) (see Fig. 21.5 above), the Class III category shown in Fig. 21.4 may be represented as shown in Eq. 21.7, where *natural transformation* p may be identified with *ontology* and *natural transformation* q with *epistemology*. If $p = q^{-1}$, or equivalently, $q = p^{-1}$, then N and F would be isomorphic (Lawvere and Schnauel 2009, p. 40) and our Universe would be a self-knowing universe, a conclusion reached in Ji (1991, p. 236) via a totally independent route without depending on any category-theoretical argument.

$$\mathbf{N} \underset{q}{\overset{p}{\rightleftarrows}} \mathbf{F} \tag{21.7}$$

If the conjectures formulated above prove to be true in the future, the Class III category presented in Fig. 21.4 for the first time may be justifiably called the category theory of everything (cTOE).

Two applications of cTOE suggest themselves:

(1) Popper (1978) divides our universe into "three interacting sub-universes" which he calls world 1 (the physical world, both living, and nonliving), world 2 (the mental and psychological world), and world 3 (the world of the products of human mind, including "languages; tales and stories and religious myths; scientific conjectures or theories, and mathematical constructions; songs and symphonies; paintings and sculptures. But also aeroplanes and airports and other feats of engineering". cTOE suggests the following internal structures of Popper's worlds:

World 1 = Gnergy-Mattergy
World 2 = Mattergy-Liformation
World 3 = Liformation-Infoknowledge.

(2) According to cTOE, the *mattergy category* (to which *energy* belongs) and the *liformation category* (to which *information* belongs) are mutually exclusive and complementary aspects of *gnergy* and hence it would be impossible to convert *information* to *energy* in the same sense that *matter* can be converted into *energy*. The correct relation between *information* and *energy* may be derived from Shannon's channel capacity equation (Shannon and Weaver 1949), according to which no information can be transmitted nor any control exerted without requisite dissipation of free energy (Sect. 4.8). Therefore, the experiments recently performed by Toyabe et al. (2010) (and many similar experiments reported in the literature during the past couple of decades) may not demonstrate any *information-to-energy conversion* as claimed but rather the *energy requirement for controlling molecular events* as entailed by the channel capacity equation of Shannon (Shannon and Weaver 1949).

Appendix A

Subject: A CONIC THEORY OF EVERYTHING
Date: Mon, 11 Jun 2001 22:15:49-0400
From: Sungchul Ji sji@rci.rutgers.edu
Reply-To: oca@cc.newcastle.edu.au
To: oca@cc.newcastle.edu.au

(The following is a post that I prepared almost a year ago but did not send to the OCA list. I now make it public because the content of this post is closely related to and is largely consistent with the more recent one posted yesterday, entitled "Two triads and two cuts in measurement." The post is rather lengthy and hence is not for everyone.)

Date: Tue 11 Jul 2000 16:55:54-0400
From: Sungchul Ji sji@rci.rutgers.edu
To: Jaehyun@home.com

As human knowledge expands rapidly – in no small part due to the global communication made possible through the Internet – it becomes almost a necessity nowadays to have a coherent THEORY OF EVERYTHING (TOE) in order to make sense of all the data that are flooding our consciousness day in and day out.

A TOE may be defined as a theory, quantitative and/or qualitative, that attempts to account for the regularities of EVERYTHING. We may recognize three categories of THEORIES OF EVERYTHING (TOE) – (1) TOE for the non-living (N), (2) TOE for the living (L), and (3) TOE for both the non-living and living (L/N), which may be naturally arranged into a triad (Fig. A.1):

The following table summarizes examples of TOE's based on my very limited knowledge in this area. There may be many other theories that can be added to this Table A.1. I provide my own references for the convenience of those who may be interested in pursuing this topic further (knowing full well that this may not sit well with some members of the OCA list.)

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8,

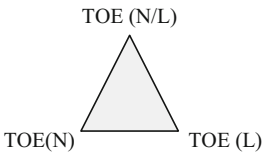


Fig. A.1 The triad of the theories of everything (TOE)

Table A.1 Examples of theories of everything

Theory of everything for	Examples
Nonliving	String theories (Mukerjee 1996; Glanz 2001)
Living	Biocybernetics/cell language theory (Ji 1991, 1997, 1999)
Nonliving and living	Peircean architectonic theory (Hausman 1997)
	Complementarism (Ji 1995)
	Conic theory (This post and my post dated 6/10/01)

Physicists have their string theories for a THEORY OF EVERYTHING NONLIVING. It is the purpose of this post to propose that a THEORY OF EVERYTHING NONLIVING and LIVING can be represented by a circular cone. The following geometric properties of a cone will be found particularly useful in this context:

A cone can be viewed as a volume generated by the rotation of a TRIANGLE around the axis passing through its apex and bisecting its base. At each angle (alpha) of the rotation, we have a triangle or a TRIAD, to be designated as "T(alpha)," with alpha varying from 0° to 360°. Therefore, we can identify a circular cone with an almost infinite number of T(alpha)'s, or triads all sharing (1) the apex (i.e., a one-dimensional point) and (2) the circular base (i.e., a two-dimensional plane).

There are an almost infinite number of points constituting the periphery of the base of a cone.

There are more or less equally numerous diameters, to be designated as "D(beta)," where beta measures the angle between a given diameter and an arbitrarily chosen standard, varying again from 0° to 360°. Notice that each diameter connects two points located OPPOSITE to each other on the periphery of the conic base.

We can form a set of an almost infinite number of equilateral right triangles, each using a diameter as its hypotenuse. Such a triangle, to be labeled as "T(beta)," will necessarily make contact with the periphery equidistance from the two points lying at extremes of its hypotenuse.

Therefore, a cone embodies two sets of triangles, or triads, one set whose members all lying within the plane of the base of the cone and the other whose members are perpendicular to the base of the cone. For convenience, we will refer to the former as the "in-plane triads," or T(beta), and the latter as the "out-of-plane triads," or T(alpha).

A Conic Theory of Everything (CTOE) consists of the following ingredients:

All the regularities of things in this Universe, both living and nonliving, can be represented in terms of triads, each consisting of a pair of opposites (A and B) and a third term, C. Geometrically speaking, all these triads form a circular cone, some forming the base plane and others the body of the cone erected on the base.

These triads, A-C-B, can be divided into two groups – epistemological triads (E-triads) and ontological triads (O-triads). One example of the E-triad is the well-known complementary relation between the wave (A) and particle (B) behaviors of light (C). An example of the O-triad is the triadic relation among Spinoza's Extension (A), Thought (B), and Substance, God, or Nature (C); or the recently postulated complementary relation among energy/matter (A), information (B) and gnergy (C) (Ji 1991, 1995). The main difference between the E- and O-triad is that the validity of the relations embodied in the former is in principle tested by scientific means, while the validity of the relations represented by the latter cannot and hence must be judged on the basis of nonscientific methods, including enlightenment (or awakening to the Tao), inspiration, and intuition/instinct. Again geometrically speaking, E-triads lie on the base of the cone, and O-triads "stand" on the base, sharing one point in common, the apex of the cone.

The Universe consists of two worlds – the Visible, consisting of E-triads, and the Invisible, converging on the Apex of the O-triads. The Visible World is characterized by multiplicity and diversity as represented by the large number of points on the periphery of the base of the cone, whereas the Invisible World is characterized by a unity as symbolized by the Apex of the cone.

In conclusion, all the triads that I have been drawing in my posts over the past one and a half years (there must have been at least 100 triads, for which I have been criticized and almost "ridiculed" by some more than once) may now find some justification, since they may be divided into E- and O-triads as defined above, and the even more numerous (by far) triads and trichotomies that Peirce described in his life may also naturally divide into E- and O-triads. This conjecture seems eminently testable by carefully analyzing Peirce's semiotics.

With all the best.
Sung

Sungchul Ji
Department of Pharmacology and Toxicology
Rutgers University
Piscataway, N.J. 08855
sji@rci.rutgers.edu
(732)445-4701

References

Glanz, J.: Even without evidence, string theory gains influence. http://www.nytimes.com/2001/03/13/science/13SWTRI.html (2001)

Hausman, C.R.: Charles S. Peirce's Evolutionary Philosophy. Cambridge University Press, Cambridge (1997)

Ji, S.: Biocybernetics: a machine theory of biology. In: Ji, S. (ed.) Molecular Theories of Cell Life and Death, pp. 1–237. Rutgers University Press, New Brunswick (1991)

Ji, S.: Complementarism: a biology-based philosophical framework to integrate western science and eastern Tao. In: Korean Academy of Psychotherapists (ed.) Psychotherapy East and West: Integration of Psychotherapies, pp. 178–223. Korean Academy of Psychotherapists, Seoul (1995)

Ji, S.: Isomorphism between cell and human languages: molecular biological, bioinformatic and linguistic implications. BioSystems **44**, 17–39 (1997)

Ji, S.: Linguistics of DNA: words, sentences, grammar, phonetics and semantics. Ann. NY. Acad. Sci. **870**, 411–417 (1999)

Mukerjee, M.: Explaining everything. Scientific American **1996**, 88–94 (1996)

This post and my post dated 6/10/01

Appendix B

Mailing List **complex-science@necsi.org** Message #6768

From: Sungchul Ji <sji at eohsi.rutgers.edu>
Sender: <yaneer at necsi.org> (Yaneer Bar-Yam)
Subject: Taxonomy of entropy-information relations based on the complementarian logic
Date: Fri, 04 Jun 2004 09:51:05 -0400
To: complex-science

In my previous post, I discussed what entropy-information relations ARE NOT (e.g., not NPI). In this post, I will discuss what I think entropy-information relations ARE, as deduced from applying the complementarian logic to the problem.

(1) The terms "entropy" and "information" occur widely in physics (Zurek 1991), mathematics (Kolmogorov 1968), philosophy (Kubat and Zeman 1975), computer science (Shannon and Weaver 1949; Gray 1990), biology (Ji 1974), and cosmology (Hawking 1994; Mukhanov 1991; Ji 1991a). From these literatures, we can recognize the following three main varieties of entropies and informations. These are listed below more or less in the chronological order of their discovery or emergence in the history of the Universe:

<Three Classes of Entropies>

(i) THERMODYNAMIC ENTROPY = Reversibly absorbed heat divided by the temperature at which the heat absorption occurs, discovered by Clausius in 1865
(ii) STATISTICAL MECHANICAL ENTROPY = Natural logarithmic function of the number of microstates compatible with a given macrostate postulated by Boltzmann in 1877 to underlie thermodynamic entropy
(iii) MATHEMATICAL ENTROPIES = Mathematical entities conforming to the general form, x log x or its variants, where x is a probability distribution, including Shannon entropy formulated in 1948 (Shannon and Weaver 1949) and Tsalis entropy formulated in 1988 (Tsallis 1999)

<Three Classes of Informations>

(i) PRIMORDIAL INFORMATION = Information that, together with energy/matter, constitutes gnergy, the primordial driving force for all self-organizing processes in the Universe (Ji 1991b). In other words, primordial information and energy/matter are the complementary aspects of Gnergy.
(ii) PHYSICAL INFORMATION = Information about the state of physical systems, similar to or identical with Brillouin's "bound" information (Brillouin 1962).
(iii) ABSTRACT INFORMATION = Information referring to nonphysical entities. Similar to or identical with Brillouin's "free" information (Brillouin 1962).

(2) It is postulated here that these six entities are related to each based on the complementarian logic (discussed on this list on numerous occasions) (Ji 1995). To make it easier to understand, these rather complex relations are described in three steps, using Figs. B.1, B.2 and B.3.
Figures B.1 and B.2 can be combined into Fig. B.3 due to the common vertex, PRIMORDIAN INFORMAITON:

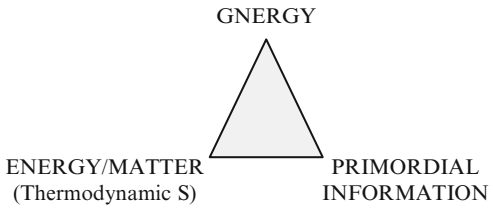


Fig. B.1 Energy/matter and primordial information as complementary aspects of gnergy, the primary driving force of all self-organizing processes in the Universe, including the Big Bang, the origin of life, and the biological evolution. Thermodynamic entropy S is viewed as an integral component of free energy and matter

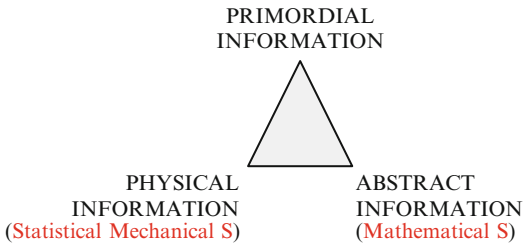


Fig. B.2 Physical (bound) information and abstract (free) information as postulated to be the complementary aspects of primordial information. Statistical mechanical entropy may be best regarded as a subset of physical information, and likewise mathematical entropy may be best viewed as a subset of abstract information

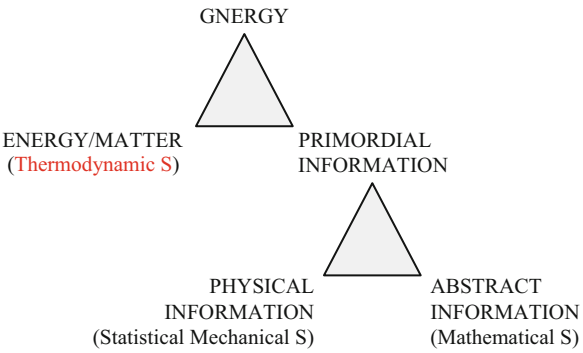


Fig. B.3 The taxonomy of entropy-information relations deduced on the basis of the complementarian logic (Ji 1995)

Table B.1 A summary of the entropy-information relations characterized by Fig. B.3. 1 = alloed; 0 = disallowed

	Entropy (S)		
Information (I)	Thermodynamic	Statistical mechanical	Mathematical
Primordial	1	0	0
Physical	0	1	0
Abstract	0	0	1

(3) The content of Fig. B.3 can also be represented in a tabular form as shown in Table B.1. The numbers in the parentheses in the "entropy vector" (i.e., the uppermost row) and the "information vector" (i.e., the leftmost column) reflect approximately the history of the emergence of different kinds of entropies or informations. Please note that the order of the elements in these vectors is fixed by history, not arbitrarily.

(4) The notation, R_i,j, indicates the relation between the ith row (information) and the jth column (entropy). There are two kinds of relations in Table B.1 – allowed and disallowed – denoted as 1 and 0, respectively.

(5) Only the diagonal (from upper left to lower right) elements in Table B.1 are allowed or realized in nature, others being disallowed. This selection rule can be characterized algebraically as

$$R\_i, j = 1, \text{ if and only if } i = j \tag{B.1}$$

(6) Based on Fig. B.1, we can identify R_1,1 as COMPLEMENTARITY (see (Ji 1995) for a general definition of this term). Based on Fig. B.2, we can characterize R_2,2 and R_3,3 as indicating SUBSETHOODS (i.e., statistical mechanical S is a subset of physical information, and mathematical entropy is a subset of abstract information).

(7) It should be pointed out that Brillouin's so-called NPI (Negentropy Principle of Information) (Brillouin 1962) is equivalent to maintaining that R_2,2 is IDENTITY (rather than SUBSETHOOD, as I claim here).

References

Brillouin, L.: Science and Information Theory, 2nd edn, pp. 152–153. Academic Press, New York (1962)

Gray, R.M.: Entropy and Information Theory. Springer, New York (1990)

Hawking, S.: Black Holes and Baby Universes and Other Essays. Bantam Books, New York (1994)

Ji, S.: Energy and negentropy in enzymic catalysis. Ann. NY. Acad. Sci. **227**, 419–437 (1974)

Ji, S.: Biocybernetics: a machine theory of biology. In: Ji, S. (ed.) Molecular Theories of Cell Life and Death, pp. 1–237. Rutgers University Press, New Brunswick (1991a)

Ji, S.: Biocybernetics: a machine theory of biology. In: Ji, S. (ed.) Molecular Theories of Cell Life and Death, pp. 152, 231–234. Rutgers University Press, New Brunswick (1991b)

Ji, S.: Complementarism: a biology-based philosophical framework to integrate western science and eastern Tao. The text available at http://www.rci.rutgers.edu/~sji (1995). See p. 524

Kolmogorov, A.: Logical basis for information theory and probability. IEEE. Trans. Info. Theory. IT **14**(5), 662–664 (1968)

Kubat, L., Zeman, J.: Entropy and Information in Science and Philosophy. Elsevier Scientific Publishing Co., Amsterdam (1975)

Mukhanov, V.F.: The entropy of black holes. In: Zurek, W.H. (ed.) Complexity, Entropy and the Physics of Information, pp. 47–52. Addison-Wesley Publishing Co, Redwood (1991)

Shannon, C.E., Weaver, W.: The Mathematical Theory of Communication. University of Illinois, Urbana (1949)

Tsallis, C.: Nonextensive statistics: theoretical, experimental and computational evidences and connections. Brazilian J. Physics **29**(1), 1–35 (1999)

Zurek, W.H. (ed.): Complexity, Entropy and the Physics of Information. Addison-Wesley Publishing Co., Redwood (1991)

Appendix C

Subject: "Microarrays, as normally used, do not measure gene expression"
From: "Sungchul Ji" <sji@rci.rutgers.edu>
Date: Fri, December 11, 2009 7:29 pm
To: –
Cc: –
Priority: Normal

Dear X,

It was great to meet you at the RECOM2009 meeting, which was one of the best conferences that I have attended in recent years.

I appreciated your advertising our poster 99 at the meeting. This poster contained the first public discussion of the concept of "genes as molecular machines".

I checked the movie advertisement shown at one of the windows at the Broad Institute, and the name of the person explaining the microarray method was …. She did an excellent job explaining how the microarray technique can be used to measure thousands of single nucleotide polymorphims (SNPs), but she, I think, committed an error (like most workers in the field do, including the two or three speakers whom I heard interpret their microarray data at the meeting): She stated that microarrays allow biologists to measure which genes are turned on and which turned off. This is an inaccurate statement because microarrays, as normally used, do not measure "gene expression" (or transcription rate) but only "RNA levels". As you know, there is a profound difference between "gene expression", interpreted as "transcription rate", and "RNA levels", because the former is a rate, dx/dt, and the latter a concentration, x. Consequently, RNA levels can change without any change in associated transcription rates, as directly demonstrated in 2004 by Garcia-Martinez et al (see Fig. 12.1. in the "Mechanisms" paper attached). This anti-intuitive observation is the natural consequence of the fact that RNA molecules are unstable inside the cell, being degraded by ribonucleases with rates varying from minutes to hours, comparable to the rates of gene expression. This simple theoretical consideration has been ignored by most workers in the field of

microarray technology since the revolutionary technique was invented in the mid-1990s, which prompted me to write several posts around 2003 (see attached), lamenting what I saw as "an intellectual crisis" in biology.

Very frankly, such a naive mistake in interpreting microarray data, as has been observed on the world-wide scale (see the term papers of two of my students), would never have happened in the field of chemistry (nor in biology, if biologists were adequately trained in basic principles of chemical kinetics). This is why I was somewhat surprised to find that even the Broad Institute, one of the premiere research centers in the world in microarray technology and its applications would partake in disseminating the inaccurate depiction of this valuable experimental method to lay public as well as to professional biomedical scientists. It is sincerely hoped that the paper* attached to this email will help correct the wide-spread misinterpretations of microarray data so that the true value of this revolutionary technique will be re-appreciated in the coming years, ushering in a new era in cell biology.

If you have any questions or comments, please let me know.

With warm regards.
Sung

*This paper is listed as Ji et al. (2009) in References on p. 717 (my addition).

Appendix D

Mailing List complex-science@necsi.org **Message #5511**
From: Sungchul Ji sji@eohsi.rutgers.edu
Sender: <yaneer@necsi.org> (Yaneer Bar-Yam)
Subject: An intellectual crisis in the field of DNA microarray data analysis
Date: Tue, 04 Nov 2003 16:29:14 -0500
To: complex-science

During the past two days, I have been attending a workshop in bioinformatics held at Rutgers. Researchers in the field of DNA microarray data analysis, ranging from young graduate students to established bioinformaticians, used the terms "mRNA level" and "gene expression" synonymously and interchangeably. When I pointed out to some of them after their lectures why I think these terms are not the same and how conflating them could lead to misinterpretations of DNA microarray data, they all seemed to agree with me.

It is not too difficult to understand why mRNA levels and gene expression rates are not the same: You can have an mRNA level rise inside the cell without any increase in the expression of the corresponding gene, if the rate of mRNA hydrolysis is decreased, which can happen independently of any gene expression. If anyone has any doubts about my conclusion here, just think about the "checking account balance-income metaphor" that I used in my 10/29/03 post: It is impossible to determine someone's income (rates of gene expression) from his checking account balance (mRNA levels).

If the explanation for the difference between mRNA levels and rates of corresponding gene expression is so simple, how is it that so many, if not all, biologists and computational scientists working in the DNA microarray area are uniformly conflating these two terms?

I have the following possible answers:

Microarrays are constructed using cDNA produced from genes. Since mRNA molecules are identified through the use of such cDNA, mRNA molecules are indirectly related to genes within the context of microarray experiment. Of course,

everybody knows that mRNA is synthesized using DNA as template inside the cell, which also contributes to the myth of the mRNA-gene connection.

It sounds more important and impressive to say that microarrays measure *genes* rather than *mRNA levels*.

Computational scientists like to simplify biological problems for mathematical treatment.

Molecular biologists tend to be awed by anything mathematical and tend to accept whatever their mathematician or computational colleagues say about the results of their analysis of DNA microarray data (conflating *mRNA levels* with *gene expression*, of course).

Because of the immense complexity involved, with respect to both the biological systems being studied and the amount and quality of data being analyzed, workers in this area may have unconsciously given up the hope of ever solving their problems through the use of critical questioning, heated debates, and rigorous logical analysis of empirical data.

The confusions and despairs that I now sense in the field of DNA microarray may be a blessing in disguise. After enough frustrations and failures to produce practical biomedical applications eagerly awaited by millions of investors around the world, both biomedical scientists and granting agencies may come to realize one day what is really missing – the COMPUTER MODEL of the LIVING CELL (CMLC). I truly believe that without CMLC it would be impossible to extract any biologically meaningful information out of DNA microarray data. A similar situation happened in physics. Physicists in the 19th and 20th centuries could not meaningfully interpret atomic spectral data without the Bohr model of the atom formulated in 1913. If biologists can succeed in constructing a working CMLC within the next 10 years, biology would be behind physics by just one century, which may be viewed as a reasonable lag time.

Appendix E

Mailing List complex-science@necsi.org Message #7074
From: Sungchul Ji sji@eohsi.rutgers.edu
Sender: <yaneer@necsi.org> (Yaneer Bar-Yam)
Subject: An intellectual crisis in the field of DNA microarray data analysis
Date: Mon, 20 Sep 2004 19:19:03 -0400
To: complex-science

About a year ago (see the attached post NECSI Message #4902 dated 13 May 2003), I formulated 5 general statements that I claimed to apply to interpreting microarray data. The post also gives a brief description of the revolutionary microarray technique which promises to usher in a new era in molecular and cell biology, medicine, and pharmaceutical industry in the coming decades.

The purpose of this post is to bring to your attention a paper just published by J. Garcia-Martinez and his colleagues at the University of Valencia, Spain ["Genomic Run-On Evaluates Transcription Rates of All Yeast Genes and Identifies Gene Regulatory Mechanisms." *Mol. Cell* **15**: 303–313 (2004), which can be located by Googling "Garcia-Martinez, genomic run-on"]. They simultaneously measured both *TR* and *mRNA levels* (also called *transcript levels*) of about 6,000 genes in glucose-starved yeast, using cDNA arrays and radiolabeling techniques. Their Figures 3 and 4 in the cited paper clearly demonstrate that the time profiles of *TR* and *mRNA levels* do not coincide, leading to the conclusion that TR (fluxes) and mRNA levels (steady-state levels) change more or less independently of each other as predicted in my posts dated May 13, 2003 (cited above) and July 15, 2002 post (see below).

Thus, the experimental results of Garcia-Martinez et al. support not only the general statements formulated in May, 2003 but also my contention made in 2002 that most of the workers in the field of microarrays unwittingly conflated *steady-state levels* and *rates* ("The 'steady-state level' vs. 'flux' confusion," NECSI Message #4082 dated 15 July 2002).

If the theory of interpretation of microarray data that I proposed in the past couple of years is basically correct, it may have two major consequences:

(1) Most, if not all, of the microarray experiments published since 1995 may have to be *re-interpreted*.
(2) The new perspective/paradigm may lead to developing more sophisticated and realistic *mathematical, kinetic, and statistical methods* for mining valuable biological information embodied in microarray data, that will allow us to identify, for example transcription units coding for siRNAs (or *microRNAs*) and *riboswitches* (Mattick 2004; Stix 2004; Gibbs 2003).

References

Gibbs, W.W.: The unseen genome: gems among the junk. Sci. Am. Nov 2003, 48–53 (2003)
Mattick, J.S.: The hidden genetic program of complex organisms. Sci. Am. Oct 2004, 60–67 (2004)
Stix, G.: Hitting the genetic off switch. Sci. Am. Oct 2004, 98–101 (2004)

Appendix F

Subject: “Microarrays, as normally used, do not measure gene expression”
From: “Sungchul Ji” <sji@rci.rutgers.edu>
Date: Sat, December 19, 2009 3:22 pm
To: –
Cc: –
Priority: Normal

Dear X,

I enjoyed your thought-provoking lecture at the 102nd Statistical Mechanics Conference at Rutgers last week . . ..

You assumed in your lecture that microarrays measure “gene expression” meaning that, if the level of a given RNA is increased by some perturbation, the rate of the expression of the gene encoding that RNA is interpreted to have increased. This assumption may be represented as follows:

$$\textbf{IncreasedRNAlevel} \rightarrow \textbf{IncreasedGeneExpression} \qquad \text{(F.1)}$$

Scheme (F.1) has been assumed by almost all workers in the field of DNA microarrays (including some researchers at the Broad Institute and the RECOM 2009 Conference; see my email to . . .) since this revolutionary technique was invented by you and others in the mid-1990s.

But, Garcia-Martinez et al. in [Mol. Cell 15: 303–313 (2004)] showed, by a simultaneous measurement of both transcript levels (TL) and associated transcription

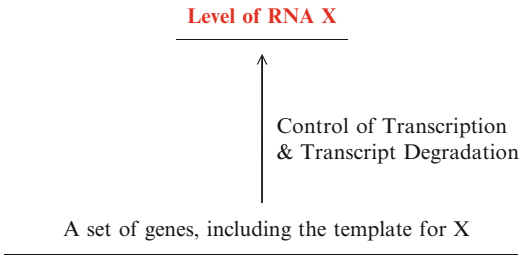
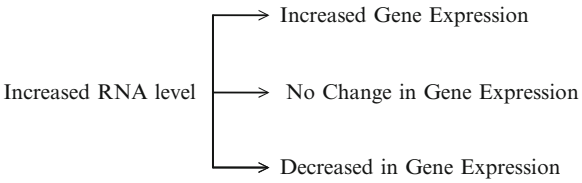


Fig. F.1 The intracellular level of one RNA molecule is postulated to be controlled by a set of n genes, where n may be 10~20 in budding yeast, that control both transcription (i.e., gene expression) and transcript degradation

rates (TR), that TL and TR vary independently of each other (see Fig. 12.1 in the attached reprint), leading to Scheme (F.2):



(F.2)

Scheme F.2 is not surprising since the level of an RNA is determined not only by its gene (i.e., its template) but also by other regions of the DNA molecule acting as promoters, enhancers, silencers, and structural genes coding for transcription factors and enzymes catalyzing transcription and transcript degradation. So it is probably very likely that for any given RNA molecule, X, there are a set of a dozen or more genes that directly or indirectly controls the intracellular level of X (Fig. F.1):

On the basis of the above analysis, it has been concluded that assuming Scheme (F.1) has led to false positive and false negative errors in interpreting microarray data in some of the major publications in the field of DNA microarrays (see two term papers of my students attached).

It is my firm belief that, one of the main reasons for the diminished popularity of the DNA microarray technique among cell biologists in recent years is due to the wide-spread mis-interpretations of RNA level data measured by this invaluable experimental method. Once the correct way of interpreting DNA microarray data is introduced into the field, it is likely that the microarray technology will finally revolutionize cell biology as once widely thought.

If you have any questions, comments or suggestions, please let me know.

With all the best.
Sung

Appendix G

Mailing List **http://necsi.org:8100/lists/complex-science/List.html**
Message #4600

From: Sungchul Ji <sji @rci.rutgers.edu>
Sender: <yaneer at necsi.org> (Yaneer Bar-Yam)
Subject: A unified theory of computing/mind/signs
Date: Mon, 03 Feb 2003 18:12:38 -0500
To: complex-science

1. A qualitative definition of "category"
2. A tetrahedron in a sphere
3. "Atorology"
4. Matter-form complementarity
5. Triple dualities of computing
6. The geometry of computing/mind/signs
7. Conclusions

1. In a previous post, I described three classes of computing based on numbers, words, and molecules. In an attempt to discern possible connections among them, I have been led to explore a larger category of which these form integral "subcategories." In addition, the new category may provide a coherent theory to integrate computing, mind, and signs that have traditionally been considered as constituting the subjects of separate fields of inquiries.
   By a "category," I will refer to any system of components (C), either formal or material, that can transform (T) a set of inputs (I) to desired outputs (O), obeying a set of axioms, rules, constraints, or laws (A). Hence, a category, Cat, so defined can be represented as a 5-tuple:

$$\text{Cat} = (\text{C},\ \text{T},\ \text{I},\ \text{O},\ \text{A}) \tag{G.1}$$

   Expression G.1 can be regarded as a qualitative abstraction of mathematical categories and as synonymous with systems, automata, and machines.

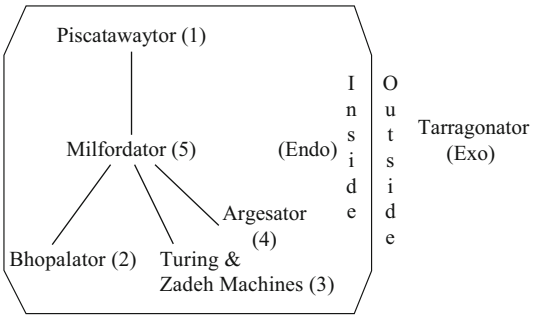


Fig. G.1 A tetrahedron in a sphere

2. The unified theory of computing, mind and signs that I will present below involves five components and two aspects. Before I describe the nature of these components and aspects, it may be helpful to introduce a geometric object that will provide a visual aid to presenting the theory. Simply put, this geometric object consists of a tetrahedron enclosed within a sphere, having the following useful properties (see Fig. G.1):

   (1) Five nodes forming the four vertices of a tetrahedron equidistant from its center of gravity.
   (2) The inside (endo) and outside (exo) aspects of the sphere.

3. I must now introduce five "ators" whose unusual looks and sounds may offend the sensibilities of some, if not most, members on this list. It is a tradition in physical chemistry to name a self-organizing system as an "X-ator", X indicating the city associated with the research done on the system of interest in one way or another. The first example of an "ator" was the "Brusselator," a formal model of the Belousov-Zhabotinsky (BZ) reaction-diffusion system developed in Brussels by Prigogine and Lefever in 1968. Another example is the "Oregonator," a chemical mechanistic model of BZ reaction proposed by Field and Noyes in Oregon.

   The first biological "ator" proposed is probably the "Bhopalator," a molecular model of the living cell based on the concepts of conformons and dissipative structures, that I proposed in 1983 in a meeting held in Bhopal, India (Ji 1985). I must confess that I am "guilty" of fathering four more of "ators" that are deemed essential in constructing the unified theory of computing, mind and signs presented here.

   The PISCATAWAYTOR = A material model of the human body (Ji 1991). The name reflects the fact that the idea of modeling the human body based on the principle of self-organization occurred to me while teaching pharmacology to pharmacy students at Rutgers in Piscataway around the mid- to late 1980s.

   Since the brain is a part of the human body, we may view the Piscatawaytor as a material model of the human brain as well. Also, since macroscopic computing before the advent of computers was done by the human body (reading and reasoning by the brain and writing and erasing by the hands), it may be justified

to consider the Piscatawaytor as the material model of macroscopic computing, in contrast to the Turing and Zadeh machines that are the formal models of human computing.

The ARGESATOR = This is a formal model of cell computing, such as the P-system (Paun 2000, 2002) and the conformons-P system (Frisco and Ji 2002, 2003). The formulation of the conformons-P system was motivated by the stimulating workshop organized by G. Paun in Curtea de Arges, Romania, in August, 2001.

The MILFORDATOR = The ontological and formal theories of signs (i.e., semiotics) developed by Charles S. Peirce (1839–1914). All of the categories that occupy the four vertices of the tetrahedron in Fig. G.2 involve SIGNS of various kinds, including numbers, words, and molecules. Peirce spent the later decades of his life (in dire poverty) in Milford, PA, developing and refining his theory of signs (Brent 1993). To pay tribute to his contributions to the theory of signs that I think is central to unifying the various forms of computation, I took the liberty of coining yet another term, the "Milfordator," defined as the category composed of the Piscatawaytor, the Bhopalator, the Turing and Zadeh machines, and the "Argesator". As is shown in Fig. G.2, the Milfordator is placed at the center of a tetrahedron to indicate its central role as the foundation or the source of the four classes of computing that occupy the four vertices.

The TARRAGONATGOR = This is a "supercategory" that represents the whole of the categories constituting the tetrahedron (see Fig. G.2). The name is chosen to acknowledge the theoretical contributions made by Carlos Martin-Vide, a mathematical linguist, and Gheorghe Paun, a mathematician and theoretical computer scientist, both active at the Rovira i Virgili University in Tarragona, Spain. Their work provided a pioneering influence in integrating mathematics, computer science, formal languages, and molecular and cell biology.

Before putting all these components together in a coherent manner, two more items must be discussed – (1) the matter-form complementarity, and (2) the notion of "triple dualities".

4. MATTER-FORM COMPLEMENTARITY The notion of the matter-form complementarity states that matter and form are not separate entities but constitute complementary aspects of a third term. The third term is related to "hylomorphism," a doctrine first advocated by Aristotle that "concrete substance consists of form in matter". Also it is related to the concept of "gnergy," defined as a physico-metaphysical entity, of which information and energy form complementary aspects (Ji 1991, 1995). H. Pattee independently formulated the notion of matter-symbol complementarity (Pattee 2001a, b), which appears closely related to both the matter-form complementarity and the information-energy complementarity. But Pattee never discussed the nature of the third entity, of which matter and symbols are the complementary aspects.

   The so-called "von Neumann-Pattee principle of matter-sign complementarity", which is rooted in Pattee's idea of matter-symbol complementarity (Pattee 2001a, b) and in some of von Neumann's ideas concerning self-reproducing automata, states that all reproducing systems embody two complementary

aspects – the physical law-governed material/energetic aspect and the evolutionary-rule governed sign aspect (Pattee 2001c). This principle is basically identical with the gnergy principle, according to which all self-organizing processes in the Universe, including self-reproduction in biology, are ultimately driven by gnergy, a complementary union of information and energy (Ji 1991, 1995). As is seen below, the matter-form complementarity constitutes one of the three dualities underlying computation.

5. THE "TRIPLE DUALITIES" OF COMPUTING can be characterized in terms of the following triad of dualities:

   (1) Macroscopic vs. microscopic computing = Macroscopic computing employs signs or symbols that are macroscopic in size so that they can be read by humans and human-made computers. In contrast, microscopic computing entails manipulating molecules such as DNA or proteins that are microscopic in size.
   (2) Material vs. formal aspects of computing = The material aspect of computing is represented by computer hardwares and the functioning human brain (modeled by the Piscatawaytor) on the macroscopic scale and by the living cell (modeled by the Bhopalator) on the molecular scale. In contrast, the formal aspect of macroscopic computing is represented by the Turing machine and Zadeh machines, while that of microscopic computing is represented by the "Argesator" (see above).

   Exo and endo aspects of computing = The category that contains all the different classes of computing systems, from the Bhopaltor to the Zadeh machine, is referred to as the Tarragonator, which can be regarded as representing the external view of the whole consisting of all the computing systems forming the internal structure of a network (see Fig. G.2). The internal counterpart of the Tarragonator may be identified with the Milfordator, which serves as the ground for, or the hub of, all the possible classes of computing systems in existence.

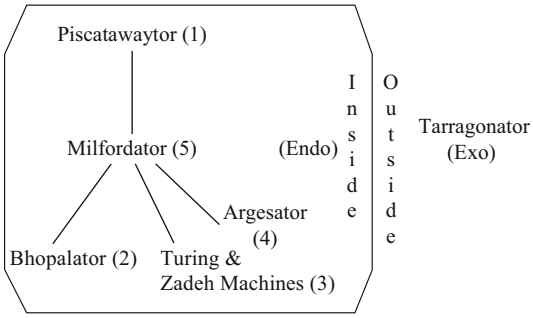


Fig. G.2 A "triply dual" model of computing/mind/signs. Micro (2 & 4) vs. macro (1 & 3), material (1 & 2) vs. formal (3 & 4), and endo vs. exo. Both the Milfordator and the Tarragonator are matter-symbol dual or information-energy complementary, viewed from inside and out, respectively. The Turing machine is a formal model of computing based on crisp logic, while the Zadeh machine is a formal model of computation based on fuzzy logic

6. Finally all of the five component categories can now be arranged into a geometric structure shown in Fig. G.2, guided by the "triple dualities" explained above.
7. Three main conclusions may be drawn based on the "triply dual" model of computing/mind/signs depicted in Fig. G.2:

   (1) Computing, mind, and living cells are but different aspects of sign processes or semiosis. In other words, computer science, cognitive science, and cell biology can be viewed as "prescinded" branches of the science of signs (or semiotics) pioneered by Peirce.
   (2) The sign processes centered at the Milfordator can act as a unit, i.e., the Tarragonator, and interact with other units in a larger category. In other words, the Tarragonator can occupy a node in a larger network of categories centered at another hub or Milfordator, etc.
   (3) The process of reduction described in (2) may be repeated in our Universe n times, where n may be a small number (between 5 and 10?).

Any questions, comments or criticisms are welcome.

With all the best.
Sung

Sungchul Ji, Ph.D.
Department of Pharmacology and Toxicology
Rutgers University
Piscataway, N.J. 08855

References

Brent, J.: Charles Sanders Peirce. Indiana University Press, Bloomington (1993)
Frisco, P., Ji, S.: Conformons-P systems. In: DNA Computing, Proceedings of the 8th International Workshop on DNA-Based Computers, Hokkaido University, Japan (2002)
Frisco, P., Ji, S.: Towards a hierarchy of conformons-P systems. Lecture Notes in Computer Science (in press). *Later published as Frisco and Ji (2003) as listed in references on p. 717 (my addition)*
Ji, S.: The bhopalator – a molecular model of the living cell based on the concepts of conformons and dissipative structures. J. Theor. Biol **116**, 399–426 (1985)
Ji, S.: Biocybernetics: a machine theory of biology. In: Ji, S. (ed.) Molecular Theories of Cell Life and Death, pp. 1–237. Rutgers University Press, New Brunswick (1991)
Ji, S.: Complementarism: a biology-based philosophical framework to integrate western science and eastern Tao. In: Korean Academy of Psychotherapists (ed.) Psychotherapy East and West: Integration of Psychotherapies, pp. 178–223. Korean Academy of Psychotherapists, Seoul (1995)
Pattee, H.: The physics of symbols: bridging the epistemic cut. BioSystems **60**, 5–12 (2001a)
Pattee, H.: Irreducible and complementary semiotic forms. Semiotica **134**, 1–18 (2001b)
Pattee, H.: von Neumann-Pattee principle of matter-sign complementarity on pp.416–417. Ann. NY. Acad. Sci **870**, 411–417 (2001c)
Paun, G.: Computing with membranes. J. Comp. System Sci. **61**(1), 108–143 (2000)
Paun, G.: Membrane Computing: an Introduction. Springer, Berlin (2002)

Appendix H

(A short talk presented at the 104th Statistical Mechanics Conference, 12/19-21, Rutgers University, Piscataway, N.J., *http://www.math.rutgers.edu/events/smm/*)

Distances between RNA trajectories are distributed according to Planck's radiation law or the Gaussian distribution law depending on their metabolic functions. Sungchul Ji and Kenneth So, Ernest Mario School of Pharmacy, Rutgers University, Piscataway, N.J. 08855 sji@rci.rutgers.edu

When the genome-wide RNA levels of budding yeast are measured with microarrays at 6 time points (0, 5, 120, 360, and 850 min after switching the nutrient from glucose to galactose) [Garcia-Martinez, Aaranda and Perez-Ortin, Mol Cell **15**, 303–313 (2004)] and plotted in the 6-dimensional "concentration-time" or "trajectory" space, a cluster of about 6000 points is obtained, each point representing the trajectory of an RNA molecule, and the whole cluster can be organized into a group of 30–50 subclusters based on the similarities among the wave shapes of individual RNA trajectories. One challenging problem facing such analyses has been the difficulty of identifying the biological functions of the subclusters. In order to overcome this difficulty, we focused on characterizing the patterns (i.e., wave shapes) of the RNA trajectories (or the RNA concentration waves) unique to specific metabolic pathways of which there are about 200 in budding yeast. To this end, we calculated the $n(n-1)/2$ Euclidean distances between all possible RNA pairs belonging to a given pathway encoded by n RNA molecules, "binned" them into classes labeled "0–10," "11–20," "21–30," etc., and counted the number of the RNA molecules belonging to each bin. The resulting data can be visualized as a histogram or a "distribution curve" specific for each metabolic pathway. We previously reported [S. Ji and K. So, Short Talk Abstract B1, The 102nd Statistical Mechanics Conference, 2009] that such distribution curves fitted an equation similar in form to Planck's (or blackbody) radiation law,

i.e., $y = a(Ax + B)^{-5}/(e^{-b/(Ax + B)} - 1)$, where a, b, A, and B are constants. The purpose of this presentation is to report the following results:

(i) PROCESS-DEPENDENT NUMERICAL VALUES FOR THE PLANCK'S RADIATION LAW-LIKE EQUATION (PRLLE). We now have determined the numerical values of the four parameters of PRLLE as functions of the processes involved. For blackbody radiation, $a = 5.0x \times 10^{-15}$, $b = 4.8 \times 10^{-13}$, $A = 1$, $B = 0$, $y =$ spectral intensity, and $x =$ wavelength; for single-molecule cholesterol oxidase enzymic activity [Lu, Xun and Xie, Science **282**, 1877–1882 (1998)], $a = 3.5 \times 10^5$, $b = 2.0 \times 10^2$, $A = 1$, $B = 0$, $y =$ frequency of occurrence of a waiting time, and $x =$ waiting time, i.e., the time an enzyme waits before it is thermally activated to perform simple catalysis; and for the distances in the "RNA trajectory space" between functionally related RNA pairs, $a = 8.8 \times 10^8$, $b = 50$, $A = 2.23$, $B = 3.21$, $y =$ frequency of occurrences of RNA distances, and $x =$ the distance classes between all possible RNA trajectory pairs belonging to a metabolic pathway. It is interesting to note that the ratio, a/b, increases progressively from blackbody radiation (1.04×10^{-2}) to single-molecule enzyme activity (1.75×10^3) to RNA trajectory pair distances (1.70×10^7). The cause underlying this regularity is unknown but may be related to the complexity of the systems being measured.

(ii) GAUSSIAN DISTRIBUTIONS. When the RNA pairs are chosen from two different metabolic pathways rather than from within a pathway (e.g., one of the two RNA molecules in a pair from glycolysis and the other from respiration), the distances between the trajectories of such inter-pathway RNA pairs no longer satisfied the Planck's radiation law–like equation but rather were found to fit the Gaussian distribution law. The means and standard deviations of the Gaussian curves for the three pairs of the pathways examined so far, i.e., (a) respiration vs. oxidative phosphorylation, (b) respiration vs. glycolysis, and (c) glycolysis vs. oxidative phosphorylation, are found to be (a) 15 and 4, (b) 17 and 7, and (c) 22 and 5, respectively.

(iii) THE POSIBLE ROLE OF THERMAL FLUCTUATIONS IN CO-ACTIVATING TRANSCRIPTOSOMES AND DEGRADASOMES. The fact that blackbody radiation, single-molecule cholesterol oxidase enzymic activity, and the distances among the whole-cell RNA trajectories (whose shapes are determined by the balance between the rates of transcription catalyzed by transcriptosomes and RNA degradation catalyzed by degradosomes) all obey the same mathematical equation formally similar to Planck's radiation law strongly indicates that thermal motions (also called thermal fluctuations or Brownian motions) are implicated in these processes. It was postulated elsewhere [S. Ji, Energy and Negentropy in Enzymic Catalysis, Ann. N. Y. Acad. Sci. **227**, 419–437 (1974); Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications, Springer, New York, 2011, to appear] that the Generalized Franck-Condon Principle entails an enzyme to undergo thermal fluctuations as a prelude to its electronic rearrangement (also called "quantum jump") leading to catalysis.

Thus it seems necessary only to assume that this two-step mechanism, i.e., "thermal fluctuations –> quantum jump", is implicated in the blackbody radiation, single-molecule enzymology, and the regulation of RNA levels inside the living cell, in order to account for the universality of the Planck radiation law–like equation described above. Just as thermal fluctuations are thought to bring a set of catalytic amino acid residues to transient proximity in the active site of an enzyme so that a quantum jump (i.e., a chemical reaction) can ensue [S. Ji, vide infra], it is here postulated that thermal fluctuations synchronously activate the enzymic activities of transcriptosomes and their associated degradasomes in such a way as to regulate the levels of RNA molecules to meet the metabolic demands of the cell. The precise mechanisms underlying the coupling between a transcriptosome and its associated degradosome have yet to be worked out, but one possibility appears to be that fluctuating transcriptosomes and degradosomes interact with one another through various types of phase-sensitive waves including the electromagnetic, chemical concentration, and nonlocal quantum waves that are generated ultimately by the covalent bond vibrations within the coupled transcriptosome-degradosome complexes [S. Ji, 1974, vide infra].

Appendix I

(A short talk presented at the 104th Statistical Mechanics Conference, 12/19-21, Rutgers University, Piscataway, N.J., *http://www.math.rutgers.edu/events/smm/*)

Decoding pathway-specific RNA waves of budding yeast undergoing glucose-galactose shift – the sounds of cell language. Lindsey Sperzel and Sungchul Ji, Ernest Mario School of Pharmacy, Rutgers University, Piscataway, N.J. 08855 sji@rci.rutgers.edu

DNA microarrays allow cell biologists to measure time-dependent changes in the intracellular levels (also called "gene expression profiles," "RNA trajectories," "RNA concentration waves," or just "RNA waves") of thousands of RNA molecules simultaneously. J. Garcia-Martinez et al. (Mol Cell 15, 303–313 (2004)) measured the time-course of the intracellular levels of about 6000 RNA molecules in budding yeast at 0, 5, 120, 360, 450, and 850 min after glucose–galactose shift. Visual inspections indicated that the shapes of the RNA trajectories (or concentration waves) belonging to the glycol sis (22 RNAs) and oxidative phosphorylation (13 RNAs) pathways (the two pathways directly affected by the glucose–galactose shift) are generally opposite to each other and differ from those of the RNA waves belonging to the other pathways of which there are about 200. To make this visual impression more quantitative, we transformed about 1000 of the original (or primary) RNA trajectories into secondary RNA trajectories or waves by using the software ViDaExpert (Visualization of high-dimensional Data Expert) developed by Zinovyev and Gorban in 2000 (http://bioinfo-out.curie.fr/projects/vidaexpert/). Our original data can be represented as a cluster of 1000 points in the 6-dimensional RNA trajectory space, each point representing the shape of one RNA trajectory or wave. ViDaExpert finds an optimal 2-dimensional "principal grid" that has the property of being as close to all the points in the 6-dimensional RNA trajectory space as possible and associates each RNA trajectory with one of the n^2 nodes of the principal grid that is closest to it, where n is the linear dimension of the principal grid. By plotting the number of RNA trajectories associated with the n^th node against n (the node number or the node address), it is possible to construct a secondary RNA wave or ribonic spectrum, "ribon" indicating an RNA trajectory. Since the topology of

the principal grid can be adjusted by changing the stretching coefficient λ, and the bending coefficient μ, it is possible to generate an indefinitely large number of secondary RNA waves or spectra from a given set of N points in the 6-dimensional RNA trajectory space. In the present case, N = 1000, which divides into about 50 distinct subclusters, each subcluster associated with one metabolic pathway. We have analyzed a total of 13 metabolic pathways using ViDaExpert with eight sets of parameters, n, λ, and μ, thereby generating eight different secondary RNA waves per pathway, from which the "average RNA wave", or the "average ribonic spectrum", can be calculated for each metabolic pathway by averaging the number of RNA trajectories mapping onto a given node number. The average RNA waves or ribonic spectra so obtained exhibited three distinct regions, denoted as A (comprising node numbers from 1 to 20), B (from 100 to 120), and C (from 210 to 230), with the following properties:

(i) The average RNA waves or ribonic spectra of the glycolysis and oxidative phosphorylation pathways have a low peak in Region B, the ratio of this peak to the next largest peak in each spectrum being 0.20–0.45, small compared to the corresponding ratio of 0.93 (with the standard deviation of 0.163 and the coefficient of variation of 17.5%) for 10 other metabolic pathways (i.e., secretion, protein folding, chromatin structure, cytoskeleton, protein glycosylation, transcription, transport, vacuole, sterol metabolism, and protein degradation).

(ii) The average ribonic spectrum of the glycolytic pathway has a major peak in Region C, that of the oxidative phosphorylation pathway has a major peak in Region A, and those of all the other pathways (except that of transport) has major peaks in Region B. In order to account for these observations, we postulate (1) that the shape of an RNA trajectory is determined by two opposing processes transcription catalyzed by a transcritosome and transcript degradation catalyzed by a "degradosome" (a term borrowed from bacteriology), (2) that there exists at least one pair of transcriptosome and degradosome for each metabolic pathway that are functionally coupled to act as a unit which is identified with the "metabolon" (Srere 1987), the "hyperstructure" (Norris et al. 1999), or the SOWAWN (Self-Organizing-Whenever-And-Wherever-Needed) machines (Ji 2011), and (3) that a pathway-specific metabolon can exist in at least three distinct states the (+)-, (−)-, or (0)-states, effectuating, respectively, an increase, a decrease, or a steady state in the intracellular levels of RNA molecules belonging to a metabolic pathway. Since all of the metabolic pathways examined so far obey the blackbody (or Planck) radiation equation (Ji 2011; Ji and So 2009, 2010) and since the single-molecule enzymic activity data of cholesterol oxidase also obey the same radiation equation (which is interpreted as an evidence that a thermal activation step is implicated in single-molecule enzymic catalysis) (Ji 2008, 2011), it is here suggested that the pathway-specific metabolons are thermally activated to occupy one of the three states, i.e., (+)-, (−)-, and (0)-states, for varying time periods of time, thereby producing pathway-specific average RNA waves with major peaks in

Regions A, B, or C in the ribonic spectra. Finally, the possibility suggests itself that these RNA waves can act as the sounds of cell language whose design features were found to be isomorphic with those of human language (Ji 1997, 1999).

References

Ji, S.: Isomorphism between cell and human languages: molecular biological, bioinformatics and linguistic implications. BioSystems **44**, 17–39 (1997)

Ji, S.: The linguistics of DNA: words, sentences, grammar, phonetics, and semantics. Ann. NY. Acad. Sci. **870**, 411–417 (1999)

Ji, S.: Modeling the single-molecule enzyme kinetics of cholesterol oxidase based on Planck's radiation formula and the principle of enthalpy-entropy compensation. In: Short Talk Abstracts, The 100th Statistical Mechanics Conference, Rutgers University, Piscataway, 13–16 Dec 2008

Ji, S.: Molecular Theory of the Living Cell: concepts, Molecular Mechanisms, and Biomedical Applications. Springer, New York (to appear) (2011)

Ji, S., So, K.: The universal law of thermal transitions applicable to blackbody radiation, single-molecule enzymology and whole-cell metabolism. In: Abstract B1, the 102nd Statistical Mechanics Conference, Rutgers University, Piscataway, 13–15 Dec 2009

Ji, S., So, K.: This conference (2010)

Norris, V., et al.: Hypothesis: hyperstructures regulate bacterial structure and the cell cycle. Biochimie **81**, 915–920 (1999)

Srere, P.A.: Complexes of sequential metabolic enzymes. Ann. Rev. Biochem. **56**, 89–124 (1987)

Appendix J

(A short talk presented at the 104th Statistical Mechanics Conference, 12/19-21, Rutgers University, Piscataway, N.J., *http://www.math.rutgers.edu/events/smm/*)

Blackbody radiation law-based estimation of the coupling constants between transcriptosomes and degradosomes in budding yeast. Weronika Szafran and Sungchul Ji, Ernest Mario School of Pharmacy, Rutgers University, Piscataway, N.J. 08855 sji@rci.rutgers.edu

When DNA microarrays are used to measure RNA levels (also called transcript levels or TLs) in budding yeast at 0, 5, 120, 360, 450 and 850 min after switching glucose to galactose, most of the over 6000 different kinds of RNA molecules undergo a decrease in their concentrations during the first 2–3 h (due to lack of ATP) followed by an increase toward the control levels after this time period when the enzymes needed to metabolize galactose to generate ATP are induced (Garcia-Martinez et al. 2004; Ji et al. 2009). We have investigated the time course of TLs (to be referred to as RNA trajectories or RNA waves) of about 300 RNA molecules belonging to 15 metabolic pathways. These trajectories can be mapped onto a cluster of 300 points in a 6-dimensional RNA concentration space. The similarity between any pair of RNA trajectories can be calculated as the Euclidean distance between two points in the concentration space. The following observations have been made: (i) Most (70–90%) of the distances between the trajectories of all possible RNA pairs belonging to a given metabolic pathway obey the blackbody radiation-like equation (BRE), i.e., $y = (a/(Ax + B)^5)/(\exp^{b/(Ax + B)} - 1)$, where x is distances between RNA trajectories, y is the frequency of observing different distance classes, and a, b, A and B are constants (Ji and So 2009, 2010). (ii) When RNA pairs are selected from two different metabolic pathways (rather than from within one pathway), the distances between the inter-pathway RNA pairs no longer satisfy BRE but obey instead the Gaussian distribution law (Ji 2010), indicating that most of the intra-pathway RNA trajectories are mutually correlated (or mechanistically coupled) with one another but the inter-pathway trajectory pairs are not. (3) Not all the distances between intra-pathway RNA pairs obey BRE. The percentage of the intra-pathway RNA pairs that satisfy BRE (which is defined

as the "coupling constant" between a transcriptosome and its "conjugate" degradosome for the reason explained below) can be computed from the "frequency versus RNA pair distance plot" based on the formula, [1−(Number of RNA pairs not obeying BRE)] × 100/(Total number of RNA pairs). The following "coupling constants" have been obtained for the three metabolic pathways examined so far: Glycolysis = 85.7%; cell wall biogenesis = 79.3%; protein degradation = 64.2%. To provide a reasonably coherent explanation for the varied "coupling constants" observed above, we find it necessary to postulate that: (a) Transcriptosomes catalyzing transcription in the interior of the nucleus (Lamond and Spector 2000) and degradosomes catalyzing transcript degradation in the cytosol (Carpousis 2002) are co-regulated by the yeast cell through as-yet-unknown mechanisms. (b) Each metabolic pathway possesses its own transcriptosome and degradosome, the combination of which can be viewed as an example of the metabolon (Srere 1987), the hyperstructure (Norris et al. 1999), or the SOWAWN (Self-Organizing-Whenever-And-Wherever-Needed) machine (Ji 2011). (c) Pathway-specific metabolons can exist in at least three internal states designated as the (+)-, (0)- and (−)-states which, respectively, catalyze the increase in, the steady state of, and the decrease in the levels of RNA molecules belonging to a given metabolic pathway. (d) The transcriptosome and degradosome constituting a pathway-specific metabolon are mechanistically coupled, and the degree of coupling is given by "the coupling constant" computed from the "frequency versus RNA pair distance plot" (see above). The coupling between transcriptosomes and degradosomes is postulated to depend on thermal co-activation of these enzyme complexes in agreement with the fact that the distances between the intra-pathway RNA pairs obey BRE, which is considered to be the Universal Law of Thermal Transitions (or Activations) (Ji and So 2009). Postulate (a) is necessary to explain the fact that the kinetics of TLs (i.e., RNA trajectories or waves) is not random but exhibit regularities as evident in the correlations found among RNA trajectories (see Observations (1) and (2)). Postulate (b) is required to account for the fact that average RNA trajectories belonging to two different metabolic pathways (e.g., glycolysis and oxidative phoshorylation) can exhibit opposite patterns (see Observation (2) and (Sperzel and Ji 2010)). Postulate (c) is mandated by the fact that the kinetics of TLs shows three distinct patterns increasing (+), decreasing (−) or remaining constant (0), which supports the assumption that the metabolon catalyzing the coupled transcription and degradation of RNAs of a metabolic pathway exists in these three states. Since TLs can increase or decrease with m different rates (where m can range from a few to dozens), it would be necessary to further assume that each of the (+)- and (−)-states of a metabolon consists of m substates, just as each electronic energy level in an atom consists of multiple vibrational levels. Postulate (d) highlights the fundamental role of thermal fluctuations (or Brownian motions) in the mechanism of co-regulating two or more enzymic complexes for the purpose of effectuating functionally significant whole-cell metabolism. If this postulate is correct, we can conclude that thermal fluctuations are fundamental not only for blackbody radiation and single-molecule enzymology (Ji and So 2009; Ji 2011) but also for co-regulating two or more enzymic complexes in whole-cell metabolism.

References

Carpousis, A.J.: The escherichia coli RNA degradosome: structure, function and relationship to other ribonucleolytic multienzyme complexes. Biochem. Soc. Trans. **30**, 150–156 (2002)

Garcia-Martinez, J., Aaranda, A., Perez-Ortin, J.E.: Genomic run-on evaluates transcription rates for all yeast genes and identifies gene regulatory mechanisms. Mol. Cell **15**, 303–313 (2004)

Ji, S.: Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications. Springer, New York (to appear) (2011)

Ji, S., Chaovalitwongse, A., Fefferman, N., Yoo, W., Perez-Ortin, J.E.: Mechanism-based clustering of genome-wide mRNA levels: roles of transcription and transcript-degradation rates. In: Butenko, S., Chaovalitwongse, A., Pardalos, P. (eds.) Clustering Challenges in Biological Networks, pp. 237–255. World Scientific Publishing Co., Singapore (2009)

Ji, S., So, K.: The universal law of thermal transitions applicable to blackbody radiation, single-molecule enzymology and whole-cell metabolism. In: Abstract B1, the 102nd Statistical Mechanics Conference, Rutgers University, Piscataway, 13–15 Dec 2009

Ji S., So, K.: Distances between RNA trajectories are distributed according to Planck's radiation law or the Gaussian law depending on their metabolic functions, (short talk, this meeting). (2010)

Lamond, A.I., Spector, D.L.: Nuclear speckles: a model for nuclear organelles. Nat. Rev. **4**, 605–612 (2000)

Norris, V., et al.: Hypothesis: hyperstructures regulate bacterial structure and the cell cycle. Biochimie **81**, 915–920 (1999)

Sperzel, L., Ji, S.: Decoding pathway-specific RNA waves of budding yeast undergoing glucose–galactose shift-the sounds of cell language, (short talk, this meeting). (2010)

Srere, P.A.: Complexes of sequential metabolic enzymes. Ann. Rev. Biochem. **56**, 89–124 (1987)

Appendix K

(The following is reproduced from a post that I wrote on August 11, 2005 for the NECSI, New England Complex Systems Institue, Boston, Mass.)

In a delightful little book entitled "Quantum Theory: A Very Short Introduction (Polkinghorne 2002)", the author compared his philosophy of quantum mechanics with that of Heisenberg:

<Heisenberg>
"In experiments about atomic events we have to do with things that are facts, with phenomena that are just as real as any phenomena in daily life. But the atoms or elementary particles are not as real; they form a world of potentialities rather than of things or facts."

<Polkinghorne>
"An electron does not all the time possess a definite position or a definite momentum, but rather it possesses the potentialities for exhibiting one or the other of these if a measurement turns the potentiality into an actuality. I would disagree with Heisenberg in thinking that this fact makes an electron "not as real" as a table or a chair. The electron simply enjoys a different kind of reality, appropriate to its nature. If we are to know things as they are, we must be prepared to know them as they actually are, on their own terms, so to speak."

I am going to apply to the above problem the principle of Peircean semiotics that all phenomena exhibit three basic elements – *Firstness* (quality, potentiality), *Secondness* (reaction, actuality, fact), and *Thirdness* (law, habit, representation, etc.). The result shown below not only accommodates both Heisenberg and Polkinghorne but also adds something new, a thirdness:

<a semiotics-based approach>
"Electrons and atoms (or any objects referred to by Herbert (1997) as 'quons') have three irreducible aspects: Quons as they really are (Firstness); qons as measured (Secondness); and quons as represented in signs or theorized (Thirdness)."

We can depict the content of this statement as shown in Fig. K.1.

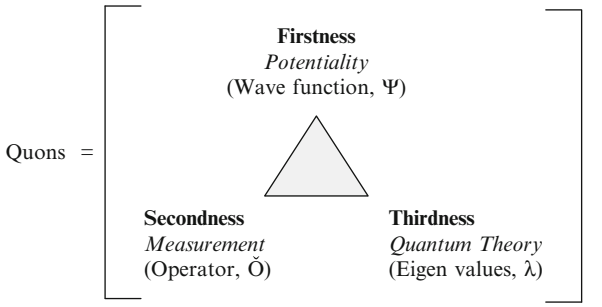


Fig. K.1 Semiotic-based metaphysics of quantum theory

The essence of Fig. K.1 is that quons are *real* entities whose complete description requires elucidating their three irreducible ontological aspects of Firstness, Secondness, and Thirdness as shown. The parentheses contain the relevant mathematical concepts. The large bracket symbolizes the irreducibility. Quons are *real* (i.e., they are as they are regardless of what we think of them), because all of the three vertices are *real*.

If the above analysis is right, it may be concluded that discussions on the metaphysics of quantum theory may benefit enormously from utilizing the semiotic framework enunciated by C. S. Peirce (1839–1914) over a century ago.

Appendix L

THE STATE UNIVERSITY OF NEW JERSEY
RUTGERS

Department of Pharmacology and Toxicology • College of Pharmacy
Busch Campus • Piscataway • New Jersey 08855-0789 • 201/932-3720

January 19, 1990

Dr. Chen-Ning Yang
The Einstein Professor and
Director
The Institute of Theoretical Physics
The State University of New York
at Stony Brook
Stony Brook, N.Y. 11794

Dear Professor Yang,

It is a great honor for me to write to you on a biological topic to which your non-Abelian gauge theory may have some interesting application.

I have been long admiring your theoretical work on nuclear forces, not as a physicist nor as a mathematician but as a physical organic chemist working in biology. Hence I do not possess the requisite mathematical knowledge to comprehend the varied technicalities of gauge theories, but over the last 7 years I have learned enough of the qualitative aspects of gauge theories and the fiber bundle theory that I have been able to perceive unexpected similarities between the strong force and what appears to be a new kind of force operating in the living cell. So the main objective of this letter is to describe the analogy between the strong force and what may be called the "cell force" and to elicit your comments on the proposal.

The analogy to be presented below was crystallized in my mind last night shortly after reading the following paragraph from your article published in 1977 (Ann. N. Y. Acad. Sci. 294:86-97);

" . . . The point here is that for electromagnetism, the gauge principle determines, all at once, the way any particle of charge qe, a conserved quantity, serves as a source of the electromagnetic field. Because the isotopic spin I is also conserved, a natural question was, "Does there exist a generalized gauge principle that determines the way in which I serves as the source of a new field?"

Another motivation for an attempt at generalization is the obervation that the conservation of I implies that the proton and the neutron are similar. Which to call a proton or, indeed, which superposition of the two to call a proton, is a convention that one can select arbitrarily (if the electromagnetic interaction is switched off). If one requires this freedom of

(Dr. C. N. Yang, 1/19/90, page 2)

choice to be independent for observers at different space-time points, that is, if one requires localized freedom of choice, one is led to a generalization of the gauge principle."

Table 1 summarizes the strong force - cell force analogy. The key hints suggesting a possible "symmetry" between the strong force and the "cell force" are as follows; (1) Proton and neutron are two states of the same entity, a nucleon = an identical cell can be judged as fit (living) or unfit (dead), depending on the nature of the environment under which it exists (i.e. proton/neutron duality = life/death duality), (2) gluons = "conformons" (defined in footnote 7)), and (3) 3 quarks to a nucleon = 3 "polarizied photons" (explained in footnote 8) to a conformon. Please keep these in mind as you go through the table and the footnotes provided.

Table 1. Toward constructing a gauge field theory of the force operating inside the living cell ("cell force") based on an analogy to the Yang-Mills theory of the strong force.

	Parameter	Strong force	"Cell force"
1	System	Nucleus	Cell
2	Particles	Nucleons	Biopolymers[1]
3	Conserved quantity	Isotopic spin (I)	"Functional spin" (F)[2]
4	Two states	Proton & neutron	Fit & unfit[3]
5	Force under which particles are distinguishable	Electromagnetic	Cell force[4]
6	Force under which particles appear similar	Strong force	Electromagnetic[5]

(Dr. C. N. Yang, 1/19/90, page 3)

(Table 1 continued)

	Parameter	Strong force	"Cell force"
7	Subparticle structure	3 Quarks per nucleon	10^2 - 10^{10} Monomers per biopolymer[6]
8	Bosons	Gluons	"Conformons"[7]
9	Boson substructure	Glueballs (?)	3 Polarized photons per conformons[8]
10	Energy requirement for force	None	Absolutely essential[9]
11	Domain of applicability	Space	Time[10]
12	Function	Stability of spatial structures	Stability of spatio-temporal structures[11]

[1]Proteins, RNA and DNA; molecular weights = 10^4 - 10^6 Daltons; linear size range = 10^{-9} m - 10^{-6} m; in constant thermal fluctuations inside the cell, interacting physically and chemically with small molecular species, e.g. H_2O, metal ions, organic chemicals, cofactors, photons, etc.

[2]The chemical or physical processes catalyzed by biopolymers may (fit) or may not (unfit) contribute to the survival of the cell under a given environmental condition at a given space-time point.

[3]I was tempted to call the two functional spin states "live" and "dead", the two fundamental states of living things. But I decided to use the terms, "fit" and "unfit", because they seem to

(Dr. C. N. Yang, 1/19/90/90, page 4)

be applicable more generally, from biopolymers to cells, to organisms to species. It would be difficult to talk about life or death of individual biopolymers; it is reasonable to define the cell as the simplest living, and hence "diable", things in nature. The set of fit and unfit states should include the set of dead and live states as a subset.

[4]"The cell force" is thought to operate in the time domain in the sense that the effect of cell force can be observed only along the time axis and only secondarily along the spatial axes. For example, it is impossible to tell whether a cell is alive (fit) or dead (unfit) unless you allow it to interact with its environment for times that are at least as long as the time it takes to measure the effect of the cell-environmental interactions and evaluate the outcomes (J. Postgate, New Scientists, May 20, 1989, pp. 43-47). It was interesting to learn just the other day that physics is also endowed with concepts whose domain of applicability is limited: (1) the inapplicability of the concept of trajectory to atomic physics, (2) the temperature concept valid only for systems consisting of a large number of particles, (3) the impossibility of defining the frequency of some vibrational process at a given instant of time, and (4) the impossibility of defining the velocity of a quantum particle as the differential quotient dr/dt (A. S. Davydov, "Quantum Mechanics", NEO Press, Ann Arobor, 1966).

[5]I think one of the most fundamental observations in biology is that a single point mutation of a gene (i.e. substitution of one nucleotide with another in a gene consisting of hundreds of nucleotides strung together in a linear sequence) can (but not always) lead to a complete loss of function ("fit-to-unfit state transition") of biopolymers (e.g. enzyme inhibition) , cells (e.g. cellular proliferation), and organisms (e.g. cancer). From the electromagnetic force point of view (i.e. quantum mechanics and statistical mechanics) the original and point-mutated entities are not much more different than protons and neutrons are from each other.

[6]The particles interacting through the "cell force" are much more complex in their internal structure than the strong froce particles, by a factor of 10^2 (for proteins) to 10^{10} (for human DNA) in terms of the number of monomers constituting the particles. This is perhaps not too surprising in view of the fact that the cell force particles must transduce both free energy and information to keep the cell alive (i.e. act as "molecular machines"), while the strong force particles are essentially equilibrium structures.

(Dr. C. N. Yang, 1/19/90, page 5)

7Conformons are defined operationally as "conformational strains of biopolymers that store free energy (due to mechanical strains) and genetic information (due to the linear sequence of the local site of biopolymer where conformons are self-trapped)". Conformons are postulated to provide the thermodynamic force and the information necessary and sufficient to drive gene-directed symmetry-breakings in space and time inside the cell (S. Ji, J. theoret. Biol. 116:399-426 (1985); a copy enclosed). During the past 10 years, it has been established that conformons are related to solitons (A. C. Scott, Comments Mol. Cell. Biophys. 3(1):15-37 (1985); R. V. Polozov and L. V. Yakushevich, J. theoret. Biol. 130:423-430 (1988), both enclosed). It is clear to me that conformons can drive either spatial symmetry breakings (thus acting similarly to solitons) or time symmetry breakings (in which case they may be compared to instantons) (please see Table 1 of my 1/12/1990 letter to Dr. Scott, enclosed). It has been estimated that one conformon can carry maximally 5 - 10 Kcal/N , where N is the Avogadro's number, and 40 - 80 bits of Shannon information (S. Ji, "The Bhopalator - A Molecular Model of the Living Cell; New Developments", in "Physics of Living Matter", R. K. Mishra, ed., Kluwer Academic Publishers, The Netherlands, 1990, preprint enclosed. Pp. 16-21.) Given a set of conformons, all cellular behaviors can be coherently accounted for (S. Ji, "Biocybernetics: A Machine Theory of Biology", in "Molecular Theories of Cell Life and Death", S. Ji, ed., The Rutgers University Press, 1990, in preparation). The detailed quantum mechanical mechanism underlying conformon generation and utilization has not been completely worked out, although several good suggestions have been made (D. E. Green and S. Ji, "The Molecular Basis for Electron Transport", J. Schultz and B. F. Cameron, eds., Academic Press, New York, 1972, pp. 1-44; S. Ji, Ann. N. Y. Acad. Sci. 227:211-226 (1974); S. Ji, "Structure and Function of Biomembranes", K. Yagi, ed., Japan Scientific Societies Press, Tokyo, 1979, pp.25-37; M. V. Volkenstein, J. theoret. Biol. 34:193-195 (1972); M. V. Volkenstein, et al., Mol. Biol. (USSR) 6(3):431-439 (1972), an English translation available from Consultants Bureau, Plenum Publishing Corp., 227 W. 17th Street, New York, N.Y. 10011; A. S. Davydov, J. theoret. Biol. 38:559-569 (1973); M. V. Volkenstein, J. theoret. Biol. 89:45-51 (1981); K. V. Shaitan and A. B. Rubin, Mol. Biol. (USSR) 16(5):1004-1018 (1982);A. C. Scott, Comments Mol. Cell. Biophys. 3(1):15-37 (1985)). Recent rapid advances in research on "vibronic interactions" (i.e. the mixing of different electronic states by nuclear displacements) in molecules and condensed matter may further aid us in rigorously characterizing the quantum statistical mechanical processes underlying conformon actions (I. B. Bersuker and V. Z. Polinger, "Vibronic Interactions in Molecules and Crystals", Springer-Verlag, Berlin, 1989; H. Umezawa, H. Matsumoto, and M. Tachiki, "Thermo Field Dynamics and Condensed States", North-Holand, Amsterdam, 1982).

(Dr. C. N. Yang, 1/19/90, page 6)

[8]Each conformon is thought to be composed of a set of three left- or right-polarized photons; since three such photons are postulated to form one conformon (similar to the stoichiometry of three quarks per nucleon), the eixistence of eight distinct kinds of conformons can be predicted. The term "photons" are used in a very general sense of the boson that mediates all electroweak and electromagnetic interactions inside and outside atoms and molecules. It may turn out that these "polarized photons" result from "vibronic excitations" of enzyme-substrate complexes whose equilibrium structures are deformed during the chemical reactions or substrate bindings that go on in them, as suggested in my 1/17/1990 letter to Dr. G. Welch (enclosed). No experimental evidence is known to me at this time that directly supports the concept of photons undergoing a boson condensation in enzyme-substrate complexes in this manner. However, I would not be surprised at all if there are already experimental observations reported in the literature that can be interpreted in this way. The set of eight different kinds of conformons predicted from the symmetry of the conformon structure divides into two subsets, L-conformons and D-conformons, which are mirror images to each other (see Table 1, my 1/17/90 letter to G. Welch). These "chiral" conformons therefore have the capacity to exert "chiral forces" on all enzymic reactions and enzyme-mediated physical processes performed by the cell. This may be a highly relevant result, which may provide a quantum mechanical explanation for (1) the well-known predominance of the L-amino acids in proteins and D-sugars in DNA (R. A. Hegstrom and D. K. Kondepudi, "The Handedness of the Universe", Scientific American 262(1):108-115 (1990)), and (2) the "phase wave" phenomena in unicellular organisms. The latter refers to the observations in the cell biology literature which seem to indicate that cells utilize three "channels of communication" in interacting with their environment - the amplitude, frequency and phase angle of various intracellular waves of H^+, Ca^{++}, ATP, ADP, cAMP, and cytoskeletal contractions (T. Ueda et al., Experimental Cell Research 162:486-494 (1986)). Of particular interest is the finding that certain unicellular organisms (e.g. Physarum plasmodium) utilize the phase angle to communicate to its appropriate intracellular metabolic systems the presence of useful vs. harmful chemicals in its environment, leading to selective directional motions toward useful chemicals or away from harmful ones (Y. Kobatake, T. Ueda, K. Matsumoto, "Perception in an Oscillating Amoeboid Cell", a lecture presented at the Third International Seminar on the Living State, Shillong, India, November, 1986; abstract available from me upon request). All these spatial and spatiotemporal symmetry breakings revealed by cell structure and function can be taken to indicate that the "fundamental" motive force in the cell is "chiral". To the best of my knowledge, the conformon theory of enzymic catalysis is the only theory that has the chirality built into its very foundation. Thinking retrospectively, the chiral behaviors of

(Dr. C. N. Yang, 1/19/90, page 7)

cells may provide a strong evidence for the chiral conformon structure proposed above, since three is the minimum number of two-state entities that can be assembled in 3-space to produce chirality.

[9]Free energy input into biopolymers is thought to be essential for generating conformons, although thermal fluctuations may produce "virtual conformons" which precede and "allow" the free energy input mechanisms such as substrate binding and chemical reactions to proceed with speeds fast enough to avoid violating the second law of thermodynamics (S. Ji, 1985, p.411).

[10]It appears to me that most of the forces discussed in physics are associated with spatial changes with time, the term "forces" being here defined generally as "something that influences events in space-time, with its degree of effectiveness either decreasing or increasing along the spatial or time axes, or both). In contrast, biology is replete with examples of another kind of forces - those influencing the timing of events independent of spatial locations ("non-local forces"?). For example, one fertilized egg of Homo sapiens can undergo more or less the same series of precisely timed cell divisions, hundreds of billions of times, to become a fully grown organism, regardless of when or where the initiation of the cell division began; monozygotic twins living in different parts of the world often develop the same kind of disease more or less synchronously and die within one week or so of each other. Such a phenomenon is called "contemporaneity" and has led L. Gedda in Rome to develop the concept of the "4-dimensional gene", implying that "timing" information is encoded in DNA in addition to structural information (see "Chronogenetics", L. Gedda, et al., eds. Charles C. Thomas, Springfield, 1978). In fact all enzymes can be viewed as what I called "molecular time-symmetry breakers" or gene-directed timing devices driven by Gibbs free energy (S. Ji, "Energy and Negentropy in Enzymic Catalysis", Ann. N. Y. Acad. Sci. 227:419-437 (1974); S. Ji, 1989). Under thermal conditions of living systems, time and space are linked through the fluctuation-dissipation theorem, hence timing information can drive spatial symmetry breakings in the cell. Can it be that the cell force is a time-dependent force in contrast to other forces in nature which are all distance-dependent? Or is it possible that some of the fundamental forces also exhibit the properties of time-dependent forces? Is it possible that the non-local nature of the electromagnetic potential in the Bohm-Aharonov experiment that you discussed in Physics Today, June, 1980, a manifestation of the time-dependent component of the electromagnetic force?

[11]Just as the spatial structures of the fundamental particles are

(Dr. C. N. Yang, 1/22/90, page 8)

maintained by a set of fundamental forces (perhaps we can call these the "distence-dependent" forces), is it possible that the spatiotemporal structures of the fundamental machines (namely cells) are maintained by a set of a new kind of "fundamental" forces that act along the positive time axis (i.e. the "time-dependent forces")? Or are the latter forces derivable from the former? In either case, it may be necessary to postulate the existence of the time-dependent forces in order to provide logically coherent explanations for living processes, including the workings of our brain. The existence of the two fundamentally distinct kinds of forces may resolve the long-standing debate about the time-reversal invariant laws of nature being responsible for irreversible processes. A simple answer to this question may be that all irreversible proceeses are primarily driven by time-dependent forces and the participation of distence-dependent forces in irreversible processes may be only circumstantial. The time-dependent forces act only along the positive time axis because their existence depends on spontaneous processes and all spontaneous processes occur along the positive time axis. The logical processes going on in our brain is driven by spontaneous free energy dissipation. To drive the human brain (without which no logical thinking would be possible and hence no physics nor biology) without dissipation of free energy would be tantamount to violating at least the second, if not both the second and the first, laws of thermodynamics. Therefore, it appears to me that the fundamental nature of irreversible processes may be intimately connected with the workings of our conciousness and the nature of the time-dependent forces.

Of the 12 items listed in Table 1, four things strike me as unusual; (1) the strong force can exist without input of energy into the atomic nuclei, while the cell force mediated by conformons cannot exist in the cell unless free energy is continuously supplied to the cell, (2) The number "3" is associated with fermions (quarks) in the strong force; while the same number is associated with the number of bosons (photons)in the "cell force", (3) the strong force acts in the spatial domain and is time-invariant, time going on in the postive direction, whereas the "cell force" acts in the time domain and is space-invariant, and (4) the "particles" that are held together by the "cell force" are immensely more complex in their internal structure than the particles connected by the strong force.

Actually all of these differences between the two forces make sense if we take into account the fact that the strong force maintains equilibrium structures, while the cell force maintains dynamic, "functional" structures, requiring a constant dissipation of free energy. In other words, these differences derive from the fact that nucleons are equilibrium structures,

(Dr. C. N. Yang, 1/22/90, page 9)

whereas bioploymers are "machines" designed by evolution to perform specific work performances which cannot be carried out without free energy dissipation. The work performance of biopolymers selected by evolution may be its ability to cause time symmetry breakings. Hence time-dependent forces cannot be exerted without biopolymers. According to Shannon it takes at least 0.693 kT joules of energy to transmit 1 bit of information (J. R. Pierce, "An Introduction to Information Theory", Dover, 1980, p. 192). Therefore it may be that at least this amount of free energy dissipation is needed to exert the minimum amount of time-dependent forces. The cell force may turn out to be one of the first, if not the first, time-dependent forces whose existence may be predicted by applying a non-Abelian gauge theory to a localized degree of freedom in the time domain.

Finally I would like to call your attention to Figure 1 in my 1/12/90 letter to Dr. A. Scott (enclosed), where I tried to represent the "functional spin" (also called the fitness vector in Scott's letter) as a tangent on the "behavior trajectory" in the fiber bundle space and compared it to the phase angle of the electromagnetic wave equation and the isotopic spin vector in your gauge field theory. It is my opinion that fiber bundle geometry will play an essential role in the study of all processes in nature that are driven by programs, whether genetic or man-made, namely machines. I believe that enzymes are the simplest physical machines in nature that cannot be further reduced without losing machine characterirstics - the ability to utilize free energy to execute programs. Therefore we may legitimately call enzymes as "fundamental machines", in analogy to fundamental particles in physics. The fiber bundle geometry seems to have the amazing ability to describe fundamental particles, fundamental machines, and complex machines such as the human brain. By applying the fiber bundle geometry to intracellular enzymic processes, I have derived what I called the "Biological Uncertainty Principle", which delimits the certainty with which we can carry out our measurements on biological processes (please refer to p. 13 of my letter to Scott).

As is evident in the above discussion, the Yang-Mills gauge theory has been instrumental in formulating our argument for the possibility that there may be a new force in the living cell that has not been recognized heretofore. This conclusion seems to me to be intuitively sound; just as the nuclear structure of atoms would fall apart without the strong force, so would the "functional structures" of the living cell without the cell force. Trying to understand the workings of the living cell with just the electromagnetic force alone would be akin to the physicists early this century trying to understand the stability of the nuclear structure of atoms without the concept of the

(Dr. C. N. Yang, 1/22/90, page 10)

strong force. What is very surprising to me and to many others, I am sure, is the possibility that the Yang-Mills theory which has been developed as a general theory of the fundamental forces in atomic physics may be found applicable to discovering new forces operating in dissipative structures in biology. Perhaps the reason for this unexpected potential is that the strong force and the cell force are not as unrelated to each other as might appear on the surface; because, without the strong force, there would no nuclei nor stable atoms to build the cell with; without the cell force, no cell nor brain can function to recognize the strong force. In this "anthropic" sense, therefore, both the strong force and the cell force may be said to be mutually dependent. We may now have recognized their proper relationship, largely due to your profound gauge theory of forces and the rich experimental information available in the biological literature, for which this country has made a major contribution.

Based on these qualitative considerations and encouraged by the unexpected fit noticed between the "cell force" and the strong force, I am tempted to venture my optimism that perhaps a Yang-Mills-tytpe gauge theory will be constructed in the near future that can be applied not only to all the fundamental forces operating in equilibrium structures but also to those operating in dissipative structures.

I would greatly appreciate any comments or suggestions you might have on any aspect of the material discussed above.

Thank you for your kind attention.

Sincerely yours,

Sungchul Ji

Sungchul Ji, Ph.D.

Associate Professor of
Pharmacology and Toxicology

池聖哲

(Dr. C. N. Yang, 1/22/90, page 11)

Encl. Letter to A. C. Scott (1/12/90)
Letter to G. R. Welch (1/17/90)
A. C. Scott reprint (Comm. Mol. Cell. Biophys.)
S. Ji reprint (J. theoret. Biol.)
S. Ji preprint (The Bhopalator, R. K. Mishra, ed.)
Polozov and Yakushevich reprint (J. theoret. Biol.)

C.c. Dr. R. Welch
Dr. A. Scott
Dr. D. Kondepudi
Dr. M. Y. Han
Dr. B. Oslen
Dr. I. Prigogine
Dr. P. W. Anderson
Dr. M. Eigen
Dr. R. Mishra
Dr. R. Snyder
Dr. Y. Kobatake
Dr. J. Colaizzi
Dr. B. Goldstein
Dr. A. Pond
Dr. P. Leath
Dr. G. Farrar
Dr. A. Robbins

Appendix M

(A short talk presented at the 106th Statistical Mechanics Conference, Rutgers University, Piscataway, N.J. 08855, December 18–20, 2011)

A category-theoretical framework for integrating *physics*, *biology*, and *informatics* based on complementarity and supplementarity principles. Sungchul Ji, Ernest Mario School of Pharmacy, Rutgers University, Piscataway, N.J. 08855. sji@rci.rutgers.edu

N. Bohr (1958) introduced into physics the principles of *complementarity* and *supplementarity* in the early decades of the twentieth century, which can be characterized as follows (Ji 2012): Supplementarity is an additive principle, i.e., A + B = C; complementarity is nonadditive, i.e., A^B = C, where the symbol ^ indicates that A and B are mutually exclusive but complementary manifestations or properties of C. The purpose of this presentation is to utilize these two principles and the category theory (Lawvere and Schanuel 2009; Hillman 1997; Rosen 1991) to integrate *physics* (i.e., energy and matter), *informatics* (i.e., information and knowledge, as summarized by Shannon and Weaver (1949), Polanyi (1958/62), Burgin (2004, 2011), and Stenmark (2001)), and *biology* (i.e., living systems and processes as summarized in Ji (2012)) in a logically consistent manner.

According to Burgin (2004), the relation between *information* and *knowledge* is akin to the relation between *energy* and *matter*. Since *energy* and *matter* are related to each other through $E = mc^2$ which is a supplementary relation, and, since the combination of *energy* and *matter* is conserved according to the first law of thermodynamics, it is natural to combine these two terms into one word, *matter-energy* or *mattergy*. Analogously, it will be found convenient to refer to the combination of *information* and *knowledge* as "information-knowledge" or "infoknowledge" more briefly.

As a theoretical cell biologist interested in elucidating the molecular mechanisms underlying living processes, I was led to conclude in 1991 (Ji 1991) that *information* and *energy* are *complementary* aspects of a third entity which I elected to call *gnergy*, a term coined by combining the Greek roots "gn-" (from

gnosis) meaning "knowledge" and "-ergy" (from *ergon*) meaning "to work." In addition, it was postulated that *gnergy* is the organizing principle of our Universe serving as the necessary and sufficient condition for all organizations, including life. More recently (Ji 2012), it was hypothesized that the relation between *information* and *life* is akin to that between *energy* and *matter* (independently of Burgin's suggested analogy between the information-knowledge relation and the energy-matter relation (Burgin 2004)), leading to the coining of another neologism, "liformation," in analogy to mattergy. Thus the *energy-matter relation* (see Scheme 1 below) has given rise to two hybrid terms, *infoknowledge* (based on Burgin's suggestion in (2004)) and *liformation* described in Ji (2012):

1. f: Matter → Energy (to be called the "mattergy category"; a category is defined below)
2. g: Knowledge → Information (to be called the "infoknowledge category")
3. h: Life → Information (to be called the "liformation category")

Based on Schemes (1) and (3), it was suggested in Ji (2012) that

Just as matter can be viewed as a highly condensed form of energy, so life may be considered as a highly condensed form of information. (4)

A category C is a mapping often represented as f: A → B, where A and B are the objects and f is the morphism (also called "transformation" or "operator") of C. We can recognize at least three hierarchical levels of categories:

Class I category ⇔ nodes = objects, arrows = morphisms
Class II category ⇔ nodes = categories, arrows = functors
Class III category ⇔ nodes = functors, arrows = natural transformations

Thus Schemes (1) through (3) are examples of the Class I category, one of the common properties of which being that they obey the *principle of supplementarity*. As examples of Class II categories obeying the *principle of complementarity*, the following schemes are suggested:

(a) Mattergy ← Gnergy → Liformation (with the first arrow being k and the second arrow m), and
(b) Mattergy ← Infoknowledge → Liformation (with the first arrow denoted as n and the second arrow as p).

The Class II category in (b) is new and reflects the postulate that mattergy and liformation are the complementary aspects of infoknowledge. The possible meanings of the arrows (i.e., functors) are as follows: k = cosmogenesis; m = the origin of life; n = the inverse of n^{-1} which reflects the physical basis of all information and knowledge processes; and p = the inverse of p^{-1} which reflects the essentiality of life for the production and utilization of information based on knowledge and data.

Since the Class II categories described in (a) and (b) above share two nodes, i.e., mattergy and liformation, they may be combined to form a Class III category:

Gnergy ⟶ Mattergy ⟶ Infoknowledge ⟶ Liformation ⟶ Gnergy

with the following arrows/functors in the order of appearance; i.e., k, n^{-1}, p, and m^{-1}.

In constructing this category, the arrows are organized in such a way that the completed network becomes cyclic, i.e., Gnergy serves as both the beginning and the end points of the cycle. The cyclic arrangement of the four arrows would follow logically if the natural transformation shown in Eq. M.1 holds:

$$n^{-1} \circ k = p^{-1} \circ m \tag{M.1}$$

The left-hand side of Eq. 5 can be identified with the N (natural) system and the right-hand side with the F (formal) system of Rosen (1991). Thus Class III category described above is an *isomorphic category* and hence the N and F systems commute. One interpretation of this isomorphic *natural transformation*, Eq. M.1, is that our Universe is closed to information and knowledge and that our Universe knows itself through *Homo sapiens*. A similar conclusion was obtained in 1991 based on applying the principle of self-organization (i.e., gnergy) to our Universe (Ji 1991). If these conjectures prove to be correct in the future, the Class III category presented here for the first time may be justifiably called the *category theory of everything* (cTOE).

Two applications of cTOE are briefly described below:

1. K. Popper (1978) divides our universe into "three interacting sub-universes" which he calls world 1 (the physical world), world 2 (the mental and psychological world), and world 3 (the world of the products of human mind, including "languages; tales and stories and religious myths; scientific conjectures or theories, and mathematical constructions; songs and symphonies; paintings and sculptures. But also aeroplanes and airports and other feats of engineering" (Popper 1978). cTOE suggests the following *internal structures* of Popper's worlds:

   World 1 = Gnergy-Mattergy
   World 2 = Mattergy-Liformation
   World 3 = Liformation-Infoknowledge

2. According to cTOE, the mattergy category (to which *energy* belongs) and the liformation category (to which *information* belongs) are mutually exclusive and complementary aspects of gnergy and hence it would be impossible to convert *information* to *energy* in the same sense that *matter* is converted into *energy*. The correct relation between *information* and *energy* may be derived from Shannon's channel capacity equation (Shannon and Weaver 1949), according to which no information can be transmitted nor any control exerted without requisite dissipation of free energy. Therefore, the experiments recently performed by Toyabe et al. (and many similar experiments reported in the literature during the past couple of decades) may not demonstrate any *information-to-energy conversion* but rather the *energy requirement for controlling molecular events* as entailed by the channel capacity equation.

References

Bohr, N.: Quantum physics and philosophy – causality and complementarity. In: Klibansky, R. (ed.) Philosophy in the Mid-Century. La Nouva Editrice, Florence (1958)

Ji, S.: Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications. Springer, New York, to appear (2012)

Lawvere, F.W., Schanuel, S.H.: Conceptual Mathematics, A First Introduction to Categories, 2nd edn., Cambridge University Press, Cambridge (2009)

Hillman, C.: A Categorical Primer, October 17, (1997), downloaded from Google on 7 Nov, 2011

Rosen, R.: Life Itself. Columbia University Press, New York (1991)

Shannon, C.E., Weaver, W.: The Mathematical Theory of Communication. University of Illinois, Urbana (1949)

Plolanyi, M.: Personal Knowledge, Corrected edition, Routledge, London (1958/62)

Burgin, M.: Data, Information, and Knowledge, Information, vol. 7, No. 1, pp. 47–57 (2004)

Burgin, M.: Theory of Information: Fundamentality, Diversity and Unification. World Scientific, Singapore (2011)

Stenmark, D.: The Relationship between Information and Knowledge. In: Proceedings of IRIS 24, Ulvik, Norway (2001)

Ji, S.: Biocybernetics: a machine theory of biology. In: Ji, S. (ed.) Molecular Theories of Cell Life and Death, pp. 1–237 Rutgers University Press, New Brunswick (1991)

Popper, K.: Three Worlds, the Tanner Lecture of Human Values, delivered at The University of Michigan, April 7 (1978)

Toyabe, S., Sagawa, T., Ueda, M., Muneyuki, E., Sano, M.: Experimental demonstration of information-to-energy conversion and validation of the generalized Jarzynski equality. Nat. Phys. **6**, 988–992 (2010)

Appendix N

Arbitrariness of signs **and** ***the cell force*** *as the complementary aspects of cell language*.

Sungchul Ji, Department of Pharmacology and Toxicology, Ernest Mario School of Pharmacy, Rutgers University, Piscataway, N.J. 08855 sji@rci.rutgers.edu.

Cells communicate with one another using a molecular language which is isomorphic with the human language Ji (1997). Communication is synonymous with information transmission in space and time, and Shannon's channel capacity equation indicates that no communication is possible without dissipating free energy. Thus *information* and *energy* are the two indispensible ingredients for communication both within and between cells. The analysis of the whole-cell RNA metabolic data measured with DNA microarrays from budding yeast undergoing glucose-galactose shift Garcia-Martinez et al. (2004) has revealed two major findings: (i) the genotype-phenotype coupling is quasi-deterministic (reminiscent of the principle of the *arbitrariness of signs* in linguistics), and (ii) the whole-cell RNA metabolic kinetic data fit a 4-parameter mathematical equation (called *blackbody radiation-like equation*, BRE) which is of the same form as the blackbody radiation formula discovered by M. Planck in 1900. It is suggested here that the first finding is related to the informational aspect and the second finding to the energetic aspect of the cell language.

It was quite surprising to find that BRE also fit data from (a) single-molecule enzymic activity and (b) protein folding. An analysis of the various sets of the BRE parameters in a parameter space revealed that blackbody radiation, single-molecule enzyme catalysis, and protein folding processes follow a common trajectory, while the whole-cell RNA metabolism deviates from it. One interpretation of this finding is that, although the molecular interactions underlying blackbody radiation, single-molecule enzyme activity and protein folding are mediated by the electromagnetic force, those in whole-cell RNA metabolism implicate, in addition, another force intrinsic to the cell – the cell force. Thus, the DNA microarray technique invented in the mid-1990's has produced the whole-cell metabolic data that appear to provide the first quantitative evidence for the information-energy dual requirement

for the cell language – *arbitrariness of signs* which maximizes the rate of information transmission [1], and *the cell force* which organizes cell metabolism guided by the genetic information stored in DNA Ji (2012).

References

Ji, S. (1997). Isomorphism between cell and human languages: molecular biological, bioinformatics and linguistic implications. *BioSystems* **44:** 17–39.

Garcia-Martinez, J., Aranda, A. and Perez-Ortin, J. E. (2004). Genomic Run-On Evaluates Transcription Rates for all Yeast Genes and Identifies Gene Regulatory Mechanisms, *Mol Cell* **15**, 303–313.

Ji, S. (2012). *Molecular Theory of the Living Cell*: *Concepts, Molecular Mechanisms, and Biomedical Applications*. Springer, New York.

Appendix O

Dear Mark,

Thank you for sending me your paper titled "Information in the Structure of the World" [*Information: Theories & Applications*, 2011, v. 18, No.1, pp. 16-32], which I read with great interest. . . . . I think your Ontological Principle O2 does apply to the concept of 'genetic information' in biology but may need further specification (as you have already done with O2g, O2a, etc.) to capture the current state of our knowledge on genetic information. For example, in 1989 (see the 5FAOB Congress abstract . . . attached below) I came to the conclusion that there are two distinct types of genetic information called the Watson-Crick and Prigoginian forms, the former is analogous to the sheet music and the latter to audio music. In addition, I think we have to recognize a third form of genetic information utilized by molecular machines which may be referred to as the 'Lumry-McClare form', in honor of the pioneering investigations carried out by Rufus Lumry at the University of Minnesota in 1950's-60's and C. W. F. McClare at the University of London in the 1960's [see D. E. Green, ed., Mechanisms of Energy Transduction in Biological Systgems, *Ann. N. Y. Acad. Sci*. 227: 46-73, 74-97 (1974)]. We can represent the interrelation among these three types of genetic information in terms of information flow from one system to another inside the cell:

$$\mathbf{N} \xrightarrow{\mathbf{P}} \mathbf{C} \tag{O.1}$$

where N is the nucleotide system, i.e., DNA and RNA (storing the Watson-Crick form of genetic information); P is the protein system including enzymes (storing the Lumry-McClare form); and C is the chemical system such as biochemical reactions and ion gradients (storing the Prigoginian form of genetic information). P is placed above the arrow indicating that it acts as a catalyst. That is, the genetic information of the cell is postulated to be distributed among the three systems – the

Watson-Crock form in N, the Lumry-McClare form in P, and the Prigoginian form in C (which, by the way, is thought to determine directly the phenotypes of the cell).

. . . . .

Diagrammatically, I think we can represent the concept of genetic information as follows:

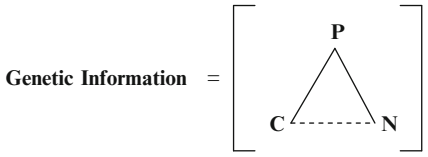


Fig. O.1 A triadic definition of *genetic information* taking into account the molecular mechanisms underlying information transduction and transfer. The dotted line indicates theirreconcilably opposite nature between C and N, the former being a dissipative structure and thelatter an equilibrium structure. P is placed at the apex because it interacts with both C and N. The square brackets symbolizes the fact that genetic information is equivalent to the totality of what the brackets contain and not to any one of the nodes in it individually, although genetic information is often exclusively associated with DNA (i.e., N) alone, which I think needs to be corrected. . . .

Program & Abstracts, *5 FAOB (Federation of Asian and Oceanian Biochemists) Congress,* Seoul, Korea, 8/13-18, 1989, p. 374.

TH:117

WATSON-CRICK AND PRIGOGINIAN FORMS OF GENETIC INFORMATION: A THEORETICAL MODEL OF GENE EXPRESSION.

Sungchul JI, Department of Pharmacology and Toxicology, College of Pharmacy, Rutgers University, Piscataway, N.J. 08854, U.S.A.

According to the Bhopalator (S. Ji, J. theoret. Biol.116:399 (1985)), the living cell can be viewed as a molecular dynamical system composed of subsystems N (nucleic acids), P (proteins) and C (diffusible chemical species). The C subsystem (e.g., heterogeneous cytoplasmic free Ca^{++} (D. W. Sawyer et al., Science 230:663(1985)) was identified with the dissipative structures of Prigogine (Adv. Biol. Med. Phys. 16:99(1977)) and termed "intracellular dissipative structures (IDS)". IDS were postulated to act as the molecular effector mechanisms for all cellular functions (F), including gene expression. A subset of C that effectuates heritable cellular functions must carry genetic information. Therefore, the genetic information contained in the C subsystem was named the "Prigoginian form" of genetic information, and the nucleotide sequence information of DNA the "Watson-Crick form" (S. Ji, J. theoret. Biol.130:239 (1988)). To transfer genetic information from N to C, information transduction and free energy dissipation must occur catalyzed by P subsystem which generates and utilizes conformons, conformational strains of biopolymers carrying both electromechanochemical free energy and genetic information (A. Scott, Comm. Mol. Cell. Biophys. 3(1):15(1985)).

Glossary

Active Processes Physicochemical processes that do not occur unless coupled to a free energy-releasing process, in contrast to passive processes that can occur by themselves. Examples include active transport of ions across cell membranes against their electrochemical gradients and the spontaneous occurrences of nonrandom processes such as directed motions of enzymes inside the cell or of cells in tissues.

Arbitrariness of Signs The idea that there is no causal relation between a sign and what it refers to. For example the word "sweet" does not taste sweet.

Biocomplexity

Biocybernetics

Bionetwork

Biopolymers

Biosemiotics

Biosemiosis

Blackbody radiation

Body-centered tetrahedron

Bosons Elementary particles having integral spins (in contrast to fermions with half-integral spins) and acting as force carriers. Examples include photons (carrying the electromagnetic force), gluons (the strong force), W and Z bosons (the weak force), and gravitons (the gravitational force). It is postulated in this book that conformons are the boson-like entities that carry the cell force.

Cellese The molecular language that living cells are thought to employ to communicate with one another or within themselves.

Cell force The physical influence confined within a living cell that is postulated to be responsible for organizing intracellular metabolism in space and time. See cytons.

Cell language

Chemiosmotic Hypothesis The hypothesis proposed by P. Mitchell in 1961 that the ATP synthesis in mitochondria involves converting the chemical energy of respiratory substrates first into the osmotic energy of the proton gradient across the inner mitochondrial membrane which then drives the energy-requiring

synthesis of ATP from ADP and Pi. Although universally accepted by textbook writers, the chemiosmotic hypothesis does not explain how chemical energy can be converted into osmotic energy and vice versa. The conformon hypothesis described in Chapter 8 may fill this explanatory gap.

Coincidence Detection The ability to sense the simultaneous occurrence of two or more events within a narrow time window.

Coincidence Detector The physical system or device capable of detecting coincident events.

Coincidence-Detecting Event The event wherein coincident processes are detected.

Communication The process by which information is exchanged between a sender and a receiver using a common system of signs.

Communication System A physical system that enables a sender to transmit information to a receiver through a channel. The channel often includes an encoder and a decoder of the information being transmitted.

Complementarity

Complexity

Conformons The mechanical energy stored in biopolymers in the form of conformational strains as in DNA supercoils and conformationally deformed enzymes. Conformons provide both the energy and the control information needed to generate the goal-directed mechanical forces that power all molecular machines.

Cosmoforce Also called *cosmic force*. The force associated with gnergy, or the conserved quantity associated with the body-centered tetrahedron (BCT) as the topological invariant of the Cosmos. The *cosmoforce* may be identical with or contain the superforce that unifies gravity, electromagnetism, and weak and strong nuclear forces.

Cosmolanguage According to the cell language theory proposed in 1997 (see Section 6.1.2), there exists a common set of rules obeyed by both human and cell languages. To explain the isomorphism between human and cell language, it was proposed that there exists a third language called the cosmolanguage of which the human and cell languages are but the local (or renormalized) version.

Covalent Bond The bond formed by sharing one or more pairs of electrons between two nuclei. The bond energy (i.e., the energy required to break the bond) is typically in the range of 30–150 Kcal/mole.

Cytons (also called *the cell force)* = The force that the living cell as a whole is postulated to exert on intracellular physicochemical processes in order to effectuate gene-directed goals (Ji 1991).

Degradosomes The enzymes that catalyze the degradation of RNA to component nucleotides.

Dissipatons (also called *dissipative structures)* = Physicochemical processes that are organized in space and time. Synonymous with "dissipative structures" or "self-organizing chemical reaction-diffusion systems" studied by Prigogine and his school (Prigogine 1977, 1978, 1980).

Dissipative Structures Any structure that disappears when energy supply is blocked, e.g., the flame of a candle.

Dissipatons A new word coined to denote dissipative structures.

DNA Deoxyribonucleic acid, the polymer composed of covalently linked nucleotides, A, C, G, and T, whose sequence encodes genetic information.

Energy The ability of a system to do work.

Double Articulation Most human languages embody two kinds of linear arrangements (or articulations) – words into sentences (called the first articulation), and letter into words (the second articulation). In this book, the linear arrangements of sentences into texts have been referred to as the third articulation. Linguists and semioticians inform us that words are needed to denote; sentences, to decide; and texts, to reason.

Dynamics The study of the causes of or changes in motion.

Enthalpy The total energy of a thermodynamic system, denoted as H.

Entropy A measure of the disorganization of a physical system. According to the First Law of thermodynamics, the entropy of the Universe increases with time.

Enzymes Proteins that can catalyze chemical reactions without themselves undergoing any net change. An enzyme may consists of a single polypeptides or a set of polypeptides forming a complex through noncovalent interactions.

Equilibrons (also called *equilibrium structures*) = Physicochemical processes that have reached their equilibrium states. Synonymous with "equilibrium structures" of Prigogine.

Ergon The material entity carrying energy. It is the energy/matter aspect of gnergy.

Fermions Elementary particles with half-integral spins; divided into two groups – quarks and leptons. Quarks make up protons and neutrons, and leptons include electrons, muons, tauons, and respective neutrinos.

Force Any influence that causes observable changes of an object. To generate a force, it is necessary to have an energy source; without energy, no force. Force is a vector quantity (i.e., has a direction and magnitude), while energy is a scalar quantity (i.e., has only the magnitude).

Franck-Condon principle

Free Energy The function of energy and entropy that decreases whenever spontaneous processes occur under specified conditions.

Generalized Fracnk-Condon Principle

Genetics

Genomics

Gibbs Free Energy The free energy of a physicochemical system under the conditions of constant temperature and pressure. Of all the various free energies, it is Gibbs free energy that decreases when spontaneous processes occur in most living systems, namely, homeotherms.

Gibbs Free Energy Landscape A surface (akin to mountain topology) in a 3-dimensional coordinate system where x and y denote the variables of the

thermodynamic system under consideration and the z axis records the Gibbs free energy level of the system.

Gluons Elementary particles with spin of 1 that cause quarks to interact. Gluons are responsible for binding quarks to form protons and neutrons.

Gnergy A hypothetical material entity postulated to embody the complementary union of information (or gnons) and energy (or ergons) in analogy to light (or quantum particles in general) viewed as the complementary union of waves and particles (Ji 1991).

Gnons The material entity carrying information. It is the information aspect of gnergy

Hadrons Any subatomic particles (e.g., protons, neutrons, mesons) that are composed of quarks and antiquarks and experience strong nuclear force mediated by gluons.

Humanese A new word coined to indicate the human language in contrast to the cell lanuage.

Hyperstructure A structure intermediate between macromolecules and the cell, e.g., a system of enzymes that catalyze glyucolysis.

IDSs (or *intracellular dissipative structures)* Dynamic arrangements of matter (e.g., chemical concentrations) and energy (e.g., mechanical stresses in the cytoskeleton) inside the cell that are maintained by continuous dissipation of free energy (Ji 1991).

Information The *memory* of (or encoded in) a physical system (e.g., enzymes, cells, brains, books, the Universe) that has resulted from one or more *selection* events it experienced in the past. Consequently, the information of a physical system can exert nonrandom influences on its observable behaviors or on its users. This definition of information is *new* and appears to accommodate the definitions of information not only given by Shannon and Kolmogorov in information theory but also tacitly assumed by biologists although they have not explicitly so articulated anywhere to the best of my knowledge. There are three aspects to information – (1) amount, (2) meaning, and (3) value. The Shannon and Kolmogorov informations deal with only the first aspect while biological information implicates all three aspects simultaneously. This is why it is much more difficult to quantify (or apply mathematical approaches to) biological information than Shannon and Kolmogorov informations.

Information-Energy Complementarity The notion that information and energy represent the irreconcilably opposite aspects of a third entity called gnergy.

Isomorphism Literally means "identical shape." The term is used in this paper loosely to indicate the relation between two objects (or systems) that obey a common set of rules or principles or share/exhibit a set of common features. The best example of isomorphism defined in this manner is provided by the same crystal form found in different minerals, for example, Calcite ($CaCO_3$) and Siderite ($FeCO_3$). Although these minerals are composed of different elements, the arrangements of the elements obey the same geometric form (or topology).

Leptons One of the two groups of matter particles (i.e., fermions). Leptons include electrons, muons, and tauons and their neutrinos.

Mattergy (also called Matter-Energy) According to the special theory of relativity, $E = mc^2$; i.e., energy (E) and matter (m) are interconvertible and two aspects of the same entity. The combination of energy and matter is therefore referred to as mattergy, in analogy to the combination of space and time, space-time, in the general theory of relativity.

Metastability –

Muons A semi-stable fundamental particle belonging to the lepton family. It has a negative electric charge and a spin of half and decays into an electron and neutrinos.

Noether's Theorem A central result in theoretical physics, according to which symmetry properties of physical laws imply the existence of conserved quantities (Goldstein 1980). For example, the conservation of *energy* is a consequence of the fact that all laws of physics are *invariant under translation through time*, i.e., they do not change when t is replaced with $(t + \Delta t)$. This theorem connects the *invariance* or *symmetry* properties of the equations representing the laws of physics and *conserved quantities*.

Non-covalent Bond The bond between molecules due to the attractive forces exerted by electrical charges, van der Waals interactions and hyrdrophobicity. The strength of non-covalent bonds is in the range of 1–10 Kcal/mole, in contrast to covalent bond strengths in the range of 30–150 Kcal/mole.

Passive Processes Physicochemical processes that can occur without help from any other processes. Examples include the influx of sodium ions and efflux of potassium ions across depolarized membranes, down their electrochemical gradients and Brownian motions of particles in liquid media at nonzero temperatures.

Phenons Synonymous with phenotypes, namely, the observable characteristics of organisms resulting from the interaction between their genotypes and environment.

Photons Packets (or quanta) of the electromagnetic field, e.g., light. A photon differs from the electron and the quark in that it has zero mass and therefore travels at the speed of light, c (in vacuum). Like all quanta, photons have both wave and particle properties.

Renormalization This term has a long history in physics (Cao and Schweber 1993), but it is used in this paper simply in the sense of "redefinition" or "regrouping."

Renormalizer Renormalization is viewed as a process and hence must be executed by some agent. Such an agent is defined here as a renormalizer. Examples of renormalizers include enzymes, cells, and organisms (see Sects. 5 and 6).

Superdissipatons Two or more dissipatons that are organized in space and/or time. This term was coined in analogy to superclusters of clusters of galaxies in astronomy.

Symmetry In mathematics, (1) an object O is said to be symmetric with respect to a given mathematical transformation T, if O remains unchanged (or invariant) when T is applied to O, and (2) two objects are said to be symmetric to each other with respect to a given group of operations (or transformations) if one is obtained from the other by some of the operations (and vice versa).

Synchrony The simultaneous occurrence of two or more events within a narrow time window (also called a time gap or a time bin).

Topology A branch of mathematics that is a generalization of geometry. Topology is a study of any relationship between connected geometric primitives that is not altered (i.e., remain invariant) by continuous transformation. That is, topology studies the properties of geometric figures that depend only on how a figure is held together, regardless of its size or shape.

Wave Function A mathematical function of a physical system used in quantum mechanics that contains all the experimentally measurable information about the system. For example, a function $\psi(x,y,z)$, appearing in Schrödinger's equation involving the coordinates of a particle of a system, carries all the measurable information about the position and energy levels of the particle in the system.

References

Abbott, D., Davies, P.C., Pati, A.K.: Quantum Aspects of Life, pp. 349–380. Imperial College Press, London (2009)

Adleman, L.M.: Molecular computation of solutions to combinatorial problems. Science **266**, 1021–1024 (1994)

Agarwal, B.K.: Quantum Mechanics and Field Theory. Asia Publications, New York (1977)

Aksimentiev, A., Balabin, I.A., Fillingame, R.H., Schulten, K.: Insights into the molecular mechanism of rotation in the F_0 sector of ATP synthase. Biophys. J. **86**, 1332–1344 (2004)

Albert, D.Z., Galchen, R.: A quantum threat to special relativity. Sci. Am. **300**(3), 32–39 (2009)

Alberts, B.: The cell as a collection of protein machines: preparing the next generation of molecular biologists. Cell **92**, 291–294 (1998)

Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., Walter, P.: The Molecular Biology of the Cell, 5th edn. Garland Science, New York (2008)

Aleksandrov, A.D., Kolomogorov, A.N., Lavrent'ev, M.A.: MATHEMATICS Its Content, Methods, and Meaning (Hirsch, K., translator), vol. 3, p. 146. MIT Press, Cambridge, MA (1984)

Aleksunes, L.M., Manautou, J.E.: Emerging role of Nrf2 in protecting against hepatic and gastrointestinal disease. Toxicol. Pathol. **35**, 459–473 (2007)

Alon, U., Barkai, N.D., Notterman, D.A., Gish, K., Ybarra, S., Mack, D., Levine, J.: Broad patterns of gene expression revealed by clustering analysis of tumor and normal colon tissues probed by oligonucelotide arrays. Proc. Natl. Acad. Sci. USA **96**(1999), 6745–6750 (1999)

Aloy, P., Russell, R.B.: Ten thousand interactions for the molecular biologist. Nat. Biotechnol. **22**(10), 1317–1321 (2004)

Alvarez, A., Romero, F.R., Archilla, J.F.R., Cuevas, J.A., Larsen, P.V: Breather trapping and breather transmission in a DNA model with an interface, ArXiv:nlin/0503062v3 [nlin.PS] (27 Mar 2006)

Amaral, P.P., Dinger, M.E., Mercer, T.R., Mattick, J.S.: The eukaryotic genome as an RNA machine. Science **319**, 1787–1789 (2008)

Amoroso, R.L. (ed.): Complementarity of Mind and Body: Realizing the Dream of Descartes, Einstein and Eccles, Nova Science Publishers, New York (2010)

Anderson, P.W.: More is different. Science **177**, 393–396 (1972)

Anderson, P.W.: Suggested model of prebiotic evolution: the use of chaos. Proc. Natl. Acad. Sci. USA **80**, 386–3390 (1983)

Anderson, P.W.: Computer modeling of prebiotic evolution: general theoretical ideas on the origin of biological information. Comments Mol. Cell. Biophys. **4**(2), 99–108 (1987)

Anderson, B., Harrison, M., Sheinberg, D.L.: A multielectrode study of the inferotemporal cortex in the monkey: effects of grouping on spike rates and synchrony. Neuroreport **17**(4), 407–411 (2006)

Andrews, F.C.: Equilibrium Statistical Mechanics. Wiley, New York (1963)
Andries, K., Verhasselt, P., et al.: A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. Science **307**, 223–227 (2005)
Arnaud, C.H.: Close quarters. Chem. Eng. News **88**(48), 9–13 (29 Nov 2010)
Ashby, W.R. An Introduction to Cybernetics. Metuen, London (1964)
Ashe, M.P., De Long, S.K., Sachs, A.B.: Glucose depletion rapidly inhibits translation initiation in yeast. Mol. Biol. Cell **11**, 833–848 (2000)
Astumian, D.: The role of thermal activation in motion and force generation by molecular motors. Philos. Trans. R. Soc. Lond. B **355**, 511–22 (2000)
Astumian, D.: Making molecules into motors. Sci. Am. **285**(1), 57–64 (2001)
Atkins, P.: Physical Chemistry, 6th edn. W. H. Freeman, New York (1998)
Atkins, P.: Four Laws that Drive the Universe. Oxford University Press, Oxford (2007)
Averbeck, B.B., Lee, D.: Coding and transmission of information by neural ensembles. Trends Neurosci. **27**(4), 225–30 (2004)
Avery, O., MacLeod, C.M., McCarty, M.: Studies on the chemical nature of the substance inducing transformation of pneumococcal types: induction of transformation by a desoxyribonucleia acid fraction isolated from pneumococcal type III. J. Exp. Med. **79**(2), 137–158 (1944)
Axelrod, D.: Total internal reflectance fluorescence microscopy. Methods Cell Biol. **30**, 245–270 (1989)
Aykan, N.F.: Message-adjusted network (MAN) hypothesis in gastro-entero- pancratic (GEP) endocrine system. Med. Hypotheses **69**, 571–574 (2007)
Babloyantz, A.: Molecules, Dynamics & Life: An Introduction to Self-Organization of Matter. Wiley-Interscience, New York (1986)
Bacciagaluppi, G., Valenti, A.: Quantum Theory at the Crossroads: Reconsidering the 1927 Solvay Conference. Cambridge University Press, Cambridge, UK (2009)
Baez, J.: This week's finds in mathematical physics (Week 73). www.math.ucr.edu/home/baez/weeks73.html (2011)
Bagshaw, C.R., Cherny, D.: Blinking fluorophores: what do they tell us about protein dynamics? Biochem. Soc. Trans. **34**, 979–982 (2006)
Baker, T.A., Bell, S.P.: Polymerases and the replisome: machines within machines. Cell **92**, 295–305 (1998)
Barab, P.: The Complementary Nature of Reality. Open Way Press, Portland (2010)
Barabasi, A.L.: Linked: The New Science of Networks. Perseus Publishing, Cambridge, MA (2002)
Barabasi, A.L.: Scale-free networks: a decade and beyond. Science **325**, 412–413 (2009)
Barbieri, M.: The Organic Codes: An Introduction to Semantic Biology. Cambridge University Press, Cambridge, UK (2003)
Barbieri, M.: Introduction to Biosemiotics: The New Biological Synthesis. Springer, New York (2008a)
Barbieri, M.: The code model of semiosis: the first steps towards a scientific biosemiotics. Am. J. Semiotics **24**(1–3), 23–37 (2008b)
Barbieri, M.: Biosemiotics: a new understanding of life. Naturwissenschaften (2008c). doi:10.1007/s00114-008-0368-x
Barbour, I.G.: Religion and Science: Historical and Contemporary &&&Issues. HarperSanFrancisco, New York (1997)
Barrow, J.D., Tipler, F.J.: The Anthropic Cosmological Principle. Clarendon Press, Oxford (1986)
Bassler, B.L., Losick, R.: Bacterially speaking. Cell **125**, 237–246 (2006)
Batey, R.T.: Structures of regulatory elements in mRNAs. Curr. Opin. Struct. Biol. **16**(3), 299–306 (2006). doi:10.1016/j.sbi.2006.05.001 DOI:dx.doi.org. PMID 16707260
Bauer, W.R., Crick, F.H.C., White, J.H.: Supercoiled DNA. Sci. Am. **243**(1), 118–133 (1980)
Bechtel, W.: The cell: locus or object of inquiry? Stud. Hist. Philos. Biol. Biomed. Sci. **41**(3), 172–82 (2010)

Bednar, J., Furrer, P., Vsevolod Katritch, V., Alicja Stasiak, A., Dubochet, J., Stasiak, A.: Determination of DNA persistence length by Cryo-electron microscopy. Separation of the static and dynamic contributions to the apparent persistence length of DNA. J. Mol. Biol. **254** (4), 579–5 (1995)

Bedregal, B.R.C., Figueira, S.: Classical computability and fuzzy turing machines. Lect. Notes Comput. Sc. **3887**, 154–165 (2006)

Beek, P.J., Peper, C.E., Stegeman, D.F.: Dynamical models of movement coordination. Hum. Mov. Sci. **14**, 573–608 (1995)

Bejan, A.: Constructal-theory network of conducting paths for cooling a heat generating volume. Int. J. Heat Mass Tran. **40**(4), 799–816 (1997)

Bejan, A., Lorente, S.: The constructal law of design and evolution in nature. Philos. Trans. R. Soc. B **365**, 1335–1347 (2010)

Bellomo, N., Bellouquid, A., Harrero, M.A.: From microscopic to macroscopic descriptions of multicellular systems and biological growing tissues. Comput. Math. Appl. **53**, 647–663 (2007)

Benham, C.J.: Sites of predicted stress-induced DNA duplex destabilization occur preferentially at regulatory sites. Proc. Natl. Acad. Sci. USA **90**, 2999–3003 (1992)

Benham, C.J.: Duplex destabilization in supercoiled DNA is predicted to occur at specific transcriptional regulatory regions. J. Mol. Biol. **255**, 425–434 (1996a)

Benham, C.J.: Computation of DNA structural variability – a new predictor of DNA regulatory regions. Comput. Appl. Biosci. **12**(5), 375–381 (1996b)

Benham, C.J., Bi, C.: The analysis of stress-induced duplex destabilization in long genomic DNA sequences. J. Comput. Biol. **11**(4), 519–543 (2004)

Ben-Naim, A.: A Farewell to Entropy. World Scientific, Singapore (2008)

Bennett, C.H.: Thermodynamics of computation - a review. Int. J. Theor. Phys. **21**(12), 905–940 (1991)

Berg, J.M., Tymoczko, J.L., Stryer, L.: Biochemistry, 5th edn, pp. 440–442. W. H. Freeman and Company, New York (2002)

Berman, H.M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T.N., et al.: The protein data bank. Nucleic Acids Res. **28**, 235–242 (2000)

Bernstein, N.: The Coordination and Regulation of Movements. Oxofrd University Press, Oxford (1967)

Beyer, A., Hollunder, J., Nasheuer, H.-P., Wilhelm, T.: Post-transcriptiona expression regulation in the yeast *Saccharomyces cerevisiae* on a genomic scale. Mol. Cell. Proteomics **3**, 1083–1092 (2004)

Beyer, R.P., et al.: Multi-center study of acetaminophen hepatotoxicity reveals the importance of biological endpoints in genomic analyses. Toxicol. Sci. **99**(1), 326–337 (2007)

Black, M.: Acetaminophen hepatotoxicity. Ann. Rev. Med. **35**, 577–593 (1984)

Blobel, G.: Nuclear-cytoplasmic transport. The 4th Morris Lecture, Robert Wood Johnosn Medical School, UMDNJ, Picataway, 4 Nov 2007

Blumenfeld, L.A., Tikhonov, A.N.: Biophysical Thermodynamics of Intracellular Processes: Molecular Machines of the Living Cell. Springer, New York (1994)

Boal, D.: Mechanics of the Cell. Cambridge University Press, Cambridge, UK (2002)

Bodanis, D.: $E = mc^2$: A Biography of the World's Most Famous Equation. Berkeley Books, New York (2000)

Bohm, D.: Wholeness and the Implicate Order. Routledge, London (1980)

Bohm, D., Hiley, B.J.: The Undivided Universe. Routledge, London (1993)

Bohr, N.: The quantum postulate and the recent developments of atomic theory. Nature **121**, 580–590 (1928)

Bohr, N.: Atomic Theory and the Description of Nature (The Philosophical Writings of Niels Bohr, vol. 1. Ox Bow Press, Woodbridge (1934)

Bohr, N.: Quantum physics and philosophy - causality and complementarity. In: Klibansky, R. (ed.) Philosophy in the Mid-Century. La Nouva Editrice, Florence (1958)

Bohr, N.: Light and life. Nature **133**, 421–423 (1933) (Part 1) and 457–459 (Part 2)

Bonasio, R., Tu, S., Reinberg, D.: Molecular signals of epigenetic states. Science **330**, 612–616 (2010)
Books, B., York, N., Bohm, D.: Wholeness and the Implicate Order. Berkley books, Routledge (1980)
Born, M., Oppenheimer, R.: Zur quantentheorie der molekeln. Ann. Physik (Leipzig) **389**, 457–484 (1927)
Bowman, J.M.: Beyond born-oppenheimer. Science **319**, 40–41 (2008)
Boyer, P.D.: Catalytic site occupancy during ATP synthase catalysis. FEBS Lett. **512**(1–3), 29–32 (2002)
Boyer, J., Allen, W.L., McLean, E.G., Wilson, P.M., McCulla, A., Moore, S., Longley, D.B., Caldas, C., Jophnston, P.G.: Phamrcogenomic identification of novel determinants of response to chemotherapy in colon cancer. Cancer Res. **66**, 2765–2777 (2006)
Brillouin, L.: Maxwell's demon cannot operate: information and entropy. I. J. Appl. Phys. **22**(3), 334–337 (1951)
Brillouin, L.: Negentropy principle of information. J. Appl. Phys. **24**(9), 1152–1163 (1953)
Brillouin, L.: Science and Information Theory, pp. 152–156. Academic, New York (1956)
Brooks, D.R., Wiley, E.O.: Evolution as Entropy. The University of Chicago Press, Chicago (1986)
Brooks, C.A., Onuchic, J.N., Wales, D.J.: Statistical thermodynamics: taking a walk on a landscape. http://www.biology-online.org/articles/statistical_thermodynamics_taking_walk.html (2009)
Bryngelson, J.D., Wolynes, P.G.: Spin glasses and the statistical mechanics of protein folding. Proc. Natl. Acad. Sci. USA **84**, 7524–7528 (1987)
Buchler, J.: Philosophical Writings of Peirce. Dover, New York (1955)
Budge, E.A.W.: The Rosetta Stone. Dover, New York (1989)
Burczynski, M.E., Oestreicher, J.L., Cahilly, M.J., Mounts, D.P., Whitley, M.Z., Speicher, L.A., Trepicchio, W.L.: Clinical pharmacogenomics and transcriptional profiling in early phase oncology clinical trials. Curr. Mol. Med. **5**, 83–102 (2005)
Brugin, M.: Data, Information, and Knowledge", Information, vol. 7, No. 1, pp. 47–57 (2004)
Burgin, M.: Theory of information: fundamentality, diversity and unification. World Scientific, Singapore (2010)
Burgin, M.: Information in the structure of the world, Inforation: Theories & Applications 18 (1), 16–32 (2011)
Burgin, M.: The Essence of Information: Paradoxes, Contradictions, and Solutions. Downloaded from http://www.infoamerica.org/documentos_pdf/wiener05.pdf (2012)
Bürglin, T.R.: Homeodomain proteins. In: Meyers, R.A. (ed.) Encyclopedia of Molecular Biology and Molecular Medicine, vol. 3, pp. 55–76. VCH Verlagsgesellschaft mbH, Weinheim (1996)
Burke, A.S., MacMillan-Crow, L.A., Hinson, J.A.: Reactive nitrogen species in acetaminophen-induced mitochondrial damage and toxicity in mouse hepatocytes. Chem. Res. Toxicol. **23**, 1286–1292 (2010)
Cahay, M.: Quantum confinement VI: nanostructured materials and devices. In: Proceedings of the International Symposium, The Electrochemical Society (ECS), Pennington, 2001
Callen, H.B.: Thermodynamics: An Introduction to the Physical Theories of Equilibrium Thermostatics and Irreversible Thermodynamics. Wiley, New York (1985)
Camillieri, K.: Bohr, Heisenberg and the divergent views of complementarity. Stud. Hist. Philos. Mod. Phys. **38**, 514–528 (2007)
Cánti, T.: The Principles of Life. Oxford University Press, Oxford (2003)
Cao, T.Y., Schweber, S.S.: The conceptual foundations and the philosophical aspects of renormalization theory. Synthese **97**, 33–108 (1993)
Caporale, L.H.: Darwin in the Genome: Molecular Strategies in Biological Evolution. McGraw-Hill, New York (2003)
Carroll, S.: Endless Forms Most Beautiful: The New Science of Evo Devo. W. W. Norton, New York (2006)

Cheetham, G.M.T., Steitz, T.A.: Structure of a transcribing T7 RNA polymerase initiation complex. Science **286**, 2305–2309 (1999)
Cheng, L., Ji, S.: Inhibition of hepatic respiration by acetaminophen: a new mechanisms of acetaminophen hepatotoxicity. The Toxicologist **4**, 78 (1984)
Chenna, R., Sugawara, H., Koike, T., Lopez, R., Gibson, T.J., Higgins, D.G., Thompson, J.D.: Multiple sequence alignment with the Clustal series of programs. Nucleic Acids Res. **31**(13), 3497–500 (2003)
Chicurel, M.E., Chen, C.S., Ingber, D.E.: Cellular control lies in the balance of forces. Curr. Opin. Cell Biol. **10**, 232–239 (1998)
Chothia, C.: One thousand families for the molecular biologist. Nature **357**, 543–544 (1992)
Chu, L.-H., Chen, B.-S.: Construction of a cancer-perturbed protein-protein interaction network for discovery of apoptosis drug targets. BMC Syst. Biol. **2**, 56–72 (2008)
Chu, M., Tsuda, T.: Fibulins in development and heritable diseases. Birth Defects Res. **72**(1), 25–36 (2004)
Ciechanover, A.: Proteolysis: from lysosome to ubiquitin and the proteosome. Nat. Rev. Mol. Cell Biol. **6**, 79–87 (2005)
Clarke, P.A., te Poele, R., Workman, P.: Gene expression microarray technologies in the development of new therapeutic agents. Eur. J. Cancer **40**, 2560–2591 (2004)
Clayton, P., Davies, P.: The Re-emergence of Emergence. Oxford University Press, Oxofrd (2006)
Colapietro, V.M.: Glossary of Semiotics, vol. 163, pp. 112–113. Paragon House, New York (1993)
Collier, J.: Causation is the transfer of information. In: Sankey, H. (ed.) Causation, Natural Laws and Explanation. Kluwer, Dordrecht (1999)
Bain & Company: Cost of Developing a New Drug Increases to About 1.7 Billion. http://www.loyaltyrules.com/bainweb/publications/publications_detail.asp?id=14245&menu_url=publications_results.asp (2007)
Cook, N.D.: The Brain Code: Mechanisms of Information Transfer and the Role of *the corpus callosum*. Methuen, New York (1986)
Corney, A.: Atomic and Laser Spectroscopy. Clarendon Press, Oxford (1977)
Costanzo, M., Bryshnikova, A., et al.: The genetic landscape of a cell. Science **327**, 425–431 (2010)
Cozzarelli, N.R.: DNA gyrase and the supercoiling of DNA. Science **207**, 953–960 (1980)
Craig, C.R., Stitzel, R.E.: Modern Pharmacology, 4th edn, pp. 275–278. Little, Brown & Company, Boston (1994)
Crick, F.: Of Molecules and Men. University of Washington Press, Seattle (1966)
Crick, F.H., Barnett, L., Brenner, S., Watts-Tobin, R.J.: General nature of the genetic code for proteins. Nature **192**(4809), 1227–32 (1961)
Crompton, M.: The mitochondrial permeability transition pore and its role in cell death. Biochem. J. **341**, 233–249 (1999)
Cuevas, J., Starikov, E.B., Archilla, J.F.R., Hennig, D.: Moving breathers in bend DNA with realistic parameters. Mod. Phys. Lett. B. **18**(25), 1319–1326 (2004)
Culler, J.: Ferdinand de Saussure. Cornell University Press, Ithaca (1991). Revised Edition
Curley, E.: A Spinoza Reader: The Ethics and Other Works, pp. 67–70. Princeton University Press, Princeton (1994)
Cushing, J.T.: Quantum Mechanics: Historical Contingency and the Copenhagen Hegemony. The University of Chicago Press, Chicago (1994)
Dahlin, D.C., Miwa, G.T., Lu, A.Y., Nelson, S.D.: N-acetyl-p- benzoquinone imine: a cytochrome P-450-mediated oxidation product of acetaminophen. Proc. Natl. Acad. Sci. USA **81**, 1327–1331 (1984)
Darden, L.: Reasoning in Biological Discoveries: Essays on Mechanisms, Interfield Relations, and Anomaly Resolution. Cambridge University Press, Cambridge, UK (2006)
Darwin, C.: On the Origin of Species by Means of Natural Selection, or the Preservation of Favored Races in the Struggle for Life. John Murray, London (1859)

Davies, P.: Superforce: The Search for a Grand Unified theory of Nature. Simon & Schuster, New York (1984)
Davies, P., Gregersen, N.H. (eds.): Information and the Nature of Reality: From Physics to Metaphysics. Cambridge University Press, New York (2010)
de Broglie, L.: Radiation – waves and quanta. Comptes rendus **177**, 507–510 (1923)
de Broglie, L..: Recherches sur la théorie des quanta (Researches on the quantum theory), Thesis, Paris (1924)
de Duve, C.: Blueprint for a Cell: The Nature and Origin of Life. Neil Patterson Publishers, Burlington (1991)
de Waal, C.: Peirce. Wadsworth/Thomson Learning, Belomont (2001)
Debrock, G.: Peirce's Categories of secondness and information. In: van Brackel, J., van Heerden, M. (eds.) Categories *to Constantinople*, pp. 13–30. Leuven University Press, Leuven (1998)
Deely, J.: Four Ages of Understanding: The First Postmodern Survey of Philosophy From Ancient Times to the Turn of the Twenty-First Century. University of Toronto Press, Toronto (2001)
Dellaire, G.: Nuclear compartment: nuclear pore. http://npd.hgu.mrc.ac.uk/compartments/nuc_pore.html (2007)
Deniz, A.A., Mukhopadhyay, S., Lemke, E.A.: Single- molecule biophysics: at the interface of biology, physics and chemistry. J. R. Soc. Interface **5**, 15–45 (2008)
DeRisi, J.L., Iyer, V.R., Brown, P.O.: Exploring the metabolic and genetic control of gene expression on a genomic scale. Science **278**, 680–686 (1997)
Dill, K.A., Chan, U.S.: From Leventhal to pathways to funnels. Nat. Struct. Biol. **4**(1), 10–19 (1997)
Dillon, M.C.: Merleau-Ponty's Ontology. Northwestern University Press, Evanston (1997)
Dobbe, E., Gurney, K., Kiekow, S., Lafferty, J., Kolesar, J.M.: Gene- expression assays: new tools to individualize treatment of early-stage breast cancer. Am. J. Health-Syst. Pharm. **65**(1), 23–8 (2008)
Dobzhansky, T.: Nothing in biology makes sense except in the light of evolution. Am. Biol. Teach. **35**(March), 125–129 (1973)
Domb, C.: The Critical Point: A Historical Introduction to the Modern Theory of Critical Phenomena. Taylor & Francis, London (1996)
Donoughue, C.: The Mystery of the Hieroglyphs: The Story of the Rosetta Stone and the Race to Decipher Egyptian Hieroglyphs. Oxford University Press, New York (1999)
Douglas, K.: Think like a muscle. NewScientist (18 Nov 1995)
Doxsey, S.: Re-evaluating centrosome function. Nat. Rev. Mol. Cell. Biol. **2**, 688–698 (2001)
Duffy, M.J., Kelly, Z.D., Culhane, A.C., O'Brien, S.L., Gallagher, W.M.: DNA microarry-based gene expression profiling in cancer: aiding cancer diagnosis, assessing prognosis and predicting response to therapy. Curr. Pharmacogenomics **3**, 289–304 (2005)
Dundr, M., Misteli, T.: Functional architecture in the cell nucleus. Biochem. J. **356**, 297–310 (2001)
Einstein, A.: On a heuristic viewpoint concerning the production and transmission of light. Ann. Phys. **17**, 132–148 (1905)
Eisen, M.B., Spellman, P.T., Brown, P.O., Botstein, D.: Cluster analysis and display of genome-wide expression patterns. Proc. Natl. Acad. Sci. USA **95**, 14863–14868 (1998)
Eisenmesser, E.Z., Bosco, D.A., Akke, M., Kern, D.: Enzyme dynamics during catalysis. Science **295**, 1520–1523 (2002)
Eldredge, N., Gould, S.J.: Punctuated equilibria: an alternative to phyletic gradualism. In: Schopf, r.J.M. (ed.) Models in Paleobiology, pp. 82–115. Freeman Cooper, San Francisco (1972)
Elsasser, W.M.: Reflections on a Theory of Organisms: Holism in Biology. The Johns Hopkins University Press, Baltimore (1998)
Emilsson, G.M., Breaker, R.R.: Deoxyribozymes: new activities nd new applications. Cell. Mol. Life Sci. **59**(4), 596–607 (2002)
Emmeche, C.: Taking the semiotic turn, or how significant philosophy of science should be done. Sats Nord. J. Philos. **3**(1), 155–162 (2002)

Emmeche, C.: Biosemiotics. In: van Huyssteen, W.V. (ed.) Encyclopedia of Science and Religion, pp. 63–64. Macmillan, New York (2003)
ENCODE Proejct Consortium: Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. Nature **447**, 799–816 (2007)
Englert, B.-G., Scully, M. O., Walther, H.: The duality in matter and light. Sci. Am. **271**(6), 86–92 (Dec 1994)
Esterline, R.L., Ray, S.D., Ji, S.: Reversible and irreversible inhibition of hepatic mitochondrial respiration by acetaminophen and its toxic metabolite, N- acetyl-p-benzoquinoneimine (NAPQI). Biochem. Pharmacol. **38**(14), 2387–90 (1989)
Evans, W.H., Martin, P.E.M.: Gap junction: structure and function. Mol. Membr. Biol. **19**, 121–136 (2002)
Faham, S., Watanabe, A., Besserer, G.M., Cascio, D., Spect, A., Hirayama, B.A., Wright, E.M., Abramson, J.: The crystal structure of a sodium galactose transporter reveals mechanistic insights into Na^+/Sugar symport. Science **321**, 810–814 (2008a)
Fall, C.P., Marland, E.S., Wagner, J.M., Tyson, J.J. (eds.): Computational Cell Biology. Springer, New York (2002)
Fan, J., Yang, X., Wang, W., Wood, W.H., Becker, K.G., Gorospe, M.: Global analysis of stress-regulated mRNA turnover by using cDNA arrays. Proc. Natl. Acad. Sci. USA **99**(16), 10611–10616 (2002)
Fehrst, A.: *Enzyme Structure and Mechanisms*, Freeman, San Francisco (1985)
Feibleman, J.: An Introduction to Peirce's Philosophy. Harper & Brothers Publishers, New York (1946)
Fenimore, P.W., Frauenfeld, H., McMahon, B.H., Young, R.D.: Proteins are paradigms of stochastic complexity. Physica A **351**, 1–13 (2005)
Fernández, E.: Signs and instruments: the convergence of Aristotelian and Kantian intuitions in biosemiotics. Biosemiotics **1**, 347–359 (2008)
Fields, S., Song, O.: A novel genetic system to detect protein-protein interactions. Nature **340** (6230), 245–6 (1989)
Finer, J.T., Simmons, R.M., Spudich, J.A.S.: Myosin molecule mechanics: piconewton forces and nanometre steps. Nature **368**, 113–9 (1994)
Fink, T.M.A., Zinovyev, A., Ahnert, S.E.: How much non-coding DNA do eukaryotes require? http://arxiv.org/abs/q-bio.GN/0611047 (2007)
Fischle, W., Wang, Y., Allis, C.D.: Binary switches and modification cassettes in histone biology and beyond. Nature **425**(6957), 475–479 (2003)
Fisher, M.E.: Renormalization group theory: its basis and formulation in statistical physics. Rev. Mod. Phys. **70**(2), 653–681 (1998)
Floridi, L.: Trends in the philosophy of information. In: Adriaans, P., van Benthem, J. (eds.) Handbook of Philosophy of Information. Elseviere, Amsterdam (2007)
Fodor, J.A.: The Language and Thought. Thomas Crowell, New York (1975)
Fodor, J.A., Piattelli-Palmarini, M.: What Darwin Got Wrong. Profile Books, London (2010)
Folgueira, M., Carraro, D., et al.: Gene expression profile associated with response to doxorubicin-based therapy in breast cancer. Clin. Cancer Res. **11**(2), 7434–7442 (2005)
Frauenfelder, H.: Function and dynamics of myoglobin. N. Y. Acad. Sci. **504**, 151–167 (1987)
Frauenfelder, H., McMahon, B.H., Austin, R.H., Chu, K., Groves, J.T.: The role of tructure, energy landscape, dynamics, and allostery in the enzymatic function of myoglobin. Proc. Natl. Acad. Sci. U. S. A. **98**(5), 2370–74 (2001)
Frieden, B.R.: Sciecne from Fisher Information: A Unification. Cambridge University Press, Cambridge, UK (2004)
Frisco, P., Ji, S.: Conformons-P systems. In: *DNA* Computing, 8th International Workshop on DNA-Based Computers, pp. 161–170. Hokkaido University, Sapporo (10–13 June 2002)
Frisco, P., Ji, S.: Towards a hierarchy of conformons-P systems. Lect. Notes Comput. Sci. **2597**, 302–318 (2003)
Frost, A.A., Pearson, R.G.: Kinetics and Mechanism: A Study of Homogeneous Chemical Reactions, 2nd edn. Wiley, New York (1965)

Fu, L., Bounelis, P., Dey, N., Browne, B.L., Marchase, R.B., Bedwell, D.M.: The posttranslational modification of phosphoglucomutase is regulated by galactose induction and glucose repression in *Saccharomyces cerevisiae*. J. Bacteriol. **7**(11), 3087–3094 (1995)

Fuqua, C., Greenberg, E.P.: Listening in on bacteria: acyl-homoserine lactone signaling. Nat. Rev. Mol. Biol. **3**, 685–95 (2002)

Gall, J.G., Bellini, M., Wu, Z., Murphy, C.: Assembly of the Nuclear Transcription and Processing Machinery: Cajal Bodies (Coiled Bodies) and Transcriptosomes. *Mol. Biol. Cell* **10**, 4385–4402(1999)

Ganeur, J., Krause, R., Bouwmeester, T., Casari, G.: Modular decomposition of protein-protein interaction networks. Genome Biol. **5**, R57 (2004)

Garand, E., Zhou, J., Manolopoulos, D.E.: Nonadiabatic interactions in the Cl + H_2 reaction probed by ClH_2^- and ClD_2^- photoelectron imaging. Science **319**, 72–75 (2008)

Garcia-Martinez, J., Aranda, A., Perez-Ortin, J.E.: Genomic run-on evaluates transcription rates for all yeast genes and identifies gene regulatory mechanisms. Mol. Cell **15**, 303–313 (2004)

Gasch, A.P.: The environmental stress response: a common yeast response to diverse environmental stresses. In: Hohmann, S., Mager, W.H. (eds.) Yeast Stress Responses, pp. 11–70. Springer, Berlin (2002)

Gasch, A.P., Werner-Washburne, M.: The genomics of yeast responses to environmental stress and starvation. Funct. Integr. Genomics **2**, 181–192 (2002)

Gerhart, J., Kirschner, M.: Cells, Embryos and Evolution. Blackwell, Oxford (1997)

Gerstein, M.B., Bruce, C., Rozowsky, J.S., Zheng, D., Du Jiang, J., Korbel, J.O., Emanuelsson, O., Zhang, Z.D., Weissman, S., Snyder, M.: What is a gene, post-ENCODE? History and updated definition. Genome Res. **17**, 669–681 (2007)

Giblin, J.C.: The Riddle of the Rosetta Stone: Key to Ancient Egypt. Harper Trophy, New York (1990)

Gillies, J.: CERN picture packs, back to creation - the story of the bigbang. http://outreach.web.cern.ch/outreach/public/cern/PicturePacks/BigBang.html (2007)

Gilson, J.G., McPherson, R.: Quantization of Boltzmann's gas constant. Downloaded from the Internet through Google on 3/18/2011. No reference was given in the document (2011)

Goodsell, D.S.: Inside a living cell. Trends Biochem. Sci. **16**, 203–206 (1991)

Gorban, A.N., Zinovyev, A.Y.: Elastic principal manifolds and their practical applications, arXiv, cond-mat/0405648vI [cond-mat.dis-nn] (2004)

Gorban, A., Zinovyev, A.: Elastic principal graphs and manifolds and their practical applications. Computing (2005). doi:10.1007/s00607-005-0122-6

Gorban, A.N., Zinovyev, A.: Elastic Maps and Nets for Approximating Principal Manifods and Their Applications. In: Gorban, A., Kegle, B., Wunsch, D., Zinovyev, A. (eds.) Principal Manifolds for Data Visualization and Dimension Reduction, LNCSE **58**, Springer, Berlin (2007).

Goudge, T.A.: The Thought of C. S. Peirce. Dover, New York (1969)

Gould, E.S.: Mechanism and Structure in Organic Chemistry. Holt, Rinehart & Winston, New York (1959)

Gray, J.V., Petsko, G.A., Johnson, G.C., Ringe, D., Singer, R.A., Werner-Washburne, M.: "Sleeping beauty": quiescence in *Saccharomyces cerevisiae*. Microbiol. Mol. Biol. Rev. **68**(2), 187–206 (2004)

Green, H.S.: Matrix Mechanics. P. Noordhoff, Groningen (1965)

Green, D.E., Ji, S.: The electromechanochemical model of mitochondrial strucutre and funciton. In: Schulz, J., Cameron, B.F. (eds.) Molecular Basis of Electron Transport, pp. 1–44. Academic, New York (1972a)

Green, D.E., Ji, S.: Electromechanochemical model of mitochondrial structure and function. Proc. Natl. Acad. Sci. USA **69**, 726–729 (1972b)

Grewal, S.I.S., Jia, S.: Heterochromatin revisited. Nat. Rev. Genet. **8**, 35–46 (2007)

Gribbins, J.: Deep Simplicity: Bringing Order to Chaos and Complexity. Random House, New York (2004)

Grishok, A., Pasquinelli, A.E., Conte, D., Li, N., Parrish, S., Ha, I., Baillie, D.L., Fire, A., Ruvkun, G., Mello, C.C.: Genes and mechanisms related to RNA interference regulate expression of the samll temporal RNAs that control *C. elegans* developmental timing. Cell **106**, 23–34 (2001)
Gurzadyan, V.G., Penrose, R.: Concentric circles in WMAP data may provide evidence of violent pre-Big-Bang activity, arXiv:1011.3706v1 [astro- ph.CO] (2010)
Hake, S.B., Xia, A., Allis, C.D.: Linking the epigenetic 'language' of covalent histone modifications to cancer. Br. J. Cancer **90**(4), 761–769 (2004)
Haken, H.: Synergetics, an Introduction: Nonequilibrium Phase Transitions and Self-Organization in Physics, Chemistry, and Biology, 3 (rev. enl)th edn. Springer, New York (1983)
Halle, J.-P., Meisterernst, M.: Gene expression: increasing evidence for a transcriptosome. Trends Genet. **12**(5), 161–163 (1996)
Han, M.Y.: Quarks and Gluons: A Century of Particle Charges. World Scientific, Singapore (1999)
Hannon, G., Rossi, J.: Unlocking the potential of the human genome with RNA interference. Nature **431**, 371–378 (2004)
Hargrove, J.L., Schmidt, F.H.: The role of mRNA and protein stability in gene expression. FASEB J. **3**, 2360–2370 (1989)
Harris, R.A.: The Language Wars. Oxford University Press, New York (1993)
Harrison, S.C., Durbin, R.: Is there a single pathway for the folding of a polypeptide chain? Proc. Natl. Acad. Sci. USA **82**, 4028–4030 (1985)
Hartshore, C., Weiss, P.: Collected Papers of Charles Sanders Peirce, vol. 1–6. Harvard University Press, Cambridge, MA (1931–1935)
Hartwell, L.H., Hopfield, J.J., Liebler, S., Murray, A.W.: From molecules to modular cell biology. Nature **402**(Suppl. 6761), C47–C52 (1999)
Hausman, C.R.: Charles S. Peirce's Evolutionary Philosophy. Cambridge University Press, Cambridge, UK (1997)
Hawking, S., Mlodinow, L.: The Grand Design. Bantam Book, New York (2010)
Herbert, N.: Quantum Reality: Beyond the New Physics, An Excursion into Metaphysics, p. 64. Anchor Books, Garden City (1987)
Herold, E.: Stem Cell Wars: Inside Stories from the Frontlines. Palgrave Macmillan, New York (2007)
Herrlich, H., Strecker, G.E.: Category Theory: An Introduction, pp. 13–14. Allyn & Bacon, Boston (1973)
Hess, B.: Energy utilization for control. In: Energy Transformation in Biological Systems. Ciba Fdn. Symp, vol. 31, pp. 369–392. Elsevier Excerpta Medica, North- Holland, Amsterdam (1975)
Heylighen, F., Joslyn, C.: Cybernetics and second-order cybernetics. In: Meyers, R.A. (ed.) Encyclopedia of Physical Science & Technology, 3rd edn, pp. 1–24. Academic, New York (2001a)
Heylighen, F., Joslyn, C.: The Law of Requisite Variety. http://pespmc1.vub.ac.be/REQVAR.html (2001b)
Hilgevoord, J.: The Uncertainty Principle, Stanford Encyclopedia of Philosophy (accessible through Google), 17 pp. (2006)
Hillman, C.: A Categorical Primer, October 17, 1997, downloaded from Google on November 7, 2011 (1997)
Hine, J.: Physical Organic Chemistry, 2nd edn, pp. 69–70. McGraw-Hill, New York (1962)
Hirayoshi, K., Lis, J.T.: Nuclear run-on assays: assessing transcription by measuring density of engaged RNA polymerases. Methods Enzymol. **304**, 351–362 (1999)
Hisakado, M.: Breather trapping mechanism in piecewise homogeneous DNA. Phys. Lett. A **227**(1–2), 87–93 (1997)
Hobert, O.: Gene regulation by transcription factors and microRNAs. Science **319**, 1785–1786 (2008)
Hockett, C.F.: The origin of speech. Sci. Am. **203**(3), 89–96 (1960)
Hoffmeyer, J.: Signs of Meaning in the Universe. Indiana University Press, Bloomington (1996)

Hoffmeyer, J.: Biosemiotics: Signs of Life and the Life of Signs. University of Scrtanton Press, Scranton (2008)
Hofstadter, D.R.: Gödel, Escher, Bach: An Eternal Golden Braid. Basic Books, New York (1980)
Holcome, W.M.L.: Algebraic Automata Theory. Cambridge University Press, Cambridge, UK (1982)
Holden, C., Vogel, G.: A seismic shift for stem cell research. Science **319**, 560–563 (2008)
Holter, N.S., Mitra, M., Maritan, A., Cieplak, M., Banavar, J.R., Fedoroff, N.V.: Fundamental patterns underlying gene expression profiles: simplicity from complexity. Proc. Natl. Acad. Sci. USA **97**(15), 8409–8414 (2000)
Horst, S.: Symbols and computation: a critique of the computational theory of mind. Mind Mach. **9**(3), 347 (1999)
Houser, N.J.R., Eller, J.R.A.C., Lewis, A.C.A., De Tienne, A.C.L., Clark, C.L., Davis, D.B.: The Essential Peirce: Selected Philosophical Writings, Volume 2 (1893–1913), p. 13. Indiana University Press, Bloomington (1998)
Huang, K.: Fundamental Forces of Nature: The Story of Gauge Fields. World Scientific, New Jersey (2007).
Huggett, N., Weingard, R.: The renormalization group and effective field theories. Synthese **102**, 171–194 (1995)
Huxley, A.F., Hanson, J.: In: Bourne, G.H. (ed.) The Structure and Function of Muscle, vol. 1, Academic Press, New York, pp. 183–227 (1960)
Huynen, M.A., van Nimwegen, E.: The frequency distribution of gene family sizes in complete genomes. Mol. Biol. Evol. **15**(5), 583–589 (1998)
Ingber, D.: The architecture of life. Sci. Am. **278**(1), 48–57 (1998)
Ingleman-Sundberg, M.: Pharmacogenetics and epigenetics of drug metabolism and action, a lecture delivered at the conference entitled "Prospects for Individualized Drug Therapy: Person-to-Person Differences in Drug Metabolism and Disposition", held at the Ernest Mario School of Pharmacy, Rutgers University, Piscataway, 26 May 2010
Ishii, Y., Yanagida, T.: Single molecule detection in life science. Single Mol. **1**(1), 5–16 (2000)
Ishii, Y., Yanagida, T.: How single molecule detection measures the dynamics of life. HFSP J. **1**(1), 15–29 (2007)
Ishijima, A., Kojima, H., Higuchi, H., Harada, Y., Funatsu, T., Yanagida, T.: Simultaneous measurement of chemical and mechanical reaction. Cell **70**, 161–171 (1998)
Ishikawa, H., Kwak, K., Chung, J.K., Kim, S., Fayer, M.D.: Direct observation of fast protein conformational switching. Proc. Natl. Acad. Sci. USA **105**, 8619–8624 (2008)
Ito, T., Chiba, T., Ozawa, R., Yoshida, M., Hattori, M., Sakai, Y.: A comprehensive two-hybrid analysis to explore the yeast protein interactome. Proc. Natl. Acad. Sci. USA **98**, 4569–4574 (2001)
Jablonka, E.: Genes as followers in evolution – a post-synthesis synthesis? Biol. Philos. **21**, 143–154 (2006)
Jablonka, E.: Extending Darwinism, SEED, posted 6 Jan. http://seedmagazine.com/news/2009/01/extending_darwinism.php (2009)
Jacob, E.B., Shapira, Y., Tauber, A.I.: Seeking the foundation of cognition in bacteria: from Schrödinger's negative entropy to latent information. Physica A **359**, 495–524 (2005)
James, W.: The Principles of Psychology. Volume One, p. 206. Dover, New York (1890)
James, L.P., Mayeux, P.R., Hinson, J.A.: Acetminophen-induced hepatotoxicity. Drug Metab. Dispos. **31**(12), 1499–14506 (2003)
Jaynes, E.T.: Information theory and statistical mechanics. Phys. Rev. **106**, 620–630 (1957a)
Jaynes, E.T.: Information theory and statistical mechanics II. Phys. Rev. **108**, 171–190 (1957b)
Jencks, W.: Binding energy, specificity, and enzymic catalysis: the circe effect. Adv. Enzymol. **43**, 219–410 (1975)
Jenuwein, T., Allis, C.D.: Translating the histone code. Science **293**(5532), 1074–1080 (2006)
Ji, S.: Energy and negentropy in enzymic catalysis. Ann. N. Y. Acad. Sci. **227**, 419–437 (1974a)
Ji, S.: A general theory of ATP synthesis and utilization. Ann. N. Y. Acad. Sci. **227**, 211–226 (1974b)

Ji, S.: A model of oxidative phosphorylation that accommodates the chemical intermediate, chemiosmotic, localized proton and conformational hypotheses. J. Theor. Biol. **59**, 319–330 (1976)
Ji, S.: A possible molecular mechanism of free energy transfer in oxidative phosphorylation. J. Theor. Biol. **68**, 607–612 (1977)
Ji, S.: The principles of ligand-protein interactions and their application to the mechanism of oxidative phosphorylation. In: Yagi, K. (ed.) Structure and Function of Biomembranes, pp. 25–37. Japan Scientific Societies Press, Tokyo (1979)
Ji, S.: The bhopalator – a molecular model of the living cell based on the concepts of conformons and dissipative structures. J. Theor. Biol. **116**, 399–426 (1985a)
Ji, S.: The Bhopalator: a molecular model of the living cell. Asian J. Exp. Sci. **1**, 1–33 (1985b)
Ji, S.: A general theory of chemical cytotoxicity based on a molecular model of the living cell, the Bhopalator. Arch. Toxicol. **60**, 95—102 (1987)
Ji, S.: Watson-crick and prigoginian forms of genetic information. J. Theor. Biol. **130**, 239–245 (1988)
Ji, S.: "Multiple metabolite-multiple target" Hypothesis as applied to benzene and acetaminophen toxicity. Toxicologist **9**(1), 161 (1989)
Ji, S.: The bhopalator – a molecular model of the living cell; New developments. In: Mishra, R.K. (ed.) Molecular and Biological Physics of Living Systems, pp. 187–214. Kluwer Academic, Dordrecht (1990)
Ji, S.: Biocybernetics: a machine theory of biology. In: Ji, S. (ed.) Molecular Theories of Cell Life and Death, pp. 1–237. Rutgers University Press, New Brunswick (1991)
Ji, S.: Complementarism: a new dialogue between science and religion based on modern biology. In: Proceedings of the Fourth KSEA (Korean Scientists and Engineers Association in America) Northeast Regional Conference, pp. 319–328. Stevens Institute of Technology, Hoboken (1993)
Ji, S.: Complementarism: a biology-based philosophical framework to integrate Western science and Eastern Tao. In: Psychotherapy East and West: Integration of Psychotherapies, pp. 517–548. Korean Academy of Psychotherapists, 178–23 Sungbuk-dong, Songbuk-ku, Seoul 136–020, Korea (1995)
Ji, S.: Isomorphism between cell and human languages: molecular biological, bioinformatics and linguistic implications. Biosystems **44**, 17–39 (1997a)
Ji, S.: A cell-linguistic analysis of apoptosis. Comment Toxicol. **5**(6), 571–85 (1997b)
Ji, S.: The cell as the smallest DNA-based molecular computer. Biosystems **52**, 123–133 (1999a)
Ji, S.: The linguistics of DNA: words, sentences, grammar, phonetics, and semantics. Ann. N. Y. Acad. Sci. **870**, 411–417 (1999b)
Ji, S.: Free energy and information contents of C*onformons* in proteins and DNA. Biosystems **54**, 107–130 (2000)
Ji, S.: Isomorphism between cell and human languages: micro- and macrosemiotics. In: Simpkins, S., Deely, J. (eds.) Semiotics 2000: "Sebeok's Century", pp. 357–374. Legas, Ottawa (2001)
Ji, S.: Microsemiotics of DNA. Semiotica **138**(1/4), 15–42 (2002a)
Ji, S.: The Bhopalator: an information/energy dual model of the living cell (II). Fundam. Inform. **49**(1–3), 147–165 (2002b)
Ji, S.: Peircean signs as 'gnergons'. Mailing List complex-science@necsi.org Message #4454 (2002c)
Ji, S.: Towards a unified theory of computing, mind, and signs. In: Cavaliere, M., Martin-Vide, C., Paun, G. (eds.) Reports, pp. 189–197. Research Group on Mathematical Linguistics, Universitat Rovira i Virgili, Tarragona (2003)
Ji, S.: A unified theory of computing/mind/signs. http://necsi.org:8100/Lists/complex-science/Message/4600.html (2003b)
Ji, S.: Molecular information theory: solving the mysteries of DNA. In: Ciobanu, G., Rozenberg, G. (eds.) Modeling in Molecular Biology, Natural Computing Series, pp. 141–150. Springer, Berlin (2004a)

Ji, S. (2004b).: Semiotics of life: a unified theory of molecular machines, cells, the mind, peircean signs, and the universe based on the principle of information- energy complementarity. In: Reports, Research Group on Mathematical Linguistics, XVII Tarragona Seminar on Formal Syntax and Semantics, Rovira i Virgili University, Tarragona, 23–27 April 2003. Available at Google and at http://grammars.grlmc.com/GRLMC/reports/SOLManuscriptsubmitted_final.doc

Ji, S.: Taxonomy of entropy-information relations based on the complementarian logic. See Appendix II. Mailing List complex-science@necsi.org Message #6768 (2004c)

Ji, S.: First, second and third articulations in molecular Ccmputing in the cell. In: Abstracts, 2005 World DNA and Genome Day, Dalian, 25–29 Apr 2005a, p. 77

Ji, S.: 'Self-assembling-whenever-and-wherever-needed (SAWAWN)' machines or systems. http://necsi.org:8100/Lists/complex-science/Message/7710.html (2005b)

Ji, S.: Info-statistical mechanics of cell metabolism. In Abstract, 56th Statistical Mechanics Conference, Rutgers University, Piscataway, 17–19 Dec 2006, p. 6.. Available at http://www.math.rutgers.edu/events/smm/smm96_shorttlks.abs.html (2006a)

Ji, S.: SOWAWN machines and life. http://necsi.org:8100/Lists/complex-science/Message/8370.html (2006b)

Ji, S.: The proteome as an autonomous molecular language. A poster presented at the DIMACS Workshop on Sequences, Structure and Systems Approaches to Predict Protein Function, Rutgers University, Piscataway, 3–5 May (2006c)

Ji, S.: S- and H-categories of entropies. Mailing List complex- science@necsi.org Message #8861 (2006d)

Ji, S.: Soft-state semiconductors of conformons. http://www.necsi.edu/community/forum/viewtopic.php?id=22 (2006e)

Ji, S.: Life an "informed" critical phenomenon? 97th Statistical Mechanics Conference, Rutgers University, Piscataway, 6–8 May (2007a)

Ji, S.: Blood as intelligent fluid, or a SOWAWN machine. http://necsi.org:8100/Lists/complex-science/Message/9051.html (2007b)

Ji, S.: 'Stochastic mechanics' of molecular machines. In: Abstract of short talks, The 99th Statistical Mechanics Conference, Rutgers University, Piscataway, 11–13 May (2008a)

Ji, S.: Modeling the single-molecule enzyme kinetics of cholesterol oxidase based on Planck's radiation formula and the principle of enthalpy-entropy compensation. In: Short talk abstracts, The 100th Statistical Mechanics Conference, Rutgers University, Piscataway, 13–16 Dec (2008b)

Ji, S.: Is Bohr's complementrity recursive? Mailing List complex-science@necsi.org Message #9692 (2008c)

Ji, S.: A category-theoretical framework to integrate physics, biology and informatics based on complementarity and supplementarity principles. A short talk presented at the 106th Statistical Mechanics Conference, Rutgers University, Piscataway, N.J., December 18–29 (2011)

Ji, S.: The Cell Language Theory: Decoding RNA Waves, the Sound of Cell Language. Imperial College Press, London (2012)

Ji, S., Ciobanu, G.: Conformon-driven biopolymer shape changes in cell modeling. Biosystems **70**, 165–181 (2003)

Ji, S., So, K.: The universal law of thermal transitions applicable to blackbody radiation, single-molecule enzymology and whole-cell metabolism. In: Abstract B1, The 102nd Statistical Mechanics Conference, Rutgers University, Piscataway, 13–15 Dec (2009)

Ji, S., Yoo, W.: From genes to modules of RNA metabolism: a comparative analysis of the transcription rates and transcript levels of budding yeast and human lung cells visualized as cell-state biomarkers in the fisher-shannon information plane. In: Abstracts, 2005 World DNA and Genome Day, Dalian, 25–29 Apr 2005, pp. 326–327

Ji, S., Zinovyev, A.: A dynamic second-order clustering method for classifying dissipative structures in living cells. In: The 29th Middle Atlantic Regional Meeting, American Chemical Society, Ursinus College, Collegeville, 20–23 May (2007)

Ji, S., Ray, S.D., Esterline, R.L., Laskin, D.L.: Endocrinouimmunotoxicology of Acetaminophen. FASEB J. **2**(6), A1680 (1988)

Ji, S., Yoo, W., Zinovyev, A.: The freezing-out method of clustering dissipative structures in the transcriptomics of budding yeast. In: DIMACS Workshop on Biomedical Computations, Rutgers University, Piscataway, 18–20 Apr (2007)
Ji, S., Chaovalitwongse, A., Fefferman, N., Yoo, W., Perez-Ortin, J.E.: Mechanism-based clustering of genome-wide mRNA levels: roles of transcription and transcript-degradation rates. In: Butenko, S., Chaovalitwongse, A., Pardalos, P. (eds.) Clustering Challenges in Biological Networks, pp. 237–255. World Scientific, Singapore (2009b)
Ji, S., Bianchini, J., Davidson, A., Kim, W.: Experimental evidence for a quasi-deterministic relation between structural and timing genes in the budding yeast Saccharomyces cerevisiae. In: Abstract, The 101st Statistical Mechanics Conference, Rutgers University, Piscataway, 10–12 May (2009b)
Ji, S., Davidson, A., Bianchini, J.: Genes as molecular machines: microarray evidence that structural genes regulate their own transcripts. A poster presented at the 2009 Joint RECOMB Satellite Conference on Regualtory Genomics, Systems Biology and DREAM4, MIT/The Broad Institute, Cambridge, MA, p. 99 (2009c)
Ji, S., So, K.: The universal law of thermal transitions applicable to blackbody radiation, single-molecule enzymology and whole-cell metabolism, Abstract B1, The 102nd Statistical Mechanics Conference, Rutgers University, Piscataway, N.J., 13–15 Dec (2009d)
Ji, S., Eom, J.K., Lee, K.J.: Identification of the Positively Drug-Responding RNAs in Human Breast Tumors by *Ribonoscopy*, a New Method for Microarray Data Analysis (manuscript under preparation) (2010)
Jin, T., Sasaki, A., Kinjo, M., Miyazaki, J.: A quantum dot-based ratiometric pH sensor. Chem. Commun. **46**, 2408–24510 (2010)
Jirsa, V.K., Kelso, J.A.S.: Coordination Dynamics: Issues and Trends. Springer, Berlin (2004)
Johansson, L.-G.: Interpreting Quatnum Mechanics: A Realistic View in Schrödinger's Vein. Ashgate Publishing Company, Burlington (2007)
Johnston, M.: Feasting, fasting and fermenting: glucose sensing in yeast and other cells. Trends Genet. **15**(1), 29–33 (1999)
Jona, G., Choder, M., Gileadi, O.: Glucose starvation induces a drastic reduction in the rates of both transcription and degradation of mRNA in yeast. Biochim Biophys Acta Gene Struct. Expr. **1491**, 37–48 (2000)
Judson, H.F.: The Eighth Day of Creation: Makers of the Revolution in Biology. Simon & Schuster, New York (1979)
Jung, C.: Synchronicity — An Acausal Connecting Principle. Routledge and Kegan Paul, London (1972)
Junge, W., Müller, D.J.: Seeing a molecular motor at work. Science **333**, 704–705 (2011)
Junge, W., Lill, H., Engelbrecht, S.: ATP synthase: an electrochemical transducer with rotatory mechanics. Trends Biochem. Sci. **22**, 420–423 (1997)
Kaku, M., Trainer, J.: Beyond Einstein: The Cosmic Quest for the Theory of the Universe. Bantam Books, Toronto (1987)
Kane, G.L., Perry, M.J., Zytkow, A.N.: The Beginning of the End of the Anthropic Principle, arXiv:astro-ph/0001197 v2 28 Jan (2000)
Kapanidis, A.N., Margeat, E., Ho, S.O., Kortkhonjia, E., Weiss, S., Ebright, R.H.: Initial transcriptionby RNA polymerase proceeds through a DNA- scrunching mechanism. Science **314**(5802), 1144–47 (2006)
Karam, Sabah: Dualogy: A Category-Theoretic Approach to Dualtiy. Downloaded from http://dualityscience.com/yahoo_site_admin/assets/docs/cdgo2007_PDF.2136 2207.pdf on 12/03/2011 (2011)
Katzung, B.G.: Lange Basic & Clinical Pharmacology, 8th edn. Lange Medical Books/McGraw-Hill, New York (2001)
Keene, J. http://mgm.duke.edu/faculty/keene/ (2006)
Kelso, J.A.S.: Phase transitions and critical behavior in human bimanual coordination. Am. J. Physiol. Regul. Integr. Comp. **15**, R1000–R1004 (1984)

Kelso, J.A.S.: Dynamic Patterns: Self-Organization in Brain Science and Behaviors. MIT Press, Cambridge, MA (1995)
Kelso, J.A.S.: Synergies. Scholarpedia **3**(10), 1611–1616 (2008)
Kelso, J.A.S.: Synergies: atoms of brain and behavior. In: Sternad, D. (ed.) Progress in Motor Control. Springer, New York (2009)
Kelso, J.A.S., EngstrØm, D.A.: The Complementary Nature. The MIT Press, Cambridge, MA (2006)
Kelso, J.A.S., Zanone, P.-G.: Coordination dynamics of learning and transfer across different effector systems. J. Exp. Psychol. **28**(4), 776–797 (2002)
Kimchi-Sarfaty, C., Oh, J.M., Kim, I.W., Sauna, Z.E., Calcagno, A.M., Ambudkar, S.V., Gottesman, M.M.: A "silent" polymorphism in the MDR1 gene changes substrate specificity. Science **315**, 525–528 (2007)
Kirschner, M., Gerhart, J.: Evolvability. Proc. Natl. Acad. Sci. USA **95**, 8420–8427 (1998)
Kirschner, M.W., Gerhart, J.C.: The Plausibility of Life: Resolving Darwin's Dilemma. Yale University Press, New Haven (2005)
Klir, G.J.: Developments in uncertainty-based information. Adv. Comput. **36**, 255–332 (1993)
Klonowski, W., Klonowska, M.T.: Biophysical time on macromolecular level. Biomathematics **80**, 28–33 (1982)
Kocsis, J.J., Jollow, D.J., Witmer, C.M., Nelson, J.O., Snyder, R. (eds.): Biological Reactive Intermedaites II. Plenum, New York (1986)
Kondepudi, D.: Introduction to Thermodynamics. Wiley, Chichester (2008)
Kondepudi, D., Prigogine, I.: Modern Thermodynamics: From Heat Engine to Dissipative Structures. Wiley, Chichester (1998)
Konig, P., Engel, A.K., Singer, W.: Integrator or coincidence detector? The role of the cortical neuron revisited. Trends Neurosci. **19**, 130–137 (1996)
Koomin, E.V., Wolf, Y.I., Karev, G.P.: The structure of the protein universe and genome evolution. Nature **420**, 218–223 (2002)
Koshland Jr., D.E.: Application of a theory of enzyme specificity to protein synthesis. Proc. Natl. Acad. Sci. USA **44**, 98–104 (1958)
Kosko, B.: Fuzzy Thinking: The New Science of Fuzzy Logic. Hyperion, New York (1993)
Koten Jr., J.W., Wood, G., Hagoort, P., Goebel, R., Propiing, P., Willmes, K., Boosma, D.I.: Genetic contribution to variation in cognitive function: an fMRI study in twins. Science **323**, 1737–1739 (2009)
Kovac, L.: Information and knowledge in biology. Plant Signal. Behav. **2**(2), 5–73 (2007)
Kovac, L.: Bioenergetics: a key to brain and mind. Communicative & Integr Biol **1**(1), 114–122 (2008)
Kragh, H.: Max Planck: the reluctant revolutionary. From Physics World, Dec 2000. Available at http://www.physicsworldarchive.iop.org (2000)
Krieglstein, W.: Compassion: A New Philosophy of the Other. Rodopi, Amdsterdam (2002)
Kruger, K., Grabowski, P.J., Zaug, A.J., Sands, J., Gottschling, D.E., Cech, T.R.: Self-splicing RNA: autoexcision and autocyclization of the ribosomal RNA intervening sequence of Tetrahymena. Cell **31**(1), 147–57 (1982)
Kuhn, T.S.: Black-Body Theory and the Quantum Discontinuity, 1894–1912. The University of Chicago Press, Chicago (1978)
Kuhn, K.M., DeRisis, J.L., Brown, P.O., Sarnow, P.: Global and specific translational regulation in the genomic response of saccharomyces cerevisiae to nonfermental carnbon source. Mol. Cell. Biol. **21**(3), 916–927 (2001)
Kundu, J.K., Suhr, Y.-J.: Nrf2-keap1 signaling as a potential target for chemoprevention of inflammation-associated carcinogenesis. Pharm. Res. **27**, 999–1013 (2010)
Kűppers, B.-O.: The context-dependence of biological infomration. In: Kornwachs, K., Jacoby, K. (eds.) Informaiton: New Questions to a Multidisciplinary Concept, pp. 137–145. Akademie Verlag, Berlin (1996)
Kurtz, P.: Science and Religion: Are They Compatible? Prometheus Books, Amherst (2003)

Kurakin, A.: Scale-free flow of life: On the biology, economics, and physics of the cell. Theoret. Biol. Med. Modelling **6**(6), 1–28 (2009) doi: 10.1186/1742-4682-6-6
Kurzynski, M.: Enzymatic catalysis as process controlled by protein conformational relaxation. FEBS Lett. **328**(3), 221–224 (1993)
Kurzynski, M.: Protein machine model of enzymatic reactions gated by enzymes internal dynamics. Biophys. Chem. **65**, 1–28 (1997)
Kurzynski, M.: The Thermodynamic Machinery of Life. Springer, Berlin (2006)
Kyriakis, J.M., Avruch, J.: Mammalian mitogen-activated kinase signal transduction pathways activated by stress and inflammation. Physiol. Rev. **81**(2), 807–869 (2001)
Laidler, K.J.: Chemical Kinetics. McGraw-Hill, New York (1965), Chapter 3
Lama, D.: The Universe in a Single Atom: The Convergence of Science and Spirituality. Broadway Books, New York (2005)
Landau, L.D., Lifshitz, E.M.: Statistical Physics, Part I, 3rd edn, pp. 446–471. Pergamon Press, Oxford (1990)
Larson, A.M., Polson, J., Fontana, R.J., et al.: Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology **42**(6), 1364–72 (2005)
Laskin, D.: Macrophages and inflammatory mediators: a battle of forces. Chem. Res. Toxicol. **22**, 1376–1385 (2009)
Laskin, D.L., Pilaro, A.M., Ji, S.: Potential role of activated macrophages in acetaminophen hepatotoxicity. II. Mechanism of macrophage accumulation and activation. Toxicol. Appl. Pharmacol. **86**(2), 216–226 (1986)
Laskin, D., Sunil, V.R., Fkhrzadeh, L., Groves, A., Gow, A.J.: Macrophages, reactive nitrogen species, and lung injury. Ann. N. Y. Acad. Sci. **1203**, 60–65 (2010)
Laszlo, E.: The Connectivity Hypothesis: Foundation of an Integral Science of Quantum, Cosmos, Life, and Consciousness. State University of New York Press, Albany (2003)
Laughlin, R.: A Different Universe: Reinventing Physics from the Bottom Down. Basic Books, New York (2005)
Lawvere, F.W., Schanuel, S.H.: Conceptual Mathematics: A First Introduction to Categories, 2nd edn. Cambridge University Press, Cambridge, UK (2009)
Layzer, D.: The arrow of time. Sci. Am. **233**, 56–69 (1975)
Lécuyer, E., Yoshida, H., Parthasarathy, N., Babak, T., Cerovina, T., Hughes, T.R., Tomancak, P., Krause, H.M.: Global analysis of mRNA localization reveals a prominent role in organizing cellular architecture and function. Cell **131**, 174–187 (2007)
Lee, M.-H., Schedl, T.: RNA-binding proteins (April 18, 2006), WormBook, ed. The C. elegans Research Community, WormBook. doi: 10.1895/wormbook.1.79.1, http://www.wormbook.org (2011)
Leff, H., Rex, A.: Maxwell's Demon: Entropy. Computing, Princeton University Press, Princeton, Information (1962)
Lehn, J.-M.: Supramolecular chemistry. Science **260**, 762–1673 (1993)
Leigh, E.: Belousov-Zhabotinsky reaction. http://oxygen.fvcc.edu/~dhicketh/Math222/spring05projects/ErikLeigh/BZ.htm (2007)
Lenhardt, J.M., Ong, M.T., Choe, R., Evenhuis, C.R., Martinez, T.J., Craig, S.L.: Trapping a diradical transition state by mechanochemical polymer extension. Science **329**(5995), 1057–60 (2010)
Leopold, P.E., Montal, M., Onuchic, J.N.: Protein folding funnels: a kinetic approach to the sequence-structure relationship. Proc. Nat. Acad. Sci. USA **89**, 8721–8725 (1992)
Lesne, A.: Robustness: confronting lessons from physics and biology. Biol. Rev. **83**, 509–532 (2008)
Leuther, K.K., Johnston, S.A.: Nondissociation of GAL4 and GAL80 in vivo after galactose induction. Science **256**(5061), 1333–1335 (1992)
Levine, A.J., Finalay, C.A., Hinds, P.W.: P53 is a tumor suppressor gene. Cell **S116**, 67–69 (2004)
Lewontin, R.C.: The Genetic Basis of Evolutionary Change. Columbia University Press, New York (1974)

Libbrecht, K.G.: A snowflake primer. www.its.caltech.edu/. . ./primer/primer.htm (2008)
Libby, W.F.: Theory of electron exchanges reaction in aqueous solution. J. Phys. Chem. **56**, 863–868 (1952)
Lindley, D.: Uncertainty: Einstein, Heisenberg, Bohr, and the Struggle for the Soul of Science. Anchor Books, New York (2008)
Link, A.J., Robison, K., Church, G.M.: Comparing the predicted and observed properties of proteins encoded in the genome of Escherichia coli K-12. Electrophoresis **18**, 1259–1313 (1997)
Livnah, O., Stura, E.A., Mideleton, S.A., Johnson, D.L., Jolliffe, L.K., Wilson, I.: Crystallographic evidence for preformed dimmers of erythropoietin receptor before ligand activation. Science **283**, 987–990 (1999)
Lloyd, S.: Programming the Universe: A Quantum Computer Scientist Takes on the Cosmos. Alfred A Knopf, New York (2006)
Lloyd, S.: Quantum mechanics and emergence. In: Abbott, D., Davies, P.C., Pati, A.K. (eds.) Quantum Aspects of Life, pp. 19–30. Imperial College Press, London (2009)
Lockless, S.W., Ranganathan, R.: Evolutionarily conserved pathways of energetic connectivity in protein families. Science **286**, 295–299 (1999)
Loftus, B.J., et al.: The genome of the basidiomycetous yeast and human pathogen cryptococcus neoformans. Science **307**, 1321–1324 (2005)
Lu, H.P., Xun, L., Xie, X.S.: Single-molecule enzymatic dynamics. Science **282**, 1877–1882 (1998)
Luiza, K.-K., Stanislaw, S., Mariusz, K., Andrzej, W., Tadeusz, R., Mariola, M.: The role of connexions in carcinogenesis: review of current knowledge. Current Signal Transduction Therapy **2**(1), 49–56 (2007)
Lumry, R.: Conformational mechanisms for free energy transduction in protein systems: old ideas and new facts. Ann. N. Y. Acad. Sci. **227**, 46–73 (1974)
Lumry, R.: The protein primer. Available at http://www.chem.umn.edu/groups/lumry/Volume_2_Protein_Primer/ (2009)
Lumry, R., Biltonen, R.: In: Timasheff, S.N., Fasman, G.D. (eds.) Structure and Stability of Biological Macromolecules, pp. 65–212. Marcel Dekker, New York (1969)
Lumry, R., Gregory, R.B.: Free-energy management in protein reactions: concepts, complications, and compensation. In: Welch, G.R. (ed.) The Fluctuating Enzymes, pp. 1–190. Wiley, New York (1986)
Lyons, J.: Language and Linguistics, pp. 23, 228–235. Cambridge University Press, Cambridge, UK (1992)
Lyons, J.: Semantics I. Cambridge University Press, New York (1993)
MacLennan, D.H., Green, N.M.: Pumping ions. Nature **405**, 633–634 (2000)
Makeyev, E.V., Maniatis, T.: Multilevel regulation of gene expression by microRNAs. Science **319**, 1789–1790 (2008)
Mamontov, E., Psiuk-Maksymowitcz, K., Koptioug, A.: Stochastic mechanics in the context of the properties of living systems. Math. Comp. Modeling **44**(7–8), 595–607 (2006)
Marcus, S.: Linguistic structures and generative devices in molecular genetics. Cahiers de linguistique: théorique et appliquée **11**, 77–104 (1974)
Maruyama, K., Nori, F., Vedral, V.: Colloquium: The physics of Maxwell's demon and information, Rev. Mod. Phys. **81**, 1–23 (2009)
Mattick, J.S.: Challenging the dogma: the hidden layer of non-protein-coding RNAs in complex organisms. Bioessays **25**(10), 930–939 (2003)
Mattick, J.S.: RNA regulation: a new genetics? Nat. Rev. Genet. **5**, 316–323 (2004)
Mayr, E.: One Long Argument: Charles Darwin and the Genesis of Modern Evolutionary Thought. Harvard University Press, Cambridge, MA (1991)
McClain, C.J., Kromhout, J.P., Peterson, F.J., Holtzman, J.L.: Potentiation of acetaminophen hepatotoxicity by alcohol. JAMA **244**(3), 251–253 (1980)
McClare, C.W.F.: Chemical machines, maxwell's demon and living organisms. J. theoret. Biol. **30**, 1–34 (1971)

McClare, C.W.F.: Resonance in bioenergetics. Ann. N. Y. Acad. Sci. **227**, 74–97 (1974)
McGervey, J.D.: Quantum Mechanics: Concepts and Applications. Academic, San Diego (1995)
McGuffee, S.R., Elcock, A.H.: Diffusion, crowding and protein stability in a dynamic molecular model of the bacterial cytoplasm. PLoS Comput. Biol. **6**(3), e1000694 (2010). doi:10.1371/journal.pcbi.1000694
McKaughan, D.J.: The influence of Niels Bohr on max delbrück. Isis **96**, 507–529 (2005)
McNeill, D., Freiberger, P.: Fuzzy Logic: The Revolutionary Computer Technology That Is Changing our World. Simon & Schuster, New York (1993)
Mendes-Ferreira, A., del Olmo, M., García-Martínez, J., Jimenez-Martí, A., Mendes-Faia, A., Pérez-Ortín, J.E., Leão, C.: Trsnscriptional response of saccharomyces cerevisiae to different nitrogen concnetrations during alcoholic fermentaion. Appl. Environ. Microbiol. **73**(9), 3049–3060 (2007)
Mermin, N.D.: Boojums All The Way Through: Communicating Science in a Prosaic Age. Cambridge University Press, Cambridge, UK (1990), Chapter 12
Merrell, F.: Semiosis in the Postmodern Age. Purdue University Press, West Lafayette (1995)
Meyer, M., Vilardell, J.: The quest for a message: budding yeast, a model organism to study the control of pre-mRNA splicing. Brief. Funct. Genomic. Proteomic. **8**(1), 60–67 (2009)
Michaelis, L., Menten, M.L.: Die kinetik der invertinwirkung. Biochem. Z. **49**, 333–369 (1913)
Mikula, S., Niebur, E.: The effects of input rate and synchrony on a coincidence detector - analytical solution. Neural Computat. **5**(3), 539–547 (2003)
Miller, K.R.: Only A Theory: Evolution and the Battle for America's Soul. Viking, New York (2008)
Miller, M.B., Bassler, B.L.: Quorum sensing in bacteria. Ann. Rev. Microbiol. **55**, 165–199 (2001)
Min, W., English, B.P., Luo, G., Cherayil, B.J., Kou, S.C., Xie, X.S.: Fluctuating enzymes: lessons from single-molecule studies. Acc. Chem. Res. **38**, 923–931 (2005)
Minton, A.P.: The influence of macromolecular crowding and macromolecular confinement on biochemical reactions in physiological media. J. Biol. Chem. **276**, 10577–10580 (2001)
Mitchell, P.: Coupling of phosphorylation to electron and hydrogen transfer by a chemiosmotic type of mechanism. Nature **191**, 144–148 (1961)
Mitchell, P.: Chemiosmotic Coupling and Energy Transduction. Glyn Research Ltd, Bodmin (1968)
Miyazawa, S.A., Jernigan, R.L.: Residue-residue potentials with a favourable contact pair term and an unfavourable high packing density term, for simulation and threading. J. Mol. Biol. **256**, 623–644 (1996)
Mogilner, A., Elston, T.C., Wang, H., Oster, G.: Molecular motors: theory. In: Fall, C.P., Marland, E.S., Wagner, J.M., Tyson, J.J. (eds.) Computational Cell Biology, pp. 320–353. Springer, New York (2002)
Mohrhoff, U.: Why the laws of physics are so. Found. Phys. **32**(8), 1313–1324 (2002)
Moin, P., Kim, J.: Tackling turbulence with supercomputers. Sci. Am. **276**(1), 62–68 (1997)
Mok, K.C., Wingreen, N.S.D., Bassler, B.L.: *Vibrio harveyi* quorum sensing: a coincidence detector for two autoinducers controls gene expression. EMBO J. **22**, 870–881 (2003)
Monod, J.: Chance and Necessity, p. 105. Vantage Books, New York (1971)
Moore, W.J.: Physical Chemistry, 3rd edn. Prentice-Hall, Englewood Cliffs (1963)
Morata, G., Sánchez-Herrero, E.: Pulling a fly's leg. Nature **392**, 657–658 (1998)
Moriyasu, K.: An Elementary Primer for Gauge Theory. World Scientific, Singapore (1985). p. vii
Morrison, M.A.: Understanding Quantum Physics: A User's Manual, p. 169. Prentice-Hall, Englewood (1990)
Mundios, S., Olsen, B.R.: Heritable diseases of the skeleton. Part I: molecular insights into skeletal development—transcription factors and signaling pathways. FASEB J. **11**, 125–132 (1997)
Murdoch, D.: Niels Bohr's Philosophy of Physics. Cambridge University Press, Cambridge, UK (1987)
Murray, J.D.: How the leopard gets its spots. Sci. Am. **258**(3), 80–87 (1988)

Myer, M., Vilardell, J.: The quest for a message: budding yeast, a model organism to study the control of pre-mRNA slicing. In: Briefings Gunctional Genomics Proteomics, **8**(1), 60–67 (2009)
Myung, J., Jencks, W.P.: There is only one phosphoenzyme intermediate with bound calcium on the reaction pathway of the sarcoplasmic reticulum calcium ATPase. Biochemistry **34**, 3077–3083 (1995)
Nahvi, A., Sudarsan, N., Ebert, M.S., Zou, X., Brown, K.L., Breaker, R.R.: Genetic control by a metabolite binding mRNA. Chem. Biol. **9**(9), 1043–1049 (2002). doi:10.1016/S1074-5521(02)00224-7 DOI:dx.doi.org. PMID 12323379
Nase, G., Singer, W., Monyer, H., Engel, A.K.: Features of neuronal synchrony in mouse visual cortex. J. Neurophysiol. **90**, 1115–1123 (2003)
Nauta, D.: The Meaning of Information. Mouton, The Hague (1972)
Nave, R.: Blackbody radiation. http://hyperphysics.phys-astr.gsu.edu/ hbase/mod6.html (2009)
Newman, S.A., Bhat, R.: Genes and proteins: dogmas in decline. J. Biosci. **32**(6), 1041–1043 (2007)
Nguyen, T., Nioi, P., Pickett, C.B.: The Nrf2-antioxidant response element signaling pathway and its activation by oxidative stress. J. Biol. Chem. **284**(20), 13291–13295 (2009)
Nicholls, D.G.: Bioenergetgics: An Introduction to the Chemiosmotic Theory. Academic, London (1982)
Nicolis, G., Prigogine, I.: Self-Organization in Nonequilibrium Systems. Wiley, New York (1977)
Nishikawa, T., Gulbahce, N., Motter, A.E.: Spontaneous reaction silencing in metabolic optimization. PLoS Comput. Biol. **4**(12), e1000236 (2008)
Norris, V.: Modeling *E. coli*: the concept of competitive coherence. Comptes Rendues de l'Academie des Sciences **321**, 777–787 (1998)
Norris, V., et al.: Hypothesis: hyperstructures regulate bacterial structure and the cell cycle. Biochimie **81**, 915–920 (1999)
Norris, V., den Blaauwen, T., Cabin-Flaman, A., Doi, R.H., Harshey, R., Janniere, L., Jimenez-Sanchez, A., Jin, D.J., Levin, P.A., Mileykovskaya, E., Minsky, A., Saier Jr., M., Skarstad, K.: Functional taxonomy of bacterial hyperstructures. Microbiol. Mol. Biol. Rev. **71**(1), 230–253 (2007a)
Norris, V., den Blaauwen, T., Doi, R.H., Harshey, R.M., Janniere, L., Jimenez-Sanchez, A., Jin, D. J., Levin, P.A., Mileyknovskaya, E., Minsky, A., Misevic, G., Ripoll, C., Saier Jr., M., Skarstad, K., Thellier, M.: Toward a hyperstructure taxanomy. Annu. Rev. Microbiol. **61**, 309–329 (2007b)
Northrup, S.H., Hynes, J.: The stable state picture of chemical reactions I formulation for rate constants and initial condition effects. J. Chem. Phys. **73**(6), 2700–2714 (1980)
Nudler, E., Mironov, A.S.: The riboswitch control of bacterial metabolism. Trends Biochem. Sci. **29**(1), 11–7 (2004). doi:10.1016/j.tibs.2003.11.004 DOI:dx.doi.org. PMID 14729327
Oerter, R.: The Theory of Almost Everything: The Standard Model, the Unsung Triumph of Modern Physics. Pi Press, New York (2006)
Okamoto, O.K.: DNA microarrays in cancer diagnosis and prognosis. Einstein **3**(1), 31–34 (2005)
Pagel, H.R.: The Cosmic Code: Quantum Physics as the Language of Nature. Simon & Schuster, New York (1982)
Pagels, H.R.: The Cosmic Code: Quantum Mechanics as the Language of Nature. Simon & Schuster, New York (1982)
Pais, A.: Niels Bohrs' Times, in Physics, Philosophy, and Polity, pp. 438–447. Clarendon Press, Oxford (1991)
Pattee, H.H.: The physical basis of coding and reliability in biological evolution. In: Waddington, C.H. (ed.) Towards a Theoretical Biology 1 Prolegomena. Aldine Publishing, Chicago (1968)
Pattee, H.: How does a molecule become a message? In: Lang, A. (ed.) Communication in Development, pp. 1–16. Academic, New York (1969)
Pattee, H.: Cell psychology: an evolutionary approach to the symbol-matter problem. Cogn. Brain Theory **5**(4), 325–341 (1982)

Pattee, H.: Evolving self-reference: matter, symbols, and semantic closure. Commun. Cogn. – Artif. Intell. **12**(1–2), 9–27 (1995)
Pattee, H.: The physics of symbols and the evolution of semiotic controls. In*:* Coombs, M., Sulcoski, M. (eds.) In Proceedings of the 1996 International Workshop on Control Mechanisms for Complex Systems*,* Issues of Measurement & Semiotic Analysis La Cruces, New Mexico, December 8–12 (1996)
Pattee, H.: The physics of symbols: bridging the epistemic cut. Biosystems Santa Fe Institute Studies in the Sciences of Complexity **60**, 5–12 (2001)
Pattee, H.: The necessity of biosemiotics: matter-symbol complementarity. In: Barbieri, M. (ed.) Introduction to Biosemiotics, pp. 115–132. Cambridge University Press, Cambridge, UK (2008)
Paun, G.: Membrane Computing: An Introduction. Springer, Berlin (2002)
Paun, A., Paun, G., Rozenberg, G.: Computing by communication in networks of membranes. J. Fnd. Comp. Sci. **13**(6), 774–798 (2002)
Pease, A.C., Solas, D., Sullivan, E.J., Cronin, M.T., Holmes, C.P., Fodor, S.P.: Light-generated oligonucleotide arrays for rapid DNA sequence analysis. Proc. Nat. Acad. Sci. USA **91**, 5022–26 (1994)
Peeva, K., Zahariev, Z.: Computing behavior of finite fuzzy machines – algorithm and its application to reduction and minimization. Inform. Sci. **178**, 4152–4165 (2008)
Peirce, C.S.: On a new list of categories. Proc. Nat. Acad. Sci. USA **7**, 287–298 (1868)
Peirce, C.S.: The categories defined. In: Houser, N. (ed.) The Essential Peirce: Selected Philosophical Writings, Volume 2 (1893–1913), pp. 160–178. Indiana University Press, Bloomington (1903)
Perou, C.M., Jeffrey, S.S., van de Rijn, M., et al.: Distinctive gene expression patterns in human mammary epithelial cells and breast cancers. Proc. Natl. Acad. Sci. USA **96**(16), 9212–7 (1999)
Perou, C.M., Sorlie, T., Eisen, M.B., et al.: Molecular portraits of human breast tumors. Nature **406**(6797), 747–52 (2000)
Perutz, M.F.: Physics and the riddle of life. Nature **326**, 555–559 (1987)
Petruccioli, S.: Atoms, Metaphors and Paradoxes: Niels Bohr and the Constructiion of a new Physics. Cambridge University Press, Cambridge, UK (1993)
Pielak, G.J.: A model of intracellular organization. Proc. Nat. Acad. Sci. **102**(17), 5901–5902 (2005)
Pierce, J.R.: Introduction to Information Theory. Second, Revised Edition. Dover, New York (1980)
Pinker, S.: The Blank Slate. Penguin Books, London. p. xi (2003)
Pinker, S.: The Riddle of Knowing You're Here. In: Your Brain: A User's Guide. Time Books, New York, pp. 12–19 (2011)
Planck, M.: On an improvement of Wien's equation for the spectrum. Verhandl. Dtsch. phys. Ges **2**, 202 (1900)
Plotnitsky, A.: Reading Bohr: Physics and Philosophy. Springer, Kindle Edition (2006)
Polanyi, M.: *Personal Knowledge*, Corrected edition, Routledge, London (1958/62)
Polanyi, M.: Life's irreducible structure: live mechanisms and information in DNA are boundary conditions with a sequence of boundaries above them. Science **160**, 1308–1312 (1968)
Polkinghorne, J.: Science & Theology. Fortress Press, Minneapolis (1998)
Polkinghorne, J.: Quantum Theory: A Very Short Introduction. Oxford University Press, Oxford (2002)
Poole, A.M., Ranganathan, R.: Knowledge-based potentials in protein design. Curr. Opin. Struct. Biol. **16**, 508–513 (2006)
Popper, K: Three Worlds, the Tanner Lecture of Human Values, delivered at The University of Michigan, April 7 (1978)
Port, R.F., van Gelder, T.: Mind as Motion: Explorations in the Dynamics of Cognition. MIT Press, Cambridge, MA (1995)

Prakash, M.K., Marcus, R.A.: An interpretation of fluctuations in enzyme catalysis, spectral diffusion, and radiative component of lifetimes in terms of electric field fluctuations. Proc. Nat. Acad. Sci. USA **104**(41), 15982–15987 (2007)

Prescott, L.F.: Paracetamol, alcohol and the liver. Br. J. Clin. Pharmacol. **49**(4), 291–301 (2000)

Pribram, K.H.: An Instantiation of eccles Brain/Mind dualism and Beyond. In: Amoroso, R.L. (ed.) Complementarity of Mind and Body: Realizing the Dream of Descartes, Einstein and Eccles. Nova Science Publishers, New York (2010)

Prigogine, I.: Dissipative structures and biological order. Adv. Biol. Med. Phys. **16**, 99–113 (1977)

Prigogine, I.: From Being To Becoming: Time and complexity in Physical Sciences, pp. 19–26. W. H. Freeman, San Francisco (1980)

Prigogine, I.: Schrödinger and the riddle of life. In: Ji, S. (ed.) Molecular Theories of Cell Life and Death, pp. 239–242. Rutgers University Press, New Brunswick (1991)

Prigogine, I., Lefever, R.: Symmetry-breaking instabilities in dissipative systems. II. J. Chem. Phys. **48**, 1695–1700 (1968)

Purves, W. K.: Life: The Science of Biology. W. H. Freeman, San Francisco (2003)

Putnam, H:. Brain and Behavior, originally read as part of the program of the American Association for the Advancement of Science, Section L (History and Philosophy of Science) (27 Dec 1961)

Qian, H.: Open-system nonequilibrium steady state: statistical thermodynamics, fluctuations, and chemical oscillations. J. Phys. Chem. B **110**, 15063–15074 (2006)

Qian, H.: Phosphorylation energy hypothesis: open chemical systems and their biological functions. Annu. Rev. Phys. Chem. **58**, 113–42 (2007)

Qian, H., Xie, S.: Generalized haldane equation and fluctuation theorem in the steady-state cycle kinetics of single enzymes. Phys. Rev. E **74**, 0100902(R) (2006)

Ramond, P.: Field Theory: A Modern Primer. Benjamin, Reading (1981)

Ravindranathan, K.P.: Free energy landscape for the allosteric conformational change of the ribose binding protein. In: Abstracts, 17th Annual Molecular Biophysics Minisymposium Center for Molecular Biophysics and Biophysical Chemistry, Rutgers University, Piscataway (6 May 2005)

Ravindranathan, K.P., Galllichio, E., Levy, R.M.: Conformational equilibria and free energy profiles for the allosteric transition of the ribose-binding protein. J. Mol. Biol. **353**, 196–210 (2005b)

Reece, R.J., Maxwell, A.: DNA gyrase: structure and function. Critical Rev. Biochem. Mol. Biol. **26**(3/4), 335–375 (1991)

Reid, R.G.B.: Biological Emergences: Evolution by Natural Experiment. MIT Press, Cambridge, MA (2007)

Revyakin, A., Liu, C., Ebright, R.H., Strick, T.R.: Abortive initiation and productive initiation by RNA polymerase involve DNA scrunching. Science **314**(5802), 1139–43 (2006)

Reynolds, W.L., Lumry, R.: Mechanisms of Electron Transfer. The Ronald Press Company, New York (1966), Chapter 1

Rhodes, D.R., Chinnaiyan, A.M.: Bioinformatics strategies for translating genome-wide expression analyses into clinically useful cancer markers. Ann. N. Y. Acad. Sci. **1020**, 32–40 (2004)

Ricard, J.: Emergent Collective Properties, Networks and Information in Biology. Elsevier, Amsterdam (2006)

Riddihough, G., Zahn, L.M.: What is epigenetics? Science **330**, 611 (2010)

Rizzzotti, M.: Defining Life: The Central Problem in Theoretical Biology. University of Padova, Padova (1996)

Roederer, J.G.: On the concept of information and its role in nature. Entropy **5**, 3–33 (2003)

Roederer, J.G.: When and where did information first appear in the universe? In: Seckbach, J. (ed.) Bioinformatics. Kluwer Academic, Dordrecht (2004)

Roldán, M.L., Lánus, H., Brandán, S.A., López, J.J., Varetti, E.L., Ben Altabef, A.: The infrared and Raman spectra of tetrachlorrphosphonium (V) oxotetrachlorovanadate (V), PCL_4VOCL_4. an experimental and theoretical study. J. Argentine Chem. Soc **92**(1/3), 53–61 (2004)

Roll-Hansen, N.: The application of complementarity to biology: from Niels Bohr to max Delbrück. Hist. Stud. Phys. Biol. Sci. **30**(2), 417–442 (2000)
Ronne, H.: Glucose repression in fungi. Trends Genet. **11**(1), 12–17 (1995)
Rosen, R.: Life Itself. Columbia University Press, New York (1991)
Rosen, R.: On the limitations of scientific knowledge. In: Casti, J.L., Karlquist, A. (eds.) Boundaries and Barriers: On the Limits of Scientific Knowledge, pp. 199–214. Perseus Books, Reading (1996)
Rosenblum, B., Kuttner, F.: Qutnaum Enigma: Physics Encouters Consciousness. Oxford University Press, New York (2006)
Ruse, M.: The Evolution-Creation Struggle. Harvard University Press, Cambridge, MA (2005)
Ryder, L.H.: Quantum Field Theory. Cambridge University Press, Cambridge, UK (1985)
Ryder, S.D., Beckingham, I.J.: ABC of diseases of liver, pancreas, and biliary system. Other causes of parenchymal liver disease. BMJ **322**(7281), 290–92 (2001)
Salthe, S.N.: Development and Evolution. MIT Press, Cambridge, MA (1993)
Salthe, S.N.: Development and Evolution: Complexity and Change in Biology, pp. 5–10, 20–25, and 131–136.MIT Press, Cambridge, MA (1996)
Salthe, S.N.: Personal communication (2009)
Sapp, J.: Beyond the Gene: Cytoplasmic Inheritance and the Struggle for *Authority in Genetics*. Oxford University Press, New York (1987)
Sawada, D., Caley, M.: Complementarity: a recursive revision appropriate to human science. Anthropol. Conscious. **4**(2), 1–8 (1993). page. Available at http:/www.anthrosource.net
Sawyer, D.W., Sullivan, J.A., Mandell, G.L.: Intracellular free calcium localization in neutrophils during phagocytosis. Science **230**, 663–666 (1985)
Schena, M., Shalon, D., Davis, R.W., Brown, P.O.: Quantitative monitoring of gene expression patterns with a complementary DNA microarray. Science **270**, 467–470 (1995)
Schmeing, M., Ramakrishnan, V.: What recent ribosome structures have revealed about the mechanism of translation. Nature **461**, 1234 (2009)
Schmucker, D., Clemens, J.C., Shu, H., Worby, C.A., Xiao, J., MUda, M.: Drosophila Dscam is an axon guidance receptor exhibiting extraordinary molecular diversity. Cell **101**(6), 671–684 (2000)
Schneuwly, S., Kuroiwa, A., Gehring, W.J.: Molecular analysis of the dominant homeotic *Antennapedia* phenotype. EMBO J. **6**, 201–206 (1987)
Scholz, J.P., Schöner, G.: The uncontrolled manifold concept: identifying control variables for a functional task. Exp. Brain Res. **126**, 289–306 (1999)
Schrödinger, E.: What Is Life? With Mind and Matter and Autobiographical Sketches. Cambridge University Press, Cambridge, UK (1998)
Schwede, T., Peitsch, M. (eds.): Computational Structural Biology: Methods and Applications. World Scientific, New Jersey (2008)
Scott, A. (ed.): Encyclopedia of Nonlinear Science. Routledge, New York (2005)
Scruton, R.: Spinoza, p. 16. Routledge, New York (1999)
Sears, C., Armstrong, S.A.: Microarrays to identify new therapeutic strategies for cancer. Adv. Cancer Res. **96**, 51–74 (2007)
Sebeok, T.A.: The sign science and the life science. In: Bernard, J., Deely, J., Voigt, V., Withalm, G. (eds.) Symbolicity, pp. 243–252. University Press of America, Lanham (1990)
Seger, R., Krebs, E.G.: The MAPK signaling cascade. FASEB J. **9**, 726–735 (1995)
Seife, C.: Decoding the Universe: How the New Science of Information Is Explaining Everything in the Cosmos, from Our Brain to Balck Holes. Viking, New York (2006)
Shadowitz, A.: Special Relativity, pp. 84–105. Dover, New York (1968)
Shannon, C.E., Weaver, W.: The Mathematical Theory of Communication. University of Illinois, Urbana (1949)
Shapiro, D.J., Blume, J.E., Nielsen, D.A.: Regulation of messenger RNA stability in eukaryotic cells. Bioessays **6**(5), 221–226 (1986)

Sheriff, J.K.: Charles Peirce's Guess at the Riddle: Grounds for Human *Significance*. Indiana University Press, Bloomington (1994)
Short, T.L.: Peirce's Theory of Signs. Cambridge University Press, Cambridge, UK (2007)
Simpson, G.G.: This View of Life, Harcourt. Brace & World, New York (1964)
Skulachev, V.P., Hinkle, P.C.: Chemiosmotic Proton Circuits in Biological Membranes. Addison-Wesley Publishing Company, London (1981)
Smith, H.A., Welch, G.R.: Cytosociology: a field-theoretic view of cell metabolism. In: Ji, S. (ed.) Molecular Theories of Cell Life and Death, pp. 282–323. Rutgers University Press, New Brunswick (1991)
Socolich, M., Lockless, S.W., Russ, W.P., Lee, H., Gardneer, K.H., Ranganathan, R.: Evolutionary information for specifying a protein fold. Nature **437**, 512–518 (2005)
Spirkin, A.: Dialectical Materialism, Progress Publishers, Moscow. The on-line edition transcribed by R. J. Cymbala in 2002 is available at document. http://www.marxists.org/reference/archive/spirkin/works/dialectical- materialism/ch02-s09.htm (1983)
Sporns, O.: Networks of the Brain. The MIT Press, Boston (2011)
Srere, P.A.: Complexes of sequential metabolic enzymes. Ann. Rev. Biochem. **56**, 89–124 (1987)
Stahl, W.R.: Dimensional analysis in mathematical biology. Bull. Math. Biophys. **23**, 355–376 (1961)
Stanley, H.E.: Scaling, universality, and renormalization: Three pillars of modern critical phenomena. Rev. Mod. Phys. **71**(2), S358–S366 (1999)
Stauffer, D., Aharony, A.: Introduction to Percolation Theory. Routlege, London (1994)
Stein, W.D., Eilam, Y., Lieb, W.R.: Active transport of cations across biological membranes. Ann. N. Y. Acad. Sci. **227**, 328–336 (1974)
Stengel, R.: Gene expression profiling of colon cancer and metastases. A seminar presented at the Institute for Advanced Studies, Princeton, 17 June 2005
Stenholm, S.: The Quest for Reality: Bohr and Wittgenstein, Two Complementary Views. Oxford University Press, Oxford (2011)
Stenmark, D.: The Relationship between Information and Knowledge. In: *Proceedings of IRIS 24*, Ulvik, Norway (2001)
Stent, G.S.: The Max Delbruck lecture: light and life – Niels Bohr's legacy to contemporary biology. Genome **31**(1), 11–15 (1989)
Stephenson, W.: William James, Niels Bohr, and Complementarity. The Psychol. Rec. **36**, 519–527 (1986)
Sternad, D., Turvey, M.T.: Control parameters, equilibria, and coordination dynamics. The Behav and Brain Sci **18**, 780–783 (1966)
Stock, A.M., Robinson, V.L., Goudreau, P.N.: Two-component signal transduction. Ann. Rev. Biochem. **69**, 183–215 (2000)
Stockholm, D., Benchaouir, R., Picot, J., Rameau, P., Neildez, T.M.A., Landini, G., Laplace-Builhe, C., Paldi, A.: The origin of phenotypic heterogeneity in a clonal cell population in vitro. PLoS One **2**(4), 3394 (2007)
Storz, G.: An expanding universe of noncoding RNAs. Science **296**, 1260–1263 (2002)
Stryer, L.: Biochemistry, 3rd edn. W. H. Freeman, New York (1995)
Stumpf, M.P.H., Thorne, T., de Silva, E., Stewart, R., An, H.J., Lappe, M., Wiuf, C.: Estimating the size of the human interactome. Proc. Nat. Acad. Sci. USA **105**, 6959–6964 (2008)
Süel, G.M., Lockless, S.W., Wall, M.A., Ranganathan, R.: Evolutionarily conserved networks of residues mediate allosteric communication in proteins. Nat. Struct. Biol. **10**(1), 59–69 (2003)
Surh, Y.J.: Cancer chemoprevention with dietary phytochemicals. Nat. Rev. Cancer **3**, 768–780 (2003). doi:doi:10.1038/nrc1189
Suter, B., Kittanakom, S., Stagljar, I.: Interactive proteomics: what lies ahead? Biotechniques **44**, 681–691 (2008)
Swanson, C.P.: The Cell, 2nd edn. Prentice-Hall, Englewood Cliffs (1964)
Swindale, N.V.: Neural synchrony, axonal path lengths, and general anesthesia: a hypothesis. Neuroscientist **9**, 440–445 (2003)

Taft, R. J. and Mattick, J.S.: Increasing biological complexity is positively correlated with the relative genome-wide expansion of non-protein-coding DNA, arXiv.org/ftp/q-biol/papers/0401/0401020.pdf. Downloaded on 01/04/2012 (2012)
Tanenbaum, A.S.: Structured Computer Organization, 4th edn. Prentice-Hall of India, New Delhi (2003). 5
Tang, J., Breaker, R.R.: Structural diversity of self-cleaving ribozymes. Proc. Natl. Acad. Sci. U.S. A. **97**(11), 5784–9 (2000)
Thompson, E.: Mind in Life. Harvard University Press, Cambridge, MA (2009)
Tjian, R.: Molecular machines that control genes. Sci. Am. **272**(2), 54–61 (1995)
Tolman, R.C.: The Principles of Statistical Mechanics, pp. 42–46. Dover, New York (1979)
Tominaga, M., Kojima, H., Yokota, E., Orii, H., Nakamori, R., Katayama, E., Anson, M., Shimmen, T., Kazuhiro Oiwa, K.: Higher plant myosin XI moves processively on actin with 35 nm steps at high velocity. EMBO J. **22**, 1263–1272 (2003)
Tong et al: Synthetic genetic analysis with ordered arrays of yeast deletion mutants. Science **294**, 2364–2374 (2001)
Toyabe, S., Sagawa, T., Ueda, M., Muneyuki, E. and Sano, M.: Experimental demonstration of information-to-energy conversion and validation of the generalized Jarzynski equality. *Nature Physics* **6**, 988–992 (2010)
Toyoshima, C., Nakasako, M., Nomura, H., Ogawa, H.: Crystal structure of calcium ion pump of sarcoplasmic reticulum at 2.6 Å resolutions. Nature **405**, 647–55 (2000)
Troester, M.A., Hoadley, K.A., Sφ rlie, T., Herbert, B.-S., Bφrresen-Dale, A.-L., Lφnning, P.E., Shay, J.W., Kaufmann, W.K., Perou, C.M.: Cell- type-specific responses to chemotherapeutics in breast cancer. Cancer Res. **64**, 4218–4226 (2004)
Trosko, J.E.: Gap Junctional intercellular communication as a biological "Rosetta Stone" in understanding, in a systems biological manner, stem cell behavior, mechanisms of epigenetic toxicology, chemoprevention and chemotherapy. J. Membrane Biol. **218**(1–3), 93–100 (2007)
Trosko, J.E., Ruch, R.J.: Cell-cell communication in carcinogenesis. Front. Biosci. **3**, D208–D236 (1998)
Tu, B.P., Kudlicki, A., Towicka, M., McKnight, S.L.: Logic of the yeast metabolic cycle: temporal compartmentalization of cellular processes. Science **310**, 1151–1158 (2005)
Tucker, B.J., Breaker, R.R.: Riboswitches as versatile gene control elements. Curr. Opin. Struct. Biol. **15**(3), 342–8 (2005). doi:10.1016/j.sbi.2005.05.003 DOI:dx.doi.org. PMID 15919195
Turing, A.: The chemical basis of morphogenesis. Phil. Trans. R. Soc. Lond., Ser. B, Biol. Sci. **237** (641), 37–72 (1952)
Turvey, M.T., Carello, C.: Dynamics of Bernstein's level of synergies. In: Latash, M., Turvey, M. T. (eds.) Dexterity and its Development, pp. 339–376. Hillsdale, Erlbaum (1996)
Turvey, M.T., Kugler, P.N.: A comment on equating information with symbol strings. Am. J. Physiol. **246**, R925–R927 (1984) (Regulatory Integrative Comp. Physiol. 15)
Uchihashi, T., Iino, R., Ando, T., Noji, H.: High-speed atomic force microscopy reveals rotary catalysis of Rotorless F_1-ATPase. Science **333**, 755–758 (2011)
Uetz, P., Giot, L., et al.: A comprehensive analysis of protein-protein interactions in *Saccharomyces cerevisiae*. Nature **403**, 623–627 (2000)
Umerez, J.: Howard Pattee's theoretical biology: a radical epistemological stance to approach life, evolution and complexity. Biosystems **60**(1–3), 159–177 (2001)
van Gelder, T., Port, R.F.: It's About time: an overview of the dynamical approach to cognition. In: Mind as Motion: Explorations in the Dynamics of Cognition, pp. 1–43. MIT Press, Cambridge, MA (1995)
van Hemmen, J.L., Morgenstern, I. (eds.): Heidelerg Colloquium on Spin Glasses. Springer, Berlin (1983)
van Oijen, A.M., Loparo, J.J.: Single-molecule studies of the replisome. Annu. Rev. Biophys. **39**, 429–48 (2010)
van't Veer, L., Bernards, R.: Enabling personalized cancer medicine through analysis of gene-expression patterns. Nature **452**(7187), 564–70 (2008)

Vitreschak, A.G., Rodionov, D.A., Mironov, A.A., Gelfand, M.S.: Riboswitches: the oldest mechanism for the regulation of gene expression. Trends Genet. **20**(1), 44–50 (2004). doi:10.1016/j.tig.2003.11.008 DOI:dx.doi.org. PMID 14698618
Vogelstein, B., Lane, D., Levine, A.J.: Surfing the p53 network. Nature **408**, 307–310 (2000)
Volkenstein, M.V.: The conformon. J. Theoret. Biol. **34**, 193–195 (1972)
Volkenstein, M.V.: Electronic-conformational interaction in biopolymers. In: Welch, G.R. (ed.) The Fluctuating Enzymes, pp. 403–419. Wiley, New York (1986)
Volkenstein, M.V.: Entropy and Information. Birkhäuser, Basel (2009)
Volkov, S.N.: Conformational breather in a DNA macromolecule. Phys. Lett. A **224**(1–2), 93–98 (1996)
von Baeyer, H.C.: Information: The New Language of Science. Harvard University Press, Boston (2004)
von Neumann, J.: In: Burks, A.W. (ed.) Theory of Self-Reproducing Automata. University of Illinois Press, Urbana, ILL, pp. 77 (1966)
Waddington, C.H.: The Strategy of the Genes. Allen & Unwin, London (1957)
Wall, F.T.: Chemical Thermodynamics: A Course of Study. W. H. Freeman and Company, San Francisco (1958)
Wang, D., Gribskov, M.: Examining the architecture of cellular computing through a comparative study with a computer. J. Roy. Soc. Interface **2**, 187–195 (2005)
Wang, Y., Liu, C.L., Storey, J.D., Tibshirani, R.J., Herschlag, D., Brown, P.O.: Precision and functional specificity in mRNA decay. Proc. Nat. Acad. Sci. USA **99**(9), 5860–5865 (2002)
Wang, H., Lin, S., Allen, J.P., Williams, J.C., Blankert, S., Christa Laser, C., Woodbury, N.W.: Protein dynamics control the kinetics of initial electron transfer in photosynthesis. Science **316**, 747–750 (2007)
Wang, Q., Zhang, Y., Yang, C., et al.: Acetylation of metabolic enzymes coordinates carbon source untilization and metabolic flux. Science **327**, 1004–1007 (2010)
Washburne, M.: "Sleeping beauty": quiescence in *Saccharomyces Serevisiae*. Microbiol. Mol. Biol. Rev. **68**, 187–206 (2004)
Waters, C.M., Lu, W., Rabinowitz, J.D., Bassler, B.L.: Quorum sensing controls biofilm formation in Vibrio cholerae through modulation of cyclic di-GMP levels and repression of vpsT. J. Bacteriol. **190**, 2527–2536 (2008)
Watson, S.J., Akil, U.: Gene chips and arrays revealed: a primer on their power and their uses. Biol. Psychiatry **45**, 533–43 (1999)
Watson, J.D., Crick, F.H.C.: Molecular structure of nucleic acid. Nature **171**, 737–738 (1953)
Watters, J.W., Roberts, C.J.: Developing gene expression signatures of pathway deregulation in tumors. Mol. Cancer Ther. **5**, 2444–2449 (2006)
Weinstein, J.N.: A postenomic visual icon. Science **319**, 1772–1773 (2008)
Welch, G.R., Keleti, T.: On the "Cytosociology" of enzyme in vivo: a novel thermodynamic correlates of biological evolution. J. Theor. Biol. **93**, 701–735 (1981)
Welch, G.R., Kell, D.B.: Not just catalysts—molecular machines in bioenergetics. In: Welch, G.R. (ed.) The Fluctuating Enzymes, pp. 451–492. Wiley, New York (1986)
Welch, G.R., Smith, H.A.: On the field structure of metabolic space-time. In: Mishra, R.K. (ed.) Molecular and Biological Physics of Living Systems, pp. 53–85. Kluwer Academic, Dordrecht (1990)
West, G.B., Brown, J.H.: Life's universal scaling laws. Phys. Today **57**, 36–42 (2004)
West-Eberhard, M.J.: Evolution in the light of developmental and cell biology, and *vice versa*. Proc. Natl. Acad. Sci. USA **95**, 8417–8419 (1998)
West-Eberhard, M.J.: Developmental Plasticity and Evolution. Oxford University Press, Oxford (2003)
Wheeler, J.A.: Information, physics, quantum: the search for links. In: Zurek, W.H. (ed.) Complexity, Entropy and the Physics of Information, pp. 3–28. Addison-Wesley, Redwood City (1990)

Wheeler, J.A.: Geons, Black Holes & Quantum Foam: A Life in Physics, pp. 340–341. W.W. Norton, New York (1998)
White, C.R., Seymour, R.S.: Allometric scaling of mammalian metabolism. J. Exp. Biol. **208**, 1611–1619 (2005)
White, K.P., Rofkin, S.A., Hurban, P., Hogness, D.S.: Microarray analysis of drosophila development during metamorphosis. Science **286**, 2179–2184 (1999)
Whitfield, J.: In the Beat of a Heart: Life, Energy, and the Unity of Nature, pp. 58–61. Joseph Henry Press, Washington, DC (2006)
Wicken, J.S.: Entropy and information: suggestions for common language. Phil. Sci. **54**, 176–193 (1987)
Widom, B.: Molecular transitions and chemical reactions rates. Science **148**, 1555–15560 (1965)
Wiedermann, J.: Characterizing the super-Turing computing power and efficiency of classical fuzzy Turing machines. Theor. Comput. Sci. **317**, 61–69 (2004)
Wiener, N.: Cybernetics, or Control and Communication in the Animal and the Machine. The Technology Press, Cambridge, MA (1948)
Wikipedia: Theranostics. http://en.wikipedia.org/wiki/Theranostics (2010)
Wilkinson, R.H.: A method of generating functions of several variables using analog diode logic. IEEE Trans. Electron. Comput. **EC12**, 112–129 (1963)
Will, C.L., Lűhrmann, R.: Spliceosome structure and function. In: Cech, T.R., Atikins, J.F. (eds.) The RNA World, 3rd edn, pp. 369–400. Cold Spring Harbor Laboratory Press, New York (2006)
Williams, R.J.P.: Electron transfer and energy conservation. Curr. Top. Bioenerg. **3**, 79–158 (1969)
Winderickx, J., Holsbeeks, I., Lagatie, O., Giots, F., Thevelein, J., de Winde, H.: From feast to famine; adaptation to nutrient availability in yeast. In: Hohmann, S., Mager, W.H. (eds.) Yeast Stress Responses, pp. 11–70. Springer, Berlin (2002)
Winkler, W.C., Nahvi, A., Roth, A., Collins, J.A., Breaker, R.R.: Control of gene expression by a natural metabolite-responsive ribozyme. Nature **428**(6980), 281–286 (2004)
Wise, M.N. (ed.): Growing Explanations: Historical Perspectives on Recent Science, pp. 1–20. Duke University Press, Durham (2004)
Wochner, A., Attwater, J., Coulson, A., Holliger, P.: Ribozyme-catalyzed transcription of an active ribozyme. Science **332**(6026), 209–12 (2011)
Woelbern, T., Eckhorn, R., Frien, A., Bauer, R.: Perceptual grouping correlates with short synchronization in monkey prestriate cortex. Neuroreport **13**(15), 1881–6 (2002)
Wolfram, S.: A New Kind of Science. Wolfram Media, Champaign (2002)
Wolynes, P.G., Omuchic, J.N., Thirumalai, D.: Navigating the folding routes. Science **267**, 1619–1620 (1995)
Xie, X.S.: Single-molecule approach to enzymology. Single Mol. **2**(4), 229–239 (2001)
Xie, X.S., Lu, P.H.: Single-molecule enzymology. J. Biol. Chem. **274**(23), 15967–15970 (1999)
Xie, X.S., Lu, H.P.: Single-Molecule Enzymology, J. Biol. Chem. **274**, 15967–15970 (1999)
Yang, E., van Nimwegen, E., Zavolan, M., Rajewsky, N., Schoeder, M., Magnasco, M., Darnell Jr., J.E.: Decay rates of human mRNAs: correlation with functional characteristics and sequence attributes. Genome Res. **13**, 1863–1872 (2003)
Yen, J., Langari, R.: Fuzzy Logic: Intelligence, Control, and Information, pp. 30–31. Prentice-Hall, Upper Saddle River (1999)
Zadeh, L.A.: Fuzzy sets. Info and Control **8**(3), 338–353 (1965)
Zadeh, L.A.: Discussion: probability theory and fuzzy logic are complementary rather than competitive. Technometrics **37**(3), 271–276 (1995)
Zadeh, L.A.: Fuzzy logic: computing with words. IEEE Trans. Fuzzy Syst. **4**(2), 103–111 (1996a)
Zadeh, L.A.: Fuzzy Sets, Fuzzy Logic, Fuzzy Systems. World Scientific, Singapore (1996b)
Zadeh, L.A.: Fuzzy logic = computing with words. IEEE Trans. Fuzzy Syst. **4**(2), 103–111 (1996c)

Zadeh, L.A.: From computing with numbers to computing with words—from manipulation of measurements to manipulation of perceptions. Int. J. Appl. Math. Comput. Sci. **12**(3), 307–324 (2002)

Zallen, J.: Morphogenesis in Drosophila, New Vistas Series, New York Academy of Sciences, New York, hosted by Paul Nurse, 29 Nov 2006

Zallen, J., Wieschaus, E.: Patterned gene expression directs bipolar planar polarity in *Drosophila*. Cell **6**, 343–355 (2004)

Zamore, P.D.: Ancient pathways programmed by small RNAs. Science **296**, 1265–1269 (2002)

Zeldovich, K.B., Shakhnovich, E.I.: Understanding protein evolution: from proteins physics to Darwinian selection. Ann. Rev. Phys. Chem. **59**, 105–127 (2008)

Zeldovich, K.B., Chen, P., Shakhnovich, B.E., Shakhnovich, E.I.: A first- principles model of early evolution: emergence of gene families, species, and preferred protein folds. PLoS Comput. Biol. **3**(7), e139 (2007a). doi:10.1371 /journal.pcbi.0030139

Zeldovich, K.B., Chen, P., Shakhnovich, E.I.: Protein stability imposes limits on organism complexity and speed of molecular evolution. Proc. Nat. Acad. Sci. USA **104**(41), 16152–16157 (2007b)

Zhaio, S., Xu, W., Jiang, W., et al.: Regulation of cellular metabolism by protein lysine acetylation. Science **327**, 1000–1004 (2010)

Zimmer, C.: Evolving Darwin. Time p. 51, 23 Feb 2009

Zinovyev, A.: Methods of Elastic Maps for Data Visualization: Algorithms, Software and Applications in Bioinformatics. Ph.D. thesis under the supervision of Prof. A. N. Gorban, Krasnoyarsk State University, Russia. ViDaExpert available at http://bionfo-out.curie.fr/proejcts/vidaexpert (2001)

Zinovyev, A.: A lecture on ViDaExpert delivered at the Center for Discrete Mathematics and Theoretical Computer Science. Rutgers University, Piscataway (2006)

Zwanzig, R.: Rate processes with dynamic disorder. Acc. Chem. Res. **23**, 148–152 (1990)

Index

S. Ji, *Molecular Theory of the Living Cell: Concepts, Molecular Mechanisms, and Biomedical Applications*, DOI 10.1007/978-1-4614-2152-8,

G

H

Q