INTEGRAL BIOMATHICS

Tracing the Road to Reality

Plamen L. Simeonov
Leslie S. Smith
Andrée C. Ehresmann
Editors

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and Andrée C. Ehresmann (Eds.)

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This book is dedicated to the memories of Alan Turing,
Erwin Schrödinger, Nicolas Rashevsky, Gregory Bateson,
Michael Conrad, Robert Rosen, Francisco Varela,
Valentino Braitenberg and all brave research pioneers
who dared to question the riddles of life.

The Editors

Adapted from an illustration to the poem Jabberwocky
A work by English illustrator Sir John Tenniel (1820–1914)

First published in Carroll, Lewis. 1871. *Through the Looking-Glass, and What Alice Found There*

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INBIOSA

SEVENTH FRAMEWORK
PROGRAMME

European Commission
Information Society and Media

Editorial

This book arises primarily from the INtegral BIOmathics Support Action (INBIOSA), funded by the EU Future and Emerging Technologies initiative under the Framework 7 programme. The main idea driving the project is that it is not possible to make significant progress in the overall transdisciplinary area delineated by computational systems biology, autonomic computing and communications without a breakthrough paradigm change towards biologically driven mathematics and computation. Turing Machines used in biology and elsewhere in science today are Newtonian in a broad sense because they deal exclusively with syntax and inference rules based on discrete logic in absolute space and time to deliver predictable behaviour. Despite this approach being *extraordinarily* useful in engineering human processes, the interactions within the real world have proven to be vague and relational in many ways. A profoundly new understanding of the role of biology in natural and engineering sciences needs to be set out. Our driving argument is that living systems have fundamentally different notions of self-organization from those in engineering sciences. We therefore propose a research programme to investigate the imperatives of computation in a new way by comprehending the fundamental principles of emergence, development and evolution in biology.

The eventual goal will be a set of novel mathematical formalisms capable of addressing the multiple facets of an integral model and a general theory of living systems within an adequate frame of relevance. INBIOSA's task was to identify, consolidate and organize transdisciplinary research in Europe around this focus. However, the gestation of the work reported here is far longer than this one-year project. At its base will be a long-term fundamental research programme in mathematics, biology and computation on a global scale that we call *Integral Biomathics*.

The critical issue in this new field is finding a way forward that brings together the various communities of researchers who are interested in novel mathematical formalisms for addressing living/non-living and $1^{st}/3^{rd}$ person issues, and seeking to develop novel approaches to biocomputation. The INBIOSA project (as funded) aims to elucidate and illuminate the area, rather than to determine a specific set of solutions to these issues, or even to define the "right" way forward. Its goal was the creation of a European based worldwide community of scientific and technical experts to produce a structured and cohesive vision of the future natural and biosynthetic ecosystems.

In the course of the project we were able to recruit and involve some distinguished thinkers from a number of disciplines worldwide in our internal discourse, 36 of which are members of our Scientific Advisory Council and 24 subscribed as scientific collaboration partners. Our work is organized through an Advanced Online Scientific Community Service (AO-SCS), also developed in the INBIOSA project.

The articles in this book are partly invited, and partly from the meetings organized under INBIOSA's auspices. These were

- *iBioMath-Am* workshop (4 August 2011), held in conjunction with the International Joint Conference on Neural Networks (IJCNN 2011) in San Jose, California,
- *iBioMath 2011-Eu* workshop (12 August 2011), held in conjunction with the European Conference on Artificial Life (ECAL 2011) in Paris, and
- First Annual Conference on Integral Biomathics (ACIB'11), 29-31 August 2011, at Stirling University, Scotland, UK.

All the papers (both invited and submitted) have been refereed.

The book starts with an Introduction by Judith Rosen, daughter of Robert Rosen, discussing his contribution to science, particularly to the aspects of science discussed in depth in this volume.

The primary material of the book is divided into five sections. Section I (Biology and Neuroscience) contains a range of papers discussing both the nature of biological living entities and the underlying neurophysiological issues for biocomputation. Section II (Mathematics and Computation) tackles the problem from the other end: what can mathematical and computational approaches tell us about biocomputation. Section III (Models and Applications) considers both actual animals and models of living systems, as well as some specific issues in modeling biocomputational systems. Section IV (Physics and Philosophy) contains papers with a variety of viewpoints that generally fit into the area of physics (which at one time, in the old Scottish Universities was called Natural Philosophy) and philosophical issues, although they are not mainstream philosophical papers.

The final outcome of the INBIOSA project is a White Paper, motivating the need for action, reflecting the impact foreseen in science, technology and society and defining goals and directions for research. This forms section V of the book. We believe that it is a defining document that can be used to direct future research in this area.

The volume finishes with an Epilogue by Arran Gare, which explains how Integral Biomathics could change the nature of science, fostering "a different way of understanding nature, society and people".

The editors would like to thank all the contributors and all the reviewers, in particular Stanley Salthe, Koichiro Matsuno, Felix T. Hong, Marcin Schroeder, Robert S. Root-Bernstein, Brian D. Josephson, Ron Cottam, Edwin Brezina, Pridi Siregar, Jaime Gomez-Ramirez, Bruno Marchal, Otto E. Rössler, Gordana Dodig-Crncovic, Michel Petitjean, David Finkelstein, Ted Goranson, Thomas S. Ray, Yukio-Pegio Gunji, Bill Seaman, William Philipps, Igor Alexander, Aloisus Louie, William C. Hoffman and Arran Gare from the INBIOSA project for their hard work, as well as Leontina di Cecco and Holger Schaepe from Springer for their encouragement and advice to produce this volume.

9th December, 2011

Plamen Simeonov
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Introduction: The Contribution of Robert Rosen to Science

By Judith Rosen

When I go to conferences, among the questions I have consistently been asked about my father's work are the following: "What was he saying that was so different from mainstream science?"; "Do you think his work should change the way we do science? Why?"; and, "What are the most important aspects of his work — and why are they important?". The answers to these questions turn out to provide a good, concise overview of Robert Rosen's total body of scientific work as well as a useful primer for those who wish to begin a study of that work for themselves via his published papers and books.

From the outset, I think it is useful to know what problem Robert Rosen was trying to solve — what question he was working to answer, as he developed into the Theoretical Biologist history knows him as. His internal focus never wavered from this one, main question (which he has referred to as his "Imperative"). He wanted to figure out "Why are living organisms ALIVE?". He wanted to understand completely what the causal entailments are for generating the emergent systemic effect we refer to as "life". By the end of his career, he had found his answers but they sure weren't what he initially thought they would be… And the journey to find them also took him places he never expected to go!

At first, he tried to find answers to his question via Physics, Thermodynamics, Mathematics and all the mainstream scientific practices and tools that have been based on their collective development. He discovered, rather quickly (even before his PhD, in fact), that it was not going to be possible to achieve his ends using those means. Just as killing and dissecting an organism somehow loses the essence of what it is we are trying to study—without any way to go back to the original, living system — current reductionist scientific theory cannot explain what living organisms ARE DOING. Indeed, the situation is even worse than that: Living organisms routinely manifest behaviors — at all levels of their systemic organization — that are explicitly *not allowed* to happen, according to the current foundations of science. I have, many times, heard and read the statement; "Nature must obey the Laws of Physics". Such hubris! I like to picture any scientist intoning such a statement as bedeviled by a large and rather grumpy Bumblebee (an insect that science once tried to tell us should not be able to fly — according to those Laws of Physics). In the inner universe of my imagination, Lady Bumblebee then proceeds to sting said physicist on the nose. Hubris always has consequences but why should the rest of us always have to pay the price for it along with those who are guilty of it? That strikes me as being decidedly unfair.

The current foundations of science tell us that our universe is one in which there is only past and present and stipulate that the future can *NEVER* act as a causal force in the present; instead we are only allowed to react to what is happening now, or what has happened in the past. Yet… trees in temperate climate zones go dormant *before* winter arrives, an entire reef of coral — millions of individuals — all somehow managing to ovulate in unison, birds build nests for the offspring they haven't given birth to yet, and all normal human female infants are born with ovaries full of eggs despite the fact that a girl won't be using them for more than a decade. The examples are everywhere and they are literally endless. The future DOES act as a causal force on the present behavior of living organisms. Nature, apparently, has Laws of its own.

This was the situation my father found himself in, as he contemplated his options. He chose to make a temporary detour from pursuing his "imperative" in order to do a detailed analysis of the historical development of science. Specifically, he was looking for errors such as mistaken assumptions or unsupported conclusions that were missed initially during the early development of science and then were never revisited again. He found several.

The worst and most damaging error was Rene Descartes' "Machine Metaphor" — the presumption that all systems in the universe can be thought of as being "just like machines". That turns out to be just plain wrong. However, compounding this error is the fact that a great many of the other errors, which have been woven into the fabric of science over time are further iterations or ramifications of this one. For example: The prohibition against the very idea of Final Causation or *functional* entailments; The definition of "objectivity" according to a total lack of any value for optimality (which in Biology and Medicine, leaves no room for any scientific notion of "health"); The Cartesian "Scientific Method" specifying a reductionist approach which, we are taught, is *always* proper and appropriate for learning about ANY system. There are many such examples and although time and space limit our discussion of them here, they are described in detail in Robert Rosen's published work. The bottom line is that, as a result of the machine metaphor and its ramifications, the foundations of science currently do not differentiate between systems, which are merely big and complicated (or otherwise intricate enough to be unwieldy yet still amenable to reductionist approaches) and relationally *complex* systems that are always permanently destroyed by fractionation. On top of that, there is currently no way within mainstream science to figure out WHY that happens.

What my father found when he went back to a period in scientific thought prior to Descartes, et al, was that there already were modes of approach available to build on for use with biological systems. These proved to be far more fruitful because using them doesn't destroy what we seek to study as part of the process of studying. Aristotle's Four Categories of Causation, in particular, provided a framework for a more productive type of analysis that allowed for four distinctly different perspectives from which to consider questions about the universe. It also allowed for such notions as optimality, function, and the complexity of TIME in the Fourth Category: Final Causation. Time, according to Robert Rosen's work, is not the linear, simple entity we often think of and represent it as. Nowhere is that more apparent to human observation than when studying biological phenomena. Imposing a linear concept of time on living phenomena leads to conundrums such as, "Which came first; the chicken or the egg?" Life, instead, reveals the existence of repeating cycles, and cycles *within* cycles, which can interact with one another even at multiple different scales of organization, simultaneously. These cycles represent closed loops of entailment, which seem to arise whole. They certainly cannot be fully understood when cut and straightened out into a unidirectional line that has a finite beginning and end — any more than a Celtic Knot can still exist or be appreciated as a knot design if treated that way.

It is an inescapable truth that some systems are permanently destroyed, by taking them apart. A Celtic Knot we can reassemble and get the whole system back with all its original properties but where systems like an atom or an organism are concerned, this is not the case. Therefore, whatever it is that makes such non-fractionable systems what they are must be not only in the parts but also in the interactions between the parts and the effects of those interactions — which means also the particular relations by which those interactions take place — and so on… within the organization of the intact system, while it IS *intact*. By following this thread of logic, my father was able to proceed with investigating his Imperative. He was ultimately able to develop new scientific tools for use with Relationally Complex Systems and use them to arrive at new discoveries — some of which, he was rather astonished to find out, pertain not only to systems that are alive but to the rest of the universe, as well. Life may be somewhat rarified, but relational complexity turns out to actually be a general feature of the universe. Simple systems like machines turn out to be non-representative of the general case. Therefore, I think Robert Rosen's work, in toto, amounts to both a correction of the theoretical foundations for science as well as a necessary expansion of the paradigm for science, itself.

Among the most significant discoveries, for science, to come out of Robert Rosen's work are:

1) The significance of relations-- as components of interactions — in generating the subsequent causal outcomes from those interactions;
2) That because relations can be causally active, there is an aspect of all systems which must be taken into consideration — the organization. System organizations which do not allow fractionation to be reversible are "complex" in the relational sense (i.e., complexity refers to something about organization, itself). Synthesis and Analysis, which are considered within Cartesian science to be inverses of one another, are *not* inverses of one another *when dealing with complex organization*;
3) The importance of developing non-destructive (non-reductionist) modes of analysis for studying relations and organization as "things in themselves", in order to develop a solid understanding in science for how it is that small changes in relations between interacting material parts/particles can potentially generate massive corresponding changes in effects (such as the difference between properties of graphite and diamonds, for example, or the difference between a living organism and a dead organism);
4) That while the current "reactive paradigm" of science IS universally applicable, some systems in the universe do not only react — they are anticipatory. Living organisms represent naturally self-organizing examples of what my father called "Anticipatory Systems".

It is this last discovery, which I consider to be my father's MOST significant achievement. He laid the rigorous and consistent theoretical foundations for an entirely new area of science devoted to living phenomena, one which has the capacity and range to explain how living organisms are able to do what they do. Anticipatory Systems Theory has the ability to explain the evolution of intelligence, the emergence of the human consciously aware mind, and even the way that human mental processes *work*. It, further, has the capacity to illuminate the peculiar dysfunctions of living organisms as well as the even more peculiar dysfunctions of human beings. We have evolved what I consider to be a second anticipatory system (the mind) which has emerged out of the original one (the soma). Very few people are willing to argue with the fact that the human mind is anticipatory, anymore, because to even argue against it is to be one's own negative proof. I think it is equally self-evident that the only reason the human mind can be anticipatory is because life is already that way.

To consider the mind as an emergent, second anticipatory system explains a great deal of human experience and behavior. Both body and mind, as distinct anticipatory systems, have their own definitions for "self" and for "health", therefore also for "optimality". These definitions don't always agree! Even so, the two are in constant interaction with one another. Anticipatory Systems Theory can begin to shed some light on previously inexplicable phenomena like The Placebo Effect, Phantom Limb Pain, Post Traumatic Stress Disorder, and Faith Healing as well as how it can be that mental stress has so many detrimental physical consequences. Some telling examples of what happens when optimality is defined differently by the body and the mind are the problems associated with trying to be monogamous in long-term loving relationships when the body is trying to guide the system to reproduce as much as possible… and the bizarre human truth to the statement that *sometimes, suicide can be one's only available form of "survival"*. If I were being forced to choose between murdering my own children or dying, myself, I would not hesitate to choose the latter. Only with the mind is it possible to build a model which can predict that there are some fates worse than death.

One of the biggest hindrances to expansion of the paradigm of science has, in what is surely one of the most ironic juxtapositions in the history of our species, turned out to be explainable from the standpoint of Anticipation: We tend to see what we expect to see. We tend to regard as important that which we have learned to regard as important. The process of learning is, at root, a process of building new mental models and we tend to build them out of stuff we already know-- integrating new information with previous life lessons. Once we *feel sure* we "know" how something works, we can go on autopilot to some extent — because we have a model predicting "this is how it will go". When it doesn't go according to our model predictions (i.e., our "expectations"), we always seem to try very hard to just tweak the model to get it to work better — rather than throwing it out and starting over. I think this is a biological pattern: it's more expensive metabolically speaking to have to start from scratch. It saves time and energy if we can just make small changes to what we already have. We might just need to attach conditional information to it, like "the boiling point of water is 212 degrees Fahrenheit" (adding the conditional information: "at sea level, on Earth"…). The trouble is that conditional information leaves the main model intact when sometimes it really does need to be tossed out and re-encoded from scratch. Conditional information even when it works also tends to get lost over time and with repetition. My father once remarked that science involves a great many If/Then Propositions, but most of the Ifs have been forgotten. It's really important not to forget them — particularly if the model is only accurate under certain conditions!

It is also important to remember that science is a tool kit created by humanity to help us learn more about ourselves and the universe we're part of — and to solve problems, *better*. Isn't it a universal human experience to discover that any job is much easier when the tools we're using are appropriate for the task at hand? This is at heart an optimality issue and, as mentioned, the concept of optimality is inherently anticipatory. If this really were a universe where only reacting is possible — then the only kind of time that would exist would be "REAL time" and past history. In such a world, there could only be *means* and they wouldn't be called that because there would be no goals — no *ENDS* — to justify them. Problem solving is not possible in a reactive universe. It's a lucky thing, then, that there would be no such thing as problems in a reactive universe — the entire concept of optimality could not exist and neither could life. A snowflake, in essence, doesn't "care" if it melts and then refreezes as hoarfrost. Nothing about its organization tries to resist the process of melting and refreezing/crystallizing differently. The organization of a snowflake is such that a snowflake, as a system, IS purely reactive (it's not capable of being anticipatory/is not alive).

"Teleology" used to be — and in some cases still is — a loaded term in the sciences, particularly Physics (or perhaps *by way of* Physics, as the wellspring of much of what is today called "science"). The reason goes directly back to the Machine Metaphor of Descartes and how it became associated with *the* "scientific" way of seeing phenomena in the universe. This *way of seeing* is still being taught in nearly all science curriculums around the world, at all levels, from earliest grade school through PhD. The "Scientific Method" is utterly and unequivocally reductionist. In his book "Life Itself", my father was uncharacteristically blunt when he wrote, "The Machine Metaphor is not just a little bit wrong, it is *entirely* wrong and *must be discarded*." I think what has happened is that we basically got our heads stuck in the machines we built. From the perspective of a machine, as a system, all the goals and ends — all issues and concepts of optimality —come from *outside* the system's own organization. The goals and ends associated with any machine come from the ones who designed and constructed the machine. We need to cook food in some way so we come up with a fireplace, a stove, a microwave oven, a barbecue grill, a hibachi….

It's no accident that the reactive paradigm of science is exactly what is supported — predicted — by studying ALL systems (including our own bodies) as if they were machines. It's a perfect example of seeing what we expect. The Machine Metaphor gives us an expectation that this is a reactive universe (so ironic, given that science is an anticipatory pursuit). However, in the historical backlash against religion within science, the mechanistic approach was viewed as a way out of seeing the fingerprints of God in the cosmos and everything else. Except for that one fly in the ointment… that insurmountable little problem of who built the machines, for what purpose. By putting ourselves essentially in the position of God to our machines, and building our entire scientific worldview around a purely reactive, machine-based perspective, we have succeeded in generating what we were trying so hard to avoid, just like poor Oedipus. Indeed, I see the Machine Metaphor as giving Intelligent Design folks their "scientific proof" of God! Yet another reason it must be expunged from scientific thinking. And people who stand on the foundations of *Science* (with a capital "S") and think they can use them to counter Intelligent Design arguments seem to have no idea just how much those foundations look like Michelangelo's painting of God imbuing Adam with life by touching him with a finger... almost as if God were flicking an on-switch.

I think what has been called "teleological" in the past is really just the observable signature of the underlying anticipatory nature of life — when interpreted via a mental model of how the universe works based on the nature and behaviors of machines. One thing I hope Robert Rosen's work ultimately achieves is a demonstration that the study of living systems can help humanity (including even devout reductionists) to recognize that *the universe is more complex than WE would have made it, if WE were building it.* Human beings build things by accretion: attach this to that, add one more piece; a modular approach to construction that is completely reversible — backwards and forwards. Addition/Subtraction … But there is no way to reach infinity that way. Systems that are complex in the relational sense have something of the infinite in them. When we take them apart, we reduce the infinite to the finite. In other words, they slide through our fingers and are gone. Reversing our procedures doesn't get them back because, as mentioned: where relationally complex systems are concerned, synthesis and analysis are not inverses of one another. This fact is particularly stark when dealing with anticipatory systems — life and mind.

Everything from the various specialties of the Medical Sciences, through the Social Sciences, Political Sciences, Environmental Sciences, even Economic Sciences…. all the way through to Psychology and Cognitive Science — is impacted by the ramifications from these ideas. In fact, any area of human study where the subject involves relationally complex systems or living organisms — in any way — requires an expansion of the scientific paradigm in order for a rigorous, accurate, and useful understanding to be possible. With human-induced global climate change rapidly gaining momentum and all the various therapies that have been proposed or will be proposed to try and deal with that, as well as all the other problems facing humanity the stakes are rising exponentially: If we continue to use a machine-based way of thinking, ***how can we trust our scientific predictions about which therapies will work and not cause terrible side effects***? How will we be able to imagine the best ways to help our planet and ourselves to cope with the future unless we expand our paradigm for science — and our worldview along with it? We need our tools to finally be appropriate for helping us understand and model biological systems like our own physiology or the biosphere. Using current science, we have trouble accurately predicting the weather more than one week into the future.

There is great wisdom in the ancient advice, "Know Thyself." I think, because Robert Rosen was a biologist, working to understand life and living phenomena rather than orbital mechanics and other cosmic or atomic (non-living) phenomena, the theoretical foundations he developed can help future generations to live up to that wise advice, far more productively — and safely. Living systems are *not* like machines. Instead, the machines and technologies we create are actually extensions of ourselves, both physically (like an automobile or diving gear or ice skates) and mentally (be it a computer, a cell phone, the internet…). The need to understand the nature and behaviors of life, and be able to accurately predict such things as the ways in which the definition (the "meaning") of *optimality* consistently changes according to changes in context and perspective, has never been more urgent in human history than it is right now.

Humanity has extended ourselves into every aspect of our planet, even into the space immediately surrounding our planet and out into our solar system, without fully understanding how these aspects are related and interacting. We are rapidly changing the relations between the gasses in our atmosphere. Who can honestly believe that will have no serious effects? But how to predict what the effects are likely to be? It's critically important to begin scientific study of the relations *between* interacting material parts/particles and the effects of changes in relations on the outcomes of interactions. The relational effects are ultimately what make life possible. That was one of the surprise discoveries to come out of my father's work. In fact, I think Robert Rosen's answer about the entailments for life in organisms can perhaps be summed up by saying that *LIFE, itself, is a relational effect.*

All human beings, regardless of profession, have a vested interest in the proposed expansion to the paradigm for science, whether we know it or not. We all have to go to the doctor, sometime. We all have multiple memberships in diverse social systems. We all have hopes, dreams, and expectations… And we all have surely experienced what happens when the world behaves in ways we were sure it wouldn't — or *couldn't.* That feeling of surprise, when our mental models have made a prediction that was not borne out in the real world, is the Achilles Heel of Anticipation. Models are only as good as the information they are encoded with and model predictions are only as good as the models, which generate them. It is the most natural thing in the world for us to want to be safe and healthy and happy — now and into the future — and to wish for our children (and future generations) a better world than what we have right now. But it isn't enough to just "mean well". Good intentions are certainly important but they are only a start. We also have to be able to trust that our tools are appropriate for what we are asking of them and we need to be able to rely on the predictions of science that what will make things better really WILL make things better.

For all these reasons, and more, it was with great pleasure that I accepted the invitation to write this short description of Robert Rosen's work as part of the Introduction for "Integral Biomathics: Tracing the Road to Reality," a book that I fervently hope will make a significant leap forward in fleshing out and driving the expansion to the paradigm for science that my father said was absolutely necessary for a sustainable, healthy, and productive future — not only for humanity, but also the biosphere on which we depend. Humanity needs to evolve into a symbiotic relationship with our environment, our home: Planet Earth. Symbiosis allows all partners to achieve things that would not be possible without that relationship. In this way, I believe that true sustainability really IS within our grasp. But first, we have work to do!

[Note: Robert Rosen's book, Anticipatory Systems: Philosophical, Mathematical, and Methodological Foundations, is being re-published as an expanded Second Edition by Springer Verlag in early 2012.]

November 3rd, 2011

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Contents

Part I: Biology and Neuroscience

Part II: Mathematics and Computation

Part III: Models and Applications

Part IV: Physics and Philosophy

Part V: INBIOSA White Paper

Part I

Biology and Neuroscience

Editorial

This part consists of eight papers, ranging from discussions about simple single-celled systems to full-scale neural systems.

Root-Bernstein sets the scene in his paper. His paper argues that a new phase of scientific development is required in which mathematicians turn to biological processes for inspiration in creating novel formalisms in mathematics appropriate to describe biological phenomena. While biological processes must obey the laws of physics, biology is not reducible to physics and therefore mathematics that have been adequate for describing physical processes are often inadequate to describe biological ones. In particular, the author claims that biologists need mathematical apparatus capable to describe phenomena involving discrete and continuous functions simultaneously, to handle spatial descriptors at the same time as kinetic data to explain developmental processes and to model the transformation of scalar processes (random diffusion) into vectorial (directional) ones. The paper describes a number of problems, suggesting that a fertile field of enquiry exists for mathematicians interested in developing new forms of biology-driven mathematics.

Danny Baranes reports *in vitro* and *in vivo* experiments indicating that the connectivity, shape and topology, of neuronal networks depend on the way the dendrites overlap and contact. They show that dendritic branches form stable contacts preferably at bifurcations and at pre-existing contacts on branches of neighboring dendrites in a non-random and activity-promoted fashion, leading to the clustering and strengthening of synaptic connections at the contact sites. This “Economical Small World Network” maximizes connectivity.

Ehresmann discusses the use of her (and Vanbremeersch’s) work modelling higher mental processes using category theory. This is a short introduction, referring the paper to their more extensive work to be found elsewhere.

Fiorillo attempts to integrate neural systems and information. To achieve this, he takes a Bayesian perspective, and grounds this in biophysics. The information at a neuron is taken from its many molecular sensors, integrated to produce a membrane voltage. This can allow us to determine a specific computational goal, specifically the reduction of uncertainty. This opens up the possibility of a general theory of nervous systems.

Gomez-Ramirez and Sanz discuss the sensitivity to its environment of the choices of behaviour made by *Escherichia coli*, a common gut bacterium. Essentially the behavioural choices are limited to a tumbling, and a running behaviour. The relationship between the environment, and these behaviours defines the “meaning” of the environment to the bacterium, and the paper discusses how these signals are integrated and interpreted, allowing a new perspective on adaptation, plasticity and learning in a very simple context.

Suichi Kato is interested in the mutual relations between environment and living creatures, here myxomycetes, which have the time period of amoeba and a short life cycle. He presents an experimental model for investigating the behaviours in its environment of a plasmodium, using electric field strength as an effective stimulus to motion control of a plasmodium on an agar-agar surface. The model shows that the electric stimulation leads to a reinforcement of the galvanotaxis and to mechanical changes, e.g., dilatation of the tubular vein in the direction of the way to escape.

Phillips discusses the importance of context sensitivity in biological organization of complexity. Starting from backgrounds as diverse as Schrödinger's "What is life?", and Phillips' earlier work on Coherent Infomax, he develops a theory of how neurons combine local reliability with more flexible techniques. Yet there remain unsolved problems, and he discusses how the approach of this paper, and Friston's approach can be reconciled.

Smith attempts to define the nature of information processing in cells. These are chosen because of their ubiquity in living systems. They seem to form a level present virtually in all living systems, and this suggests that characterizing how they use information is an appropriate and important task.

Processes and Problems That May Define the New BioMathematics Field

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Abstract. Historically, mathematics developed hand-in-hand with the physical sciences. While biological processes must obey the laws of physics, biology is not reducible to physics (otherwise we would not be able to distinguish one set of phenomena from the other!), and therefore mathematics that have been adequate for describing physical processes are often inadequate to describe biological ones. In consequence, I argue that the a new phase of scientific development is required in which mathematicians turn to biological processes for inspiration in creating novel forms of mathematics appropriate to describe biological functions in a more useful manner than has been done so far. Many the kinds of problems that seem to remain unaddressable at present involve forms of mathematics that currently have competing assumptions. For example, biologists need to describe phenomena that involve discrete and continuous functions simultaneously (control of metabolism through binding of single molecules to unique gene promoters; the statistical description of continuously varying molecular complexes); they need to handle spatial descriptors (geometry?) at the same time as kinetic data (calculus?) to explain developmental processes; they need to explain how scalar processes (random diffusion) gave rise to vectorial ones (facilitated transport). These, and other hybrid problems described in this paper, suggest that a fertile field of enquiry exists for mathematicians interested in developing new forms of biologically-inspired mathematics. I predict the result of the development of this new field of biologically-inspired mathematics will be as fundamentally revolutionary as physics-inspired mathematics was during the original Scientific Revolution.

Keywords: Positivism, biological mathematics, Scientific Revolution, history of science, scalar-vector transitions, developmental biology, set theory, autopoetic sets, modularity.

I once took a graduate course on the history of physics that focused on the work of Laplace. The professor teaching the course pointed out a phenomenon that he found very surprising. Laplace, he noted, had a very checkered career. He seemed to work on physics or astronomy for several years and then drop whatever he was working on and switch to studies of pure mathematics for a few years; then suddenly, he would switch back to physics or astronomy, and so forth for decades (Gillispie, 2000).

The professor could think of no good reason for such erratic behavior. I, however, suggested a very simple explanation. I believe that Laplace was such a productive scientist *and* mathematician because the two fields were completely integrated in his mind. He derived his mathematical problems from his astronomical and physical researches and his astronomical and physical problems from the regions in which existing mathematical methods failed. So in practice, what Laplace did was to study a physical process, develop a model for the behavior of the system that would, in turn, yield a set of equations describing the model. More often than not, because Laplace focused on processes that had no adequate physical explanation, he would find that it was impossible to solve the equations needed to model the system. Being a first-rate mathematician, he would therefore refocus his efforts on deriving from first principles the new methods necessary to solve the sets of equations he had invented. This effort often took him several years. Once he had satisfactorily set that new area of mathematics to rights, he would go back to his astronomical or physical studies, apply his new mathematical insights to his models, and see what kinds of new problems these revealed.

I recount this story about understanding Laplace's methods because it is important in devising a new field of biomathematics that those undertaking the work understand that, historically, both science and mathematics have provided *each other* with fruitful problems and methods. Laplace was not a mathematical physicist or a physical mathematician – he was both, simultaneously. I understand full well that this integral (or back-and-forth) view of the relations between science and mathematics is quite at odds with the dominant (and long-outmoded) Comteian positivistic philosophy of science that still predominates among scientist and mathematicians today. Positivism explicitly posits the notion that mathematics drives progress in the rest of science so that it is possible to rank-order the scientific reliability of a field on the degree to which it has become mathematized. The increase in "positive knowledge" is always from mathematics through physics to the "softer" sciences.

There are two errors in this positivistic philosophy. One is that even pseudoscience can be expressed in equations, this process making the pseudoscience no more "true" than it was when expressed only in words. The other error is to mistake the purpose of mathematization as being primarily a means of validating scientific research. To the contrary, I believe that mathematics can provide novel tools for exploring scientific problems. But that said, I also believe that existing mathematics does not contain all the possible tools that scientists may need. Like Laplace, present-day mathematicians are likely to find fascinating and valuable mathematical problems by learning enough biology to understand where existing mathematical tools fail. From this perspective, mathematics is useful to any given science only to the extent to which it is appropriate to addressing the problems posed by that science. Simply mathematizing biology using existing methods does not, in fact, add anything to our understanding of biology unless the mathematics illuminates points that non-mathematical statements of the same models or theories cannot address. Unfortunately, many scientists make their models conform to existing mathematical methods rather than doing what Laplace did, which is to devise an appropriate model and then invent the mathematics to describe it. Thus, historically, "mathematical biology" has not yielded many deep insights.

My studies of the history of science suggest a second reason that mathematics has not been as useful in the biological sciences as in the physical sciences. Scientists tend to ascribe the power of physical sciences to their mathematization, but I would argue that the real power has come from the ability of astronomers and physicists to define their problems accurately and precisely enough for mathematical methods to be valuable. My emphasis here is on problem finding and defining. Historically, chemists, biochemists, biologists, and social scientists have rarely been able to define their problems with the precision and accuracy of the physicist or astronomer, making the mathematical investigation of their relatively “fuzzy” problems difficult. Thus, one reason for the lack of mathematics in biology is that the lack of well-defined problems has made the field less amenable to mathematization than, say, physics. Recognizing that categories in non-physical systems are often “fuzzy” is, in fact, what led Zadeh to invent his theory of “fuzzy sets”, a major advance for both mathematics and modeling in biological and social sciences (Zadeh, 1996). I would therefore argue that the degree to which we can define our biological problems accurately and precisely enough to intrigue mathematicians will determine whether we make progress in developing biomathematics.

The third reason that biology has so far failed to benefit from mathematization to the degree that physics and astronomy have, is that the mathematics that is used to describe physics and astronomy developed hand-in-hand with those sciences but has not developed hand in hand with biological problems. Laplace is hardly unique in having had hands in both mathematics and physics simultaneously – think Descartes, Leibnitz, Lagrange, Fourier, Poincare, etc. Unfortunately, the mathematical methods developed to model physical processes do not (in general) illuminate biological problems. Biology is not chemistry which is not physics. Simple hierarchical reasoning states that we can recognize a new level of organization when the principles, properties and models that worked for the previous level of organization can be ignored (Weiss, 1971). Chemistry becomes chemistry and not physics at the point where we can ignore the physical properties of the components carrying out the chemistry. We don’t need an understanding of nuclear physics to describe the kinetics of a chemical reaction; we don’t need to know the movements of every molecule in a gas to measure its temperature or volume; we don’t need an understanding of electron shells to explain how DNA encodes genetic information. Similarly, biology becomes biology and not chemistry when we can ignore the chemical properties of the components carrying out the biology. For example, Mendelian genetics was invented without any concept of the structure of a gene, let alone what macromolecular structure encoded genetic information. Darwinian evolution by survival of the fittest does not rely upon any chemistry at all! This is not to say that biological systems are not comprised of chemicals or to deny that they obey the laws of physics, but rather to make the point that biological systems are recognizably biological because they have organizational properties that allow them to carry out processes that cannot be accounted for purely on the basis of the physics and chemistry of their individual components. So what we need is a new mathematics and a new form of computing that permits us to model the emergence of new properties resulting in the carrying out of novel processes as a result of innovative forms of organization within complex systems. Or, put more simply, a mathematics appropriate to biology must be motivated by problems that are biological in their origins and nature, just as a mathematics appropriate to physics was physical in its origin and nature.

In order, therefore, to develop a new field of biomathematics, I would therefore hope that we will behave as a community as Laplace and his colleagues did, by going back and forth between the science and the mathematics, letting each inform the other. Biology has much to contribute to mathematics, especially to the development of new forms of mathematics appropriate to solving the kinds of problems that make biology different than physics or astronomy. And biologically-inspired mathematics can be expected to return to biology the same kinds of gifts that physics-inspired mathematics returned to physics. Indeed, not until we abandon the Comteian idea that mathematics should *drive* science will biology benefit as it should from mathematics. I maintain that reversing the equation and permitting biology to *drive* the mathematics (at least half of the time!) may yield us new insights as important as those generated by Laplace and the other physicist-mathematicians who founded their fields. Moreover, it may revolutionize mathematics itself, just as the focus on physical problems motivated many of the great mathematicians of the past.

So what kinds of well-defined biological problems exist that seem not to be amenable to current mathematical approaches, or have simply been overlooked by mathematicians who already have the kinds of novel approaches that would open up these biological areas to formal analysis? I and my collaborators and colleagues have been struggling with five such areas, all of which are general enough to have broad implications both in and beyond biology and are therefore potentially worth the effort of a mathematician to explore. All of them, in one way or another, share the common feature that the systems that need to be described combine some type of continuous function with some type of discontinuous function and some add the fillips of vectorial and geometrical aspects as well. The mathematical challenge is how to analyze biological problems that currently exist in two or more of these (as far as I know) essentially unrelated domains of mathematics.

My first problem concerns the modeling of a cell as a dynamic process. The cell itself is a discrete object yet the flow of materials in, out, and through a cell is continuous. Moreover, if one asks what defines the cell at any given time, the details of this description will differ at any other time point. For example, when a cell replicates, it breaks down its Golgi apparatus, its actin fibers, and various other cell organelles, into the molecular constituents from which they are assembled. These molecular constituents are randomly distributed into the two daughter cells. Both of the resulting cells are still cells of the same species as the parent cell, yet neither has exactly the same number or even exactly the same proportion of cellular constituents as the parent cell or as each other. So clearly there is variance in the absolute numbers and in the proportions of the constituents of a cell within which the cell can still function as a cell. Moreover, the rates at which these constituents turn over, are replenished and excreted also vary from cell to cell and from time point to time point. Now, this variance is clearly open to experimental manipulation. One can dehydrate cells and find out how little or how much water they require or can sustain and continue to live. One can destroy particular cellular constituents, or block particular receptors or transporters, and see how these modifications affect the proportions of other cellular constituents in relation to whether, and how, the cell continues to function. So we can obtain plenty of quantitative data. But what do these data mean in terms of what the interactive variances in constituents can be within a living system? The problem becomes even more complicated when we start playing with cellular structures and macromolecules. While there are so many molecules of water or glucose or ATP in a cell that it might be acceptable to model cellular dehydration as a continuous function, one cannot vary the numbers of actin fibrils, Golgi apparatus, mitochondria, chloroplast, ribosomes, nucleoli, centrosomes, chromosomes, etc. as continuous functions. These are very discrete variables, with variances that are measured in discrete units. The mathematical problem therefore becomes one of finding means to utilize all of this information – both continuous and discrete – in an integrated model that lets us understand what are the limits of variance, and therefore the limits of life, for a functioning cell.

The posing of the question of what constitutes a cell in this way has caused me to become interested in set theory as a possible basis of a new biological mathematics. But the current state of set theory (at least as available to a novice such as myself) seems inadequate in two fundamental ways. First, cells are autopoetic – they form themselves. Indeed, evolutionary theory asserts that cells evolved from primordial aggregates of self-organizing compounds built from even simpler interactive modules, back to the primordial soup. Sets, at least as they exist in mathematical forms, are not autopoetic. There is always a "god" – the mathematician – who defines the criteria for what is a set and what is not. What would happen if one did not have the mathematician "god" to define sets, but created a system of definitions that would permit sets to form autopoetically? This is, in a sense, what complexity theory is about (e.g., Kauffmann, 1993), but complexity theory does not incorporate most of the useful features of set theory. Could a mathematics that described autopoetic sets through complexity-like theory exist? Might it shed light on the evolution of the "sets" we call "cellular life" by permitting us to describe continuous functions that produce rules that then limit the entry and exit of possible components of the set and that can undergo transformations (metabolism) within the set? After all, this *is* what cells do, so why cannot there be a mathematics that describes what nature can already do?

The second way in which modern set theory (again in my limited experience) seems to fail to inform biological problems is because biological sets have the variance property I described above. Any given cell must have chromosomes, but their number can vary (as they do in cancers and parthenogenotes) and still be viable; they can have many ribosomes and mitochondria or few and still live; they can accumulate certain amounts of toxins or lose a certain amount of key ions and still function; etc. So in addition to inventing autopoetic sets, is it possible to invent sets that are not defined by specific numbers of constituents, but by variances within which all of these constituents must exist. A bacterial cell that becomes dehydrated may die, or it may sporulate. How can some form of set theory be devised that models the process of switching between stable states when certain variances are exceeded? What, in general, does such a state-sensitive, mathematical set look like? How does it behave? What properties does it have that sets, as currently defined in mathematics, do not?

How might these new set properties inform living systems and perhaps even our understanding of social processes, supply chains, and other useful functions?

So one thing that is needed in our new biomathematics are ways to model self-emergent sets (origins of first cells; self-assembly of viruses, etc.) But these self-emergent sets would seem to need the ability to carry out functions (selecting/rejecting among possible components; minimizing what a physicist thinks of as free energy; etc). So one possible focus of a new biomathematics would be to invent an appropriate theory of self-emergent sets that can carry out functions within variances. Such a set theory would preferably incorporate the work that has been done on understanding hierarchical systems, emergent properties, complexity theory and so forth. Such a mathematics would therefore be extrordinarily integrative, a point to which I shall return below.

A biological problem related to their set-like properties is that their organization strictly limits their variance through the formation of modules in a manner that requires novel approaches to probability theory. Imagine a clueless, blind "watchmaker" of the sort that Richard Dawkins likes to put in charge of evolutionary processes. But let this watchmaker carry out a process first investigated by Herb Simon in one of his little-known and under-appreciated essays on evolutionary processes (Simon, 1981). Combining Dawkins's and Simon's watchmakers produces the following scenario that I believe exemplifies one of the critical problems that needs to be addressed in the origins and evolution of life. I imagine two watchmakers, the first of which must randomly assemble 25 parts in order to put together a "watch". This completely ignorant watchmaker must explore every possible combination of the 25 parts he has in front of him, which is to say 25!, or about 1.55 x 10^{25} possibilities! If it took a single minute for each of these possibilities to be explored, our watchmaker would not succeed in making even a single watch within the lifetime of the universe! Moreover, because he's just a random assembler and cannot learn from experience, he has to explore all these possibilities each and every time he tries to build a watch! Clearly, such an entity working by such a process would, for all intents and purposes, never succeed, making *de novo* evolution of life virtually impossible.

But what Simon first recognized, and I have developed (Root-Bernstein and Dillon 1997; Hunding, et al., 2006), is that an equally dumb, blind and random watchmaker who uses stable modules built on the principle of molecular complementarity would succeed, and astoundingly quickly! Simon's model assumed that the watchmakers knew how to make a watch (a clearly un-biological assumption), from which he derived the following equation: The time required for the evolution of a complex form from simple elements depends critically on the number and distribution of potential intermediate stable forms. In particular, if there exists a hierarchy of potentially stable 'sub-assemblies', with about the same span, s, [i.e., the number of parts or components required to form each stable subunit] at each level of the hierarchy, then the probability that a subassembly process will be completed within any given time, T, can be expected to be about $1/(1 - p)^s$, where p is the probability that the assembly process will be interrupted during time T. Clearly the less stable each step is in the assembly (i.e., the greater p is) and the larger the number of components that must be assembled to achieve a complete assembly (s), the less probable any particular assemblage is to evolve. Conversely, the more stable each step in assembly is (i.e., the smaller p gets) and the smaller the number of components required to produce a completed assembly (s), the greater the probability an assemblage is to evolve, (Simon, 1981, p. 203). The implication of Simon's model is that we should therefore expect evolution to be characterized by the selection of semi-stable modules arranged in a hierarchical fashion that minimizes wasted time, effort and resources. This is precisely what we do see. But Simon's model is not an accurate portrayal of the biological problem.

The problem with Simon's model is that evolutionary watchmakers do not know how to make a watch and must search randomly for stable modules. Fortunately, molecular complementarity between compounds naturally forms such stable modules, so these come into existence in just the kind of random fashion that needs to be assumed. So once again assume our modular watchmaker needs to make a watch from 25 pieces, but also assume that she makes her watches in stable sets of five parts. Assume also that all other combinations of the five parts are unstable. Stable five-element modules could be built by exploring only 5! possibilities, or just 120 combinations. Then our modular watchmaker would need to explore randomly the 5! possible combinations of these five modules, or another 120 possibilities. Altogether, the modular watchmaker explores only 720 possible combinations, which, if they could be explored at one possibility per minute, would yield a watch every two hours. Quite a difference from 1.55 x 10^{25} minutes to explore the original 25! Combinations! The impossible becomes highly likely (Root-Bernstein, 2011)!

Now obviously, the advantage of modularity is not as great as I have just stated for a real, molecularly complementary system. In the first place, stable modules might not result from any given set of five components so that our modular watchmaker may have to explore more sets than I have assumed. Secondly, the specificity of module building is not perfect and some non-functional modules will also likely be stable, confusing final assembly. We can also assume that the proper modules will outcompete the improper ones in producing complete watches, but this may not be the case if improper modules, inefficient at assembly as they may be, so out-number the proper ones as to swamp them. Finally, there is no biological reason to assume that stable modules have five components – the number could vary from two or three to two or three dozen per module. And this is exactly the point at which current probability theory fails. How do I model the kind of system I have just propounded in which modular sets are formed in a chemically reversible manner (describable as a continuous function), may contain variable numbers of components, and compete with each other in a probabilistic scenario? To solve this problem requires a mathematics that can simultaneously deal with continuous variations in chemical kinetics yet yields information about modular probabilities. Again, such a mathematics must exist since Nature already performs these functions, but what does that mathematics look like?

The importance of being able to address this modularity-probability problem can be seen by the fact that the formation of complementary module building within complex systems can prune out huge numbers of possibilities at each step of hierarchical assembly. In general, the greater the number of pieces, and the more modular steps involved in the process, the more efficient the process becomes. Given the mathematics of these probabilities, there must be some optimal number of pieces per module, and an optimal number of modules per functional unit, and an optimal stability that must be attained. All of these variables must be optimized so as to maximize the rate at which functional modules are generated while minimizing the number of possibilities that must be explored. My guess is that nature has already solved this problem, and that the answer is about 3 to 6 elements per module. Analyzing naturally occurring modular hierarchies for rules of optimization might therefore have vast implications for not only understanding the evolution of life, but also, as Simon (1981) notes in his original essay, for the most efficient design of chemical, technological, and even human systems of organization.

Now, I have already alluded above to various biological problems that require working at the interfaces between continuous and what might be called "grainy" functions (e.g., continuous flow of elements through discrete sets; modular probabilities determined by continuous chemical kinetics). One might posit that most of biology consists of sets of problems that exist at this continuous-grainy interface. For example, chemical neurotransmitters (describable as continuous functions) release a single electrical discharge (a discrete function); individual organisms such as bacteria (discrete) can potentially interact more or less strongly with other individuals by means of chemical messages (continuously variable) that determine whether they develop as many individuals or transform themselves into a single super-organism (a biofilm). How can we mathematically handle interactions that may vary continuously but act on a small set of definable individuals? These are not amenable to modeling solely using mathematics that assume continuous or infinitely small functions.

I am particularly interested in these continuous-grainy problems from the perspective of complementarity. Any given species of molecule may interact more or less with any other type of molecule, so that in a very diverse mixture of molecules, a large number of weak interactions may overwhelm a small number of strong ones. The same can be true among sets of cells or in species or social interactions that involve what Csermely has called "weak links" (Csermely, 2006) and I call "complementarity" (Root-Bernstein and Dillon, 1997; Root-Bernstein, 2011). There appears to be no good way to model such systems mathematically at present, yet such systems occur at every level of biological complexity. Again, since biological systems are able to integrate units with continuous functions, surely there is a mathematics that is appropriate for modeling how biological systems do so.

A fourth set of problems are also very intriguing and currently resistant to mathematical analysis. One of the characteristic features of biological systems is that some of their properties involve transformations from scalar to vector quantities. Now we know from tensor calculus that multiplying a scalar and a scalar gives a scalar; and multiplying a scalar times a vector gives a vector; and multiplying a vector times a vector gives a scalar; but how does one get from purely scalar quantities to a vectorial one? How do racemic mixtures of chemicals give rise to chiral handedness in living systems? How does a chemical neurotransmitter signal (scalar diffusion) become a directional electrical signal? How does one evolve from random diffusion (scalar) to facilitated transport systems (vectorial)? How does one evolve from all possible reactions occurring (primordial soup, laboratory bench) to reaction pathways (vectorial)? In all these cases (and many more) scalar processes result in vectorial ones, yet mathematics generally treats either scalar quantities or vectorial quantities, but not the transformation of scalar to vector. Do we need a new mathematical formalism to do so?

If I might speculate, what we may need is a mathematics in which one assumes that every scalar quantity is actually a pair of inverse vectors that normally cancel each other out, but which, under the appropriate circumstances can be disentangled. For example, in all vectorial systems in biology of which I am aware, an inflow of one kind of molecule is always balanced by an outflow of another; selection for right-handed sugars occurs only where there is concomitant selection for left-handed amino acids. So is it possible that in fact the overall balance of vectors in a biological system is always conserved and that the local manifestation of one half of an inverse vector pair (e.g., inflow) is always balanced by the expression of the opposite vector pair (outflow) in the opposing process? Is there a mathematics that can help us investigate the rules that might govern such processes by integrating vectorial reasoning into the kinds of set thinking postulated above so we can understand how molecules move directionally through cells as a result of metabolic processes, etc.?

My fifth and final type of problem involves the linkage of form and function. Biologists who deal with almost any level of biological organization recognized that natural selection attempts to optimize forms to carry out particular functions, but since novel functions evolve from existing forms, these attempts may be seriously limited. The mathematical challenges involved in attempting to model these form-function interactions are far from trivial. On the one hand, we do not have geometrical tools that can easily model processes such as the complex folding of proteins or chromosomes let alone embryological development. Fractals and other forms of mathematics that generate lovely images that look like the final products of some of these processes (e.g., the branching structure of the bronchioles in the lungs) share nothing of the actual biological processes that give rise to these structures. Thus, our mathematical geometries generally do not illuminate the processes that give rise to biological geometries, but only their outward forms. More importantly, the interesting things about biological forms is not their geometries per se, but the ways in which these forms are reifications of the biochemical processes they carry out or make possible. For example, it has become evident that the folding of chromosomes is a prerequisite to bringing together genes that would otherwise be spatially separated; and that spatial proximity permits the rapid diffusion and control of interactive gene products that would otherwise be unable to interact in a reasonable biological time frame across an unfolded genome (Junier, et al., 2011). But what kind of mathematics would make it possible to model simultaneously the effects of geometry (spatial structure) on continuous functions such as diffusion that in turn regulate on-off gene regulatory switches that act discontinuously or digitally?

Similarly, in developmental biology, we now have excellent data concerning the sets of genes that must be turned on and when they must be activated or inactivated in order to produce proper embryological development (e.g., Carroll, 2005), yet the discrete information generated from combinations of individual genes is expressed as continuous flow of proteins and hormones that produce gradients which must be reified as organized groupings of cells that have a specific form. So once again, embryology is stymied by the lack of mathematical approaches that can link discrete, continuous and geometrical information simultaneously. Current approaches to these sorts of problems rely on modeling one aspect of the problem with one form of mathematics, switching to another sort of mathematics to address the next aspect, and to a third to describe yet another. All this switching is an indication of how inadequate our mathematical tools are for addressing these problems. Biological systems function at all of these levels simultaneously, so why cannot our mathematics?

I maintain that it is not the biology that is too messy to be modeled in these cases, but the mathematics that is inadequate (because inappropriate) to addressing these sorts of biological problems. This is why we need a new biomathematics! Indeed, I speculate that complementarity might be the solution to both the biological and the mathematical problems here. What we seem to need are the means to describe all of the biological problems listed above as manifestations of a single problem that can be examined using a single, new type of math – a mathematics that treats continuous functions, sets, vectors and geometries within a single formalism or through complementary formalisms that are integratable.

To summarize, my contention is that the reason that biology has failed to develop a viable set of mathematical methods appropriate to solving its problems is that we have relied too long on mathematics developed to model physical problems that are intrinsically different. The assumption has been that biology can be reduced to chemistry and eventually to physics and therefore that a physics-derived mathematics should be sufficient. But hierarchy theory suggests that reductionism can never explain how novel properties and processes emerge. Biological entities have properties that are different from chemical and physical ones and which require novel mathematics to describe. What we need is not, therefore, more detailed physical models of biological systems that can handle greater and greater amounts of detailed data from increasingly find-grained studies of the components of systems, but ways of identifying the biological properties that are as unique to such complex conglomerations as temperature is to a set of molecules. What we lack, in short, is a uniquely evolutionary mathematics that deals with the emergence of organization from non-random selection among replicating variations within complex populations of things. The challenge of a biological mathematics, or biomathematics, is to invent what a mathematics of such emergent properties and organization look like. This new biomathematics will have to integrate at a minimum concepts of continuous mathematics with discrete mathematics, vector formalisms, and geometrical principles. Such a biologically relevant mathematics does not currently exists.

In conclusion, if I may be permitted one final speculation, I feel compelled to ask whether biomathematics may revolutionize mathematics itself by finding novel links between set theory, probability theory, hierarchy theory, network theory, vectorial mathematics etc. leading to a new type of super-mathematics that integrates (hopefully through fundamentally simple insights) disparate areas of both mathematics and the sciences. Since I have to think about biological systems in all of these ways in order to model them, and since biological processes are intrinsically carried out in these integrated ways by Nature itself, it seems to me logical that real and useful connections must exist within the mathematical formulations of these natural processes as well. Indeed, as I have indicated in passing several times above, I believe that biology is just one of many such sets of emergent properties resulting from spontaneous organization within complex systems. In consequence, the principles that are derived from our studies of biomathematics should apply to an understanding of how novel properties can emerge in complex systems of any kind, whether ecological, social, behavioral, technological or economic. Thus, just as the Scientific Revolution provided us with physics-based mathematics that made possible the investigation of whole new realms of science, so can we expect the development of a biology-based mathematics to have equally far-reaching and revolutionary results.

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Overlap among Dendrites in Neuronal Networks Is a Designed Entity onto Which Functional Topology Is Coded

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Abstract. Information processing in the brain is performed by propagating data through an array of neuronal networks, each having unique structural and topological architectures. However, the mechanisms that specify these architectures are not well understood. We found that neuronal networks *in vitro* determine the pattern and strength of their connectivity by designing the way dendrites overlap. The branches of neighboring dendrites converge in a collective and ordered fashion, leading to a network configuration that enables axons to innervate multiple and remote dendrites using short wiring lengths. In addition, the convergence sites are associated with synaptic clusters of higher density and strength than found elsewhere, leading to patchy distribution of synaptic strength in the network. Thus, controlled design of the overlap among dendrites patterns and strengthens neuronal connectivity in neuronal networks.

Keywords: neuronal networks, dendro-dendritic contact, synaptic strength.

1 Introduction

Neurons integrate information through tree-like protrusions extending from their cell body termed dendrites. Dendrite arborization patterns are critical determinants of neural circuit formation and function as they can influence the type and location of inputs a neuron is able to receive, and how these inputs are integrated [1, 2]. The mechanisms that underlie these influences are not clear, but are likely to be found within the context of dendritic morphogenesis.

Dendritic arbor development is a highly dynamic process, characterized by extension, branching and retraction of branches, followed by their stabilization [3-5]. This process is influenced largely by the combined actions of intrinsic signals, guidance cues, and neuronal activity [3, 6, 7]. But, the action of these diffusible cues is too broad to resolve specific tree architectures.

A finer tuning of dendritic morphogenesis *in vivo* occurs through stabilization of dendritic branches through dendrite-dendrite physical interactions [8]. This mechanism has a profound influence on determining the size and shape of the dendritic tree by specifying growth directions and by allowing individual cells to refine dendritic targeting to their appropriate area and ensure appropriate synaptic contacts [9]. Also, the increase in the dendrite-dendrite proximity at the contact area has physiological consequence. When such distances are shorter than a few microns, the current produced by one active branch can spread through the extracellular matrix space to alter the membrane potential of an adjacent branch, potentially causing activity synchronization.

Hence, physical interactions among dendrites play a role in both structure and function of dendrites and may serve as a link between them. Therefore, considering the geometrical map of dendro-dendritic contacts is essential for understanding development and function of neuronal networks.

Based on this conclusion, we raised the following **working hypothesis:**

a. **Dendrite-dendrite contacts are allocated in an ordered and controlled fashion. This structure wiring principle leads to development of distinct distribution maps of dendrite-dendrite contacts.**
b. **Contact maps serve as the template onto which specific topological and synaptic maps are coded.**

We found that dendritic branches form stable contacts preferably at bifurcations and at pre-existing contacts on branches of neighboring dendrites in a non-random and activity-promoted fashion [10-12]. This directed growth led to clustering and strengthening of synaptic connections at the contact sites and formation of an Economical Small World network configuration [13], which broadens network connectivity. Hence, this new dendritic behavior shapes and links structure and topology in neuronal networks.

2 Methods

Imaging the Structural Dynamics: The main working system here was cultured neuronal networks, prepared from rat brain hippocampus (an organ related to learning and memory), since in culture dendrites and axons are relatively sparse and their wiring is readily monitored. Neural cells were extracted, plated on a glass dish and allowed to grow and reconnect while being imaged through a phase contrast light microscope.

Imaging Wiring and Synaptic Connectivity: In addition, cultured cells were tagged by fluorescent antibody markers specific for dendrites (anti-MAP2), axons (anti-NFM) and synaptic connections (anti-synaptophysin), and imaged through a fluorescence microscope. The strength of synaptic connections was imaged using the synaptic vesicle recycling fluorescence probe FM1-43. In one set of experiments, cells were labeled by transfection of the green-fluorescent protein cDNA for visualizing inter-dendritic contacts. Several experiments were performed on rat brain tissue sections.

Definition of Dendrite-dendrite Contacts: Contacts were identified using MAP2 images. Contacts of more than two dendritic branches were considered only if the branches were not associated through fasciculation.

Analysis of Network Configuration: Checking for ESWN was performed by manually converting MAP2 images into a graph, using MATLAB.

3 Results

3.1 Ordered Dendrite-Dendrite Interactions That Shape Network Structure

We first defined three basic structural components (Fig. 1):

Dendritic segments – sections of dendritic branches, spanning between two branch points or between a branch point and dendrite endings
Dendritic bifurcations – sites where a dendritic segment splits into two daughter segments
Dendrite-dendrite intersection (or contact) – a single point of overlap between two dendritic segments or between a segment and a bifurcation

These three components interacted in various manners forming three contact motifs (see Fig. 1):

Structural motif 1 [10]: ***directed construction of multi-dendritic intersections*** **(MDIs):** Dendritic branches grow directly toward pre-existing intersections between other branches and cross them, forming multi-dendrite intersections (Fig. 1, see also Fig. 2A1-A4). Such directed growth could begin dozens of microns away from the intersection.

Structural motif 2 [11]: ***directed crossing of dendritic bifurcations:*** dendro-dendritic contacts occur frequently between dendritic branches at sites of bifurcations. We termed the new structure **bifurcation dendrite intersection (BDI).**

Structural motif 3 [12]. ***collective branch convergence:*** Time lapse recordings of cultures at different ages revealed massive convergence of dendritic branches, either by the growth of processes towards preexisting contact sites between other processes or by the lateral movement of several processes towards a single area (see Fig. 2b1-b3). Such behavior resulted in the formation of clusters, several microns in width, comprising contact sites of multiple processes. We termed these structures **dendrite-dendrite contact clusters (DCCs)**.

Motif stability: How stable are the structural motifs? We performed time lapse experiments over 7 days, which revealed that many of the motifs were stable throughout the experiment duration (Figs. 2C, 2D). We also found that rates of formation and dissolution of the motifs were approximately equal and constant, keeping the overall motifs density per cell constant during the entire experiment. Thus, dendrites seem to form stable and long lasting contacts at the above structural motifs.

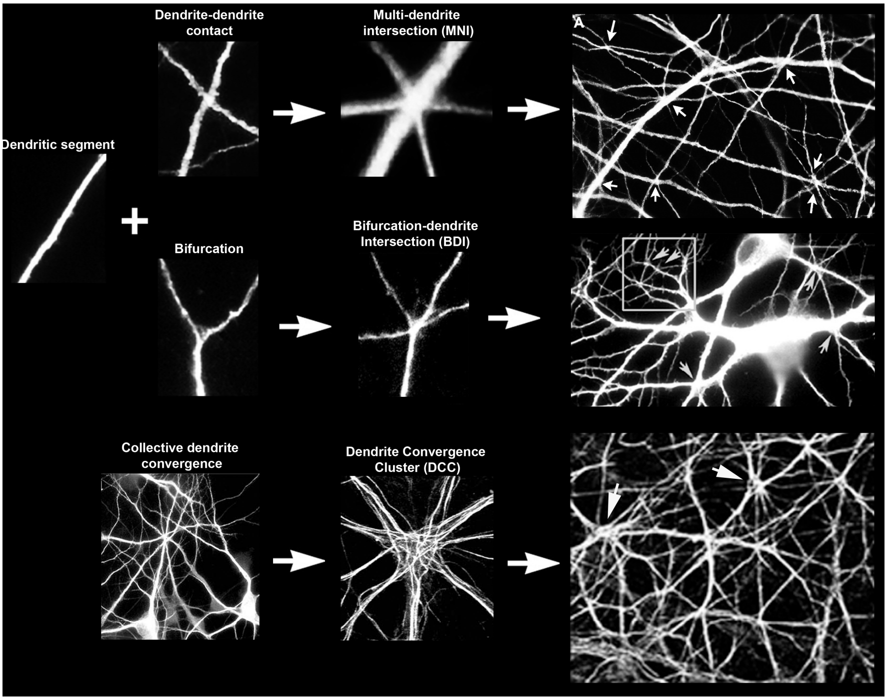

Fig. 1. MDIs, BDIs and DCCs — novel structural motifs of dendro-dendritic contact: All images are of MAP2 labeled 12 days old cultures of hippocampal neurons. (Upper two rows) Contact between three elementary dendritic structural units, segments, dendrite-dendrite contact (or intersection) and bifurcations produces MDIs and BDIs at high frequencies (arrows, upper right and middle right). To be considered part of a contact structure, each dendrite must be distinct and not arrive at the contact structure by fasciculation. (Bottom row) dendritic branches converge, producing DCCs. DCCs are frequent and when linked to each other produce ordered network (bottom right).

Evidence for non-randomness in the formation of the above motifs

High frequency of occurrence: The directed growth of dendritic branches toward the site of the motif construction (Fig. 2A1-A4) led us to assume that the motifs are formed non-randomly. A support for a directed formation came from the finding that the frequency of the motifs in the real network surpassed that found in simulations of random neuron distribution (Fig. 2E).

Motifs construction involves non-self recognition: We found that the occurrence of MDIs and BDIs between dendritic branches of different neurons was significantly higher than within single dendritic trees (Fig. 2F). Thus, neurons employ a mechanism of non-self recognition to construct hetero-cellular structural motifs among their dendrites.

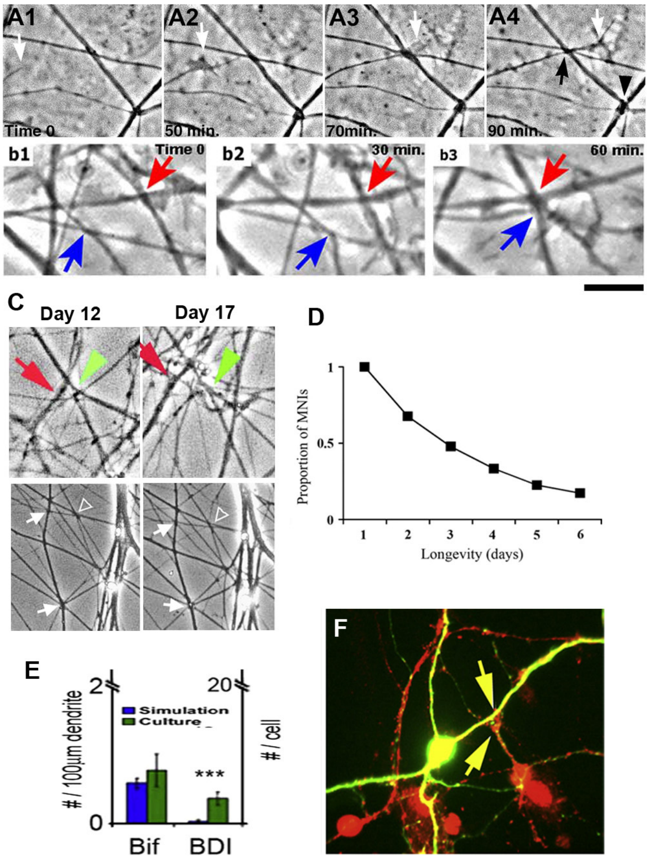

Fig. 2. MDIs, BDIs and DCCs are stable, hetero-cellular non-random entities: (A1-A4) growth of neuronal processes toward pre-existing intersections is directed (white arrows). (B1--3) Lateral movements of intersections produce sites of convergence. (C) Example of the dynamic character of the network structure. Upper two panels show contacts configuration disabled after 5 days. Bottom panels show a stable configuration (white arrows – stable, arrowhead –dismantled). (D) Longevity distribution of contacts made by three processes, as an example. Note that 20% lasted more than 6 days. (E) Neuronal cultures exhibit significantly higher level of BDIs per dendritic length compared to that found in simulations of random dendritic distribution. (F) BDI preferably form by the interaction of dendritic branches of two different cells (arrows). (Yellow – a combined MAP2 and GFP staining, red – MAP2). Scale bar: A-C – 15µm; F – 25µm.

The role of the motifs in the design of dendritic and network structures

The three motifs are expected to affect the morphology of single dendritic trees and the network as follows:

a. The growth of dendritic branches toward the motif sites shapes dendritic trees by affecting the growth direction and branch length (Figs. 1, 2).

b. From the second week in culture on, most dendritic branches were involved in at least one motif and many were involved in more than one (Figs. 1, 2), suggesting that the motifs are frequent enough to affect the structure of entire dendritic network.

c. The ‘non-self’ manner by which dendritic branches contract the motifs indicates that sister branches undergo ‘self avoidance’, and that by preferentially associating with non-sister branches they highly increase the overlap among different dendritic trees.

Studies describing dendritic morphology based on analysis of single dendritic trees often have led to the conclusion that dendritic ramification is random and that the growth directionality is unbiased toward specific targets. We present here a different explanation for dendritic tree morphogenesis, where the interaction of a tree with other trees is a major player in the design of the final dendritic morphology.

According to our model, the growth of dendritic branches is preferentially directed toward areas of high dendritic proximity and to sites of bifurcation and intersection to form MDIs, BDIs and DCCs. Thus, the development of particular dendritic tree architectures can be predicted by considering the distribution and density of DCs around the growing trees. By the same token, the morphology of entire networks of dendritic trees can be described by considering the number, location and size of their DCs, bundles and DCCs. Thus, studying dendritic proximity maps may enable us to proceed beyond the structure of individual dendritic arbors to that of full dendritic networks.

3.2 Evidence for a Role of the Motifs in Network Functional Connectivty

Dendrite-dendrite contacts and their structural motifs influence the growth pattern of axons, their choice of targets and the efficiency of connectivity in the entire network in the following ways:

Motifs are preferable crossing sites for axons: The tendency to prefer dendritic intersections as a contacting target appeared also in axons. Many axonal edges directed their growth toward the center of intersections and crossed them (Fig. 3a), developing their structure according to the distribution of the surrounding intersections (Fig. 3b). This type of growth also leads axons to select specific dendritic targets, namely those located at the crossed intersections.

Motifs facilitate target switching by axons: Many of the axons fasciculate with dendrites and follow their path, but frequently when reaching an intersection they turn and switch dendrites (Fig. 3C1-C3). At DCCs, due to the high proximity among targets, only a few microns of growth suffice for axons to switch between many targets (up to several dozen, depending on the DCC size) (Figs. 3D-3F). This high targets/axon ratio means that single neurons would connect to a higher number of neurons in the network than would be the case in non-aggregated networks. The outcome of this wiring mechanism may be an all-to-all connectivity.

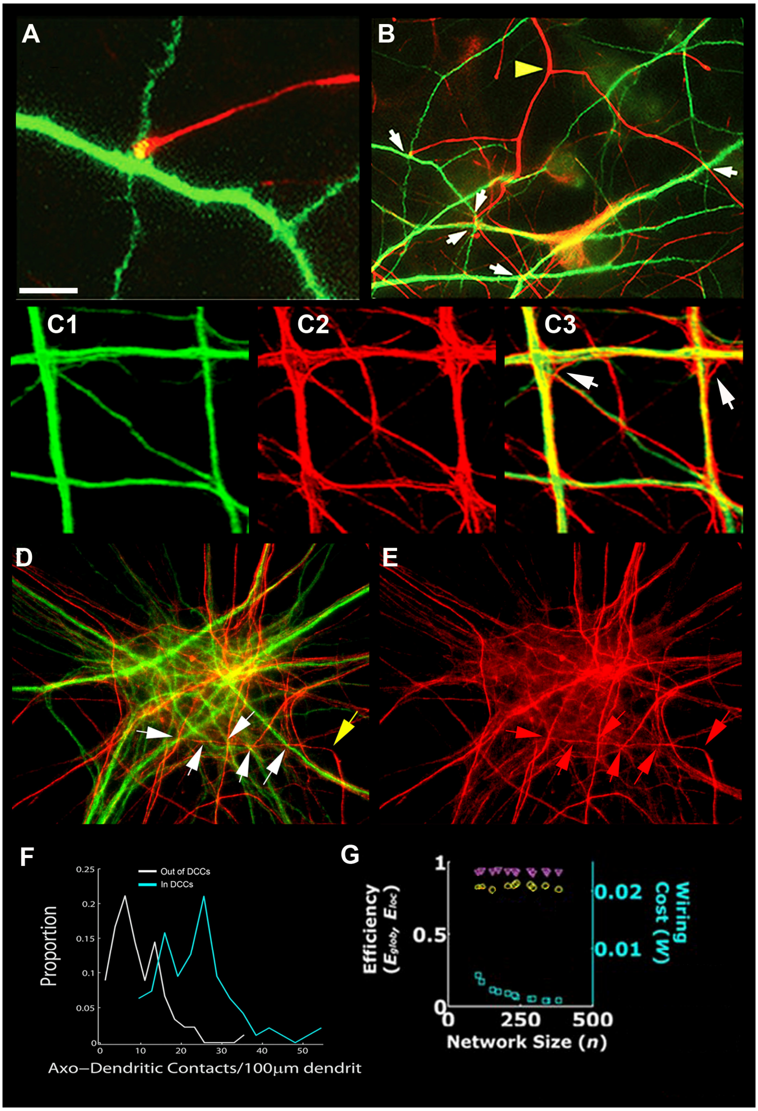

Fig. 3. MDIs, BDIs, and DCCs shape axonal wiring and increase network connectivity: In all images, red=axons, green=dendrites. (A) A portion of the axons grow directly toward dendrite-dendrite contacts. Shown is an axonal growth cone approaching such a contact. (B) An axon shaping its structure by crossing five dendrite-dendrite contacts. (C1-C3) An ordered growth of dendrites (C1) leads to organized axonal growth (C2, same area as C1), as many of axons fasciculate with the dendrites and follow their paths. Several axons turn at intersections and switch targets (arrows in C3, a merger of C1 and C2). (D, E) A large DCC in which axons turn (an example pointed at by a yellow arrow), and form a complex mesh (see only axons in (E)). The turning axons make contact with several different dendritic branches at relatively short lengths (white arrows in (D)). (F) Quantification showing a shift to the right in the number of axo-dendritic contacts per axonal length at in vs. outside DCCs. Scale bar: (A-C) - 10μm; (D, E) – 20μm.

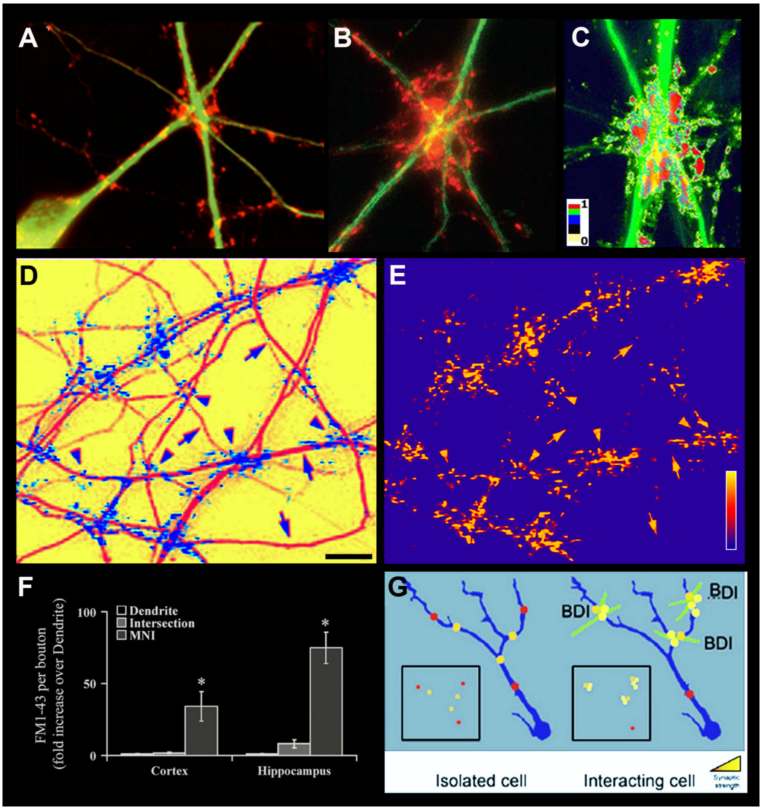

Fig. 4. MDIs, BDIs and DCCs lead to clustering and strengthening of synaptic connectivity: (A, B) At the contact site among dendritic branches (green), the density of synaptic connections (red, anti-synaptophysin) is higher than along non-crossing regions, and the size of the connections increases (B). (C) A DCC in which the strength of synaptic connections (secretion level by FM1-43) is higher than elsewhere. (D) Due to the synaptic enrichment at contacts, the map of denditic contacts and motifs (red) dictates a patchy distribution of synaptic connections in the network. (E) A look up table of the synaptic image in (D) showing that synaptic connections of the highest strength are located in hubs of DCCs. (F) Synaptic strength per connection increases with increased number of dendritic branches participating in the studied motif. (G) Dendro-dendritic intersections cause a patchy distribution of synaptic connections and synaptic strength along the dendritic arbor. Scale bar: (A-C) 10μm; (D, E) 15μm.

Ordered dendrite overlap increases efficiency of connectivity [12]: In relating to dendritic proximity by describing dendritic networks as graph of connections among dendrite-dendrite contacts we were able to show that in culture, such networks assemble into ESWN configurations (Fig. 3G). The main anatomical consideration of such a configuration is that a dendritic network exhibits 'shortcuts' that connect distant dendrites. Such an arrangement would have significant implications for axonal directionality and patterning, as many of the axons fasciculate with dendrites and follow their tracks (Fig. 3C1-C3). This means that if axons have access to 'shortcuts', their chances of innervating distant dendrites are increased, enhancing the connectivity of the entire network.

3.3 A Role for the Structural Motifs in Network Activity

Causing synaptic clustering: It was found that synaptic connections assembled into clusters at dendrite-dendrite contacts, and the synaptic density of such clusters was further enhanced in MDIs, BDIs (Figs. 4A, 4B) and DCCs (Figs. 4C-4E). Hence, synaptic density is elevated in the presence of dendritic contacts and structural motifs.

Leading to synaptic strengthening: Using a fluorescent probe for the strength of synaptic secretion (see methods), we found that synaptic connections accumulating at dendrite-dendrite contacts were of higher strength than found elsewhere (Figs. 4C-4E). Moreover, the increase in synaptic strength was proportional to the number of intersecting dendrites in the motifs (Fig. 4F). Eventually, the presence of the structural motifs led to increase in synaptic strength in the network and produced patchiness in it distribution (Figs. 4D, 4G).

Motifs formation and synaptic clustering are regulated by the network activity: The density of motifs and clustering of synaptic connections were reduced in the presence of inhibitors of synaptic activity. Thus, ordered contacts, synaptic clustering and strengthening are all activity-dependent.

4 Discussion

Our work demonstrates that interactions of a dendritic tree with its dendritic neighbors are non-random and therefore should be included when attempting to model or explain dendritic trees morphogenesis. Our results imply that the pattern of branching in a dendritic tree is related to the pattern of contacts that this tree makes with adjacent trees of other neurons. A broader consequence of such a relation is that structural modification of a particular tree, due to growth or retraction, may be propagated to other trees and alter their structure via generation and disassembly of MDIs, BDIs and DCCs. Hence, the dynamic ramification of single and network of dendrites can be better understood by considering the pattern of their branching and hetero-neuronal contacts.

We conclude that the proximity among dendritic branches of neighboring neurons is a functional structural entity. Being upregulated by synaptic activity and associated with enrichment in synaptic density and strength, dendritic proximity affects the conversion of synaptic information into a map of synaptic connections and synaptic strength distributions (see fig. 5). Accordingly, when neuronal network activity increases, the network architecture becomes more aggregated through DCC and bundle formation, leading to an increase in synaptic clustering and strength. This structure-mediated, activity-dependent synaptic strengthening may serve as a novel structural-based mechanism of plasticity.

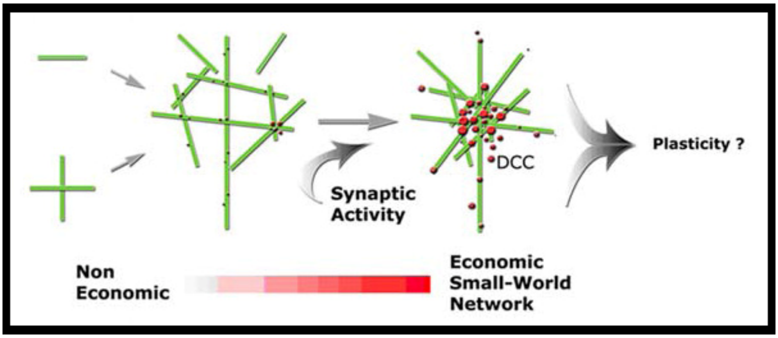

Fig. 5. Conceptual model of network structure-based data consolidation. Green rods - dendrites, Red circles - synaptic clusters (darker colors refer to higher density and synaptic strength). For simplicity, axons are omitted from the model. When single or intersecting dendritic branches converge, DCC are formed and the network becomes more aggregated. This process is promoted by synaptic activity. Synaptic clustering and strengthening becomes prominent at the DCCs. The geometric architecture of the dendritic network results in an Economic Small-World organization, a scenario that increases network connectivity and it produces local enhancement in synaptic strength. It therefore may serve as a new mechanism of synaptic plasticity.

Acknowledgment. I thank Drs. Pablo Blinder, Joshua Cove, Elia Abi-Jaoude and Miriam Lafreniere-Roula and Professor Luc Devroye for participating in this research.

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MENS: From Neurons to Higher Mental Processes up to Consciousness

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Abstract. How do higher mental processes, learning, intentions, thoughts, emotions, arise from the functioning of the brain? That is the question which, with Jean-Paul Vanbremeersch, we have attempted to approach in the model MENS (for *Memory Evolutive Neural Systems*), proposing a unified frame for the functioning of the neural, mental and cognitive systems. It is an application to neuro-cognitive systems of our Memory Evolutive Systems, a model for self-organized multi-scale dynamic systems, based on a 'dynamic' theory of categories (a summary on MES is given by Ehresmann & Simeonov, 2011, in this volume). Here I just indicate the main ideas; for more details, cf. Ehresmann & Vanbremeersch (2007, 2009).

Keywords: neural system, cognition, mental object, consciousness, category, complexification.

In spite of the diversity of the brain areas, there is a common process in their dynamics, already described in the forties by Hebb (1948): the formation, persistence and intertwining of more or less complex and distributed neuronal assemblies, which 'synchronously' activate specific 'mental objects'; this association is not 1-1 due to the "*degeneracy* property of the neural code" emphasized by Edelman (1989). Assuming this process, a mental object can be represented as the 'binding' of each of the more or less complex "polychronous" (in the sense of Izhikevich & *al.* 2004) neuronal assemblies which, either simultaneously or at different times, can synchronously activate it.

This binding process plays a central role in the formation of the hierarchical evolutive system MENS: the level 0 models the neural system (with the neurons and synaptic paths between them). Higher level components, called *category-neurons*, represent more and more complex mental objects or processes constructed (using the "complexification process" introduced in MES to model the formation of increasingly complex objects) as the iterative binding of more and more complex polychronous assemblies of lower level (category-)neurons. Thus a category-neuron is a multiform 'conceptual' object emerging from physical states of the brain; and it has multiple physical realizabilities into polychronous hyper-assemblies of neurons, obtained by successive decompositions of C which unfold one of its ramifications down to the neural level.

We show how the degeneracy of the neural code (formalized in MES by the Multiplicity Principle) is at the root of the formation of category-neurons representing mental objects, elaborate comportments and cognitive processes of increasing complexity order. In particular we describe how different brain areas interact as hybrid systems to generate an "*algebra of mental objects*" (in the terms of Changeux 1983), and to develop a robust though flexible *memory*, able to adapt to changes.

In the memory, we distinguish a subsystem, the *Archetypal Core* AC (based on the "neural core", Hagmann & al. 2008), which integrates and intertwines significant memories of perceptual, behavorial and emotional experiences; it acts as a flexible though permanent internal model, embodying the personal identity/self.

AC consists of category-neurons of higher complexity order, with many ramifications and possibility of switches between them; they are connected by strong and fast links which form *archetypal loops* self-maintaining their activation, and diffusing it to a larger domain through the unfolding of ramifications.

If a significant event activates part of AC, it leads to the activation of a longer term *global landscape* **GL** (to be compared to the "theater" of Baars, 1997) in which higher mental and cognitive processes can develop. In particular, *consciousness* is characterized as an integration of the temporal dimensions, through the development (in **GL**) of:

(i) a *retrospection process* to make sense of the recent past, and
(ii) a *prospection process* to conceive long-term strategies by iteratively constructing virtual landscapes in which sequences of strategies can be tried and evaluated.

Thus MENS proposes a new approach to the brain-mind problem.

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A New Approach to the Information in Neural Systems

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Abstract. Given the tremendous advances that have been made in our understanding of the mechanics of neural systems, there has been remarkably little progress in understanding how they process information. Here is it proposed that a major obstacle has been confusion about the concepts of information and probability. It is suggested that the correct definition of probabilities is strictly Bayesian, in which probabilities are always entirely conditional on information. It is further proposed that to best understand the brain, we should use Bayesian principles to describe what the brain knows about its world. Although such a "first-person" Bayesian approach has recently become prominent, its success has so far been almost entirely restricted to accounts of phenomena such as perception and cognition. The present work demonstrates how the Bayesian approach can be grounded in biophysics. Boltzmann's distribution from statistical mechanics is used to derive probability distributions that are conditional entirely on the information held within single molecular sensors. By integrating information from a multitude of sensors within its membrane voltage, a neuron thereby reduces its uncertainty about the state its world. A major virtue of this integrated view of information and biophysics is that it allows us to identify a single and general computational goal for the function of the nervous system, which is to minimize its uncertainty (about the biological goals of the animal). This computational goal has recently served as the basis for a general theory of information processing within the nervous system (Fiorillo, 2008).

Keywords: Bayesian inference, general theory, prediction, probability, information, nervous system.

1 The Computational Goal of the Nervous System

There has been a tremendous growth in our knowledge of the mechanisms that underlie brain function. Despite the fact that mechanics and information processing are believed to go hand in hand, there has been relatively little progress in understanding how the brain processes information. I recently published a general theory of information processing within the nervous system in which information was presumed to be a property of biophysical mechanisms (Fiorillo, 2008). The foundation of the theory, and the proposal that it qualifies as "general," was based upon the identification of a single computational goal and a quantitative biophysical description of how the brain achieves the goal. It was proposed that the function of all nervous systems can be viewed as "decision-making," or the selection of motor outputs, to promote future biological fitness. The only problem in making decisions is uncertainty about the state of the world, and the computational goal of the brain is therefore to minimize its uncertainty (or equivalently, to make accurate predictions, estimates, inferences, hypotheses, etc.). Thus it was proposed that all of the many specific computational problems that the brain faces result from uncertainty (lack of information) about some aspect of the world. This general view of brain function has been prominent since at least the time of von Helmholz (1896), and it has grown stronger recently with the application of Bayesian probability theory. Here I suggest that to fully appreciate the potential of the Bayesian approach, it must be grounded within biophysics.

2 The Definition of Probability and Information

To appreciate the proposed computational goal of the nervous system, one must accept a strictly Bayesian definition of probabilities. The importance of the definition of probability is obvious given that information (a reduction in uncertainty, or entropy) is itself defined as a function of a probability distribution. For at least the last century, there has been a debate about the proper definition of probabilities. The account given here is based on that of Jaynes (2003), who argued throughout his career in favor of the Bayesian definition. The alternative view is that probabilities are essentially equivalent to frequencies, and that they are properties of a physical system, independent of knowledge about that system. The distinction between Bayesian and frequentist definitions is easily illustrated by an example. "There are 4 possible outcomes to an event, A, B, C, and D. What is the probability of each outcome?" According to a "Bayesian" definition, if the only information is that there are 4 possible outcomes, then all outcomes must be equally likely, and the probability of each outcome is 1/4, or 0.25. If additional information becomes available at a later time, the probabilities may change. The probabilities simply describe the information. Alternatively, if probabilities derive from frequencies, then the appropriate response to the question is that it is not possible to know the probabilities until one observes the frequencies of the outcomes. Thus the notion of probability does not apply to the information that "there are 4 possible outcomes." The two definitions of probability can yield the same probabilities (numbers) in some special cases, but in general they are contradictory.

According to Jaynes and others, the frequentist definition has no redeeming features or advantages. Over the last decades, it has gradually lost adherents, and it can be expected to fade away eventually. However, the frequentist view still exerts a profound influence within neuroscience (even though few neuroscientists are aware of the distinct definitions of probability). Textbooks on computational neuroscience don't acknowledge any distinction (e.g. Dayan and Abbott, 2001)). There are numerous examples that could be given, but I will mention only one. Friston (2010) recently advocated a Bayesian approach as providing a path towards a "unified brain theory." As one component of his theoretical framework, he defines a mathematical measure of "surprise" as a function of probabilities, without specifying any information upon which the probabilities are conditional. He then goes on to state that "A system cannot know whether its sensations are surprising..." This only makes sense if the probabilities are a property of something external to the nervous system, such as the "long-run" frequency of an external event, rather than being conditional on information within the brain (for a more detailed critique of Friston's theoretical framework, see Fiorillo (2010)). This is but one of many examples in which advocates of a Bayesian approach to the brain do not adhere to a strictly Bayesian definition of probability. The term "Bayesian" is often used among neuroscientists to refer to any methods that utilize Bayes's theorem, whereas I follow Jaynes and others who have used the term to refer to the more important matter of the definition of probability. The Bayesian definition is strongly supported by philosophical arguments, and it is mathematically superior to the frequentist approach, insofar as it produces more accurate results (Jaynes, 2003). However, its validity is not the main reason that it is invaluable with respect to understanding the brain. In most applications of probability theory, our interest is in quantifying our information, as scientists, about some aspect of the world, such as the brain. However, the critical feature of Bayesian probability theory is that it can be used, in principle, to quantify the information of any entity. The importance of this is evident in the fact that different brains have different information, even about the same aspects of the world. Rather than quantifying our information about the brain, we can quantify the information of the brain about its world. Thus we can view brain function from the unique "first-person" or "neurocentric" perspective of the brain, rather than from one of the many "xenocentric" perspectives of a "third-person" observer of the brain.

People routinely apply a first-person approach to understand other people. Psychologists have now taken this approach towards understanding human and animal behavior, as illustrated clearly by their rejection of Skinner's behaviorism. Skinner sought to understand behavior purely through examination of the brain's "input-output" function, without regard to what information might lie within the brain. The brain was simply viewed as a "black box" which performed an input-output transformation. Although this approach has been rejected with respect to behavior, and "high-level, cognitive" aspects of brain function, it is still very dominant in the way neuroscientists view the function of "lower" neural systems (i.e., sensory and motor systems, and simple nervous systems). In particular, the function of single neurons is virtually always viewed from a xenocentric perspective, in which we describe our knowledge of neurons by specifying their input-output function. Perhaps the best example of this is to be found in the highly influential book *Spikes: Exploring the Neural Code* (Rieke et al., 1997), which is the most thorough exploration to date of the relationship of information theory to neurons. The authors quantify the information that the neuron's spike output provides to them about the neuron's input, given their prior knowledge of the frequency distribution of the neuron's inputs, and their knowledge of the statistics of neuron's input-output relationship. They do not even discuss processes occurring within the neuron, but instead treat the neuron as a "black box," fully analogous to Skinner's approach to understanding behavior. Other prominent work on the neuronal basis of Bayesian inference has taken the same approach, deriving probability distributions that are entirely conditional on the information of the scientists themselves, with no consideration of the inner workings of the neuron (e.g. Ma et al., 2006; Beck et al., 2008).

The xenocentric approach taken by Rieke and colleagues (1997) did not reflect a philosophical commitment to a third-person, xenocentric perspective. To the contrary, they actually made a strong argument as to the virtues of "taking the neuron's point of view." They suggested that this approach, which I denote as "neurocentric," will lead to greater insights and simpler descriptions of neural function. The fact that Rieke and colleagues did not actually take a neurocentric approach, by identifying probability distributions conditional upon the biophysics of the neuron, could reflect underlying frequentist notions of the definition of probability, the natural inclination of scientists to view the world from their own perspective (which is xenocentric with respect to a neural system under study), or uncertainty as to how one could identify probabilities conditional only upon biophysical mechanisms.

3 The Need to Unite Information with Biophysics

Work related to information theory and Bayesian inference has carried on mostly in the absence of biophysics. In particular, probability distributions have not been conditional exclusively on biophysical mechanisms. There have been many papers published recently that have successfully utilized Bayesian principles to understand phenomena such as perception and cognition, but most of these have not even speculated about its neural basis (e.g. Kording and Wolpert, 2004). Those that have speculated have done so in the absence of compelling evidence (for example, evidence linking a specific neural circuit to a specific Bayesian operation; e.g., Friston, 2010). Work that has applied information theory to "the neural code" (e.g. Rieke et al., 1997) has neglected biophysical mechanisms, taking the view that informational relationships between inputs and outputs depends only on their statistical properties, as observed from a xenocentric perspective. Whatever physical reality may lie between inputs and outputs is inconsequential with respect to information (note the analogy to Searle's "Chinese room"). By contrast, according to the neurocentric Bayesian approach described below, knowledge of the world is grounded exclusively within the biophysics of neurons, as described through probabilities of external states that are conditional only on the neuron's information.

If information and inference can be identified as properties of physical systems, it would become relatively easy, in principle, to specify the computational goal of the nervous system as the minimization of uncertainty, and to show how it is accomplished. The goal of minimizing uncertainty (of the brain about its world) is exclusively from a neurocentric perspective. It is clear that the outputs of a system depend upon the information and mechanics of the system, and thus it is desirable to have a computational goal that is defined through reference to the internal information and mechanics of the system. Thus the difficulty becomes apparent of defining a computational goal from a xenocentric perspective.

4 The New Neurocentric Approach to Neurons

The agenda here is to first describe the information held within single molecules, and then work up to single neurons and systems of neurons. A neuron receives information about a "macroscopic" quantity, such as the local concentration of a chemical, through its "microscopic" sensors. The field of statistical mechanics addresses the relationship between microscopic (molecular) and macroscopic variables. Specifically, it specifies the probabilities of microscopic states given macroscopic factors such as pressure and temperature. It was pointed out by Jaynes (1957) that that these probabilities are best understood as the result of rational inference (the maximum entropy principle) given knowledge of the macroscopic variables. Here we will use the same principle, but in the opposite direction, to specify the probability distribution of a macroscopic variable given the information of one or more molecules.

In the simplest case, a molecular sensor can exist in either of two conformations (Figure 1A). (Proteins typically can exist in multiple configurations, but a model of a protein could consist of multiple and interacting two-state sensors.) Boltzmann's distribution from statistical mechanics specifies the probability (P_2) that it will be in one state rather than the other given the energy difference between the two states (E_2-E_1), the temperature (T), and Boltzmann's constant (k_B) (Hille, 2001).

$$P_2 = \frac{1}{1+e^{\frac{E_2-E_1}{k_B T}}} \tag{1}$$

Since this is a sensor, the energy difference depends upon a quantity such as voltage or the binding of a ligand. For a voltage sensor, the energy difference between the two states is

$$E_2 - E_1 = ze\left(V_{1/2} - V\right) \tag{2}$$

where '*z*' is the number of equivalent elementary charges, '*e*' is the elementary charge in coulombs, '*V*' is voltage, and '$V_{1/2}$' is the voltage required to counterbalance the inherent energy difference between the two states so that they are equally probable (the voltage at which half the sensors are expected to be in one of the two states).

These equations are commonly used to predict the state of molecules, such as ion channels, given macroscopic quantities such as neuronal membrane voltage or chemical concentration. The simple point made here is that they also describe the inverse relationship. Given the inherent properties of the molecule, and its current state, these equations specify the probability distribution of a macroscopic quantity conditional only on the information within the molecule (Figure 1C). If the information from multiple sensors is integrated through a physical medium, then the probability distribution conditional on that integrated information becomes narrower and uncertainty is further reduced with increasing numbers of sensors (Figure 1D). Bayes's theorem specifies how to describe the integrated information of all the sensors, although in a

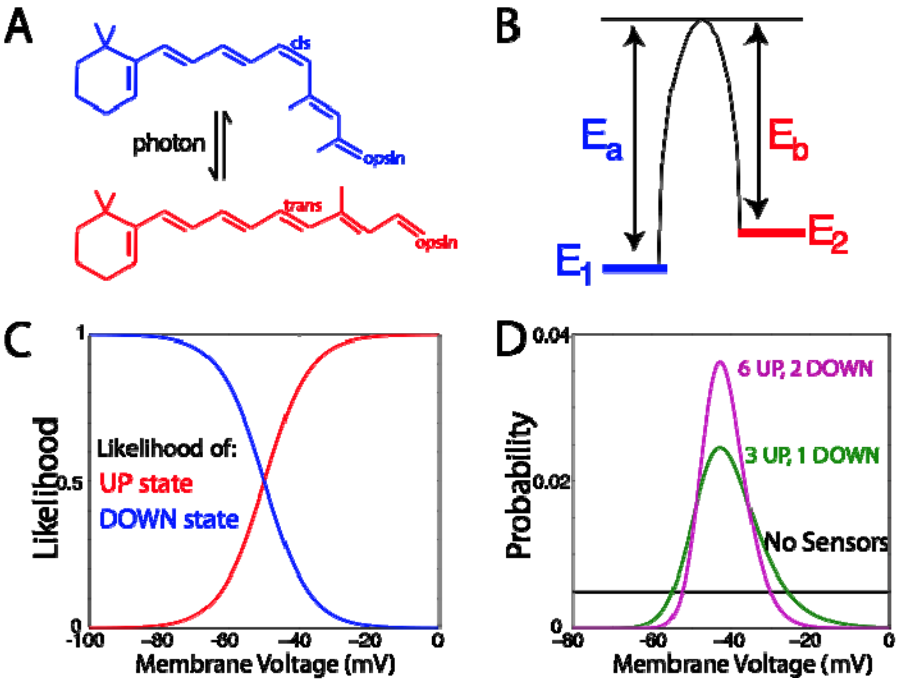

Fig. 1. The information in two-state sensors. **A.** The structure of retinal, a photosensor that is part of rhodopsin. Absorption of a photon changes its conformation from 'cis' to 'trans.' **B**. An energy diagram of a sensor with two states. The difference in energy levels determines the probability that a sensor will be in the "UP" state or "DOWN" state, as described by Boltzmann's distribution (equation 1). The energy levels are sensitive to a quantity such as voltage or ligand concentration. **C.** The probability of a state depends on that quantity (equations 1-2), as shown in this likelihood function. This function represents the probability that a two-state sensor is in a particular state given the particular value of a macroscopic quantity such as voltage. However, viewed "from the molecule's perspective," this implies that the probability distribution of the macroscopic quantity, given only the information in the molecule, has this same form. **D.** If information from multiple sensors is physically integrated, uncertainty decreases as the number of sensors increases. The probability distributions represent the estimate of voltage made by integrated information from 0, 4, and 10 voltage sensors. Each sensor has the same properties as shown in panel C, corresponding to a sigmoidal probability distribution. These sigmoidal functions were multiplied by one another to derive the distributions shown in 'D.'

typical and realistic model, the sensors found in neurons function independently of one another (physically), and Bayes's theorem therefore indicates that the probabilities conditional on single sensors should simply be multiplied (Figure 1D).

The molecules of interest here are ion channels within the membrane of a neuron, and integration is performed within the voltage across the neuron's membrane. Neurons receive information from many ion channels, with distinct groups of ion channels conveying information from distinct points in space and time (Fiorillo, 2008).

However, all of these ion channels are proposed to convey information about the same aspect of the world, which we can refer to as the neurons "stimulus." The stimulus could be a very abstract aspect of the world, but it is easiest to imagine the case of an early sensory neuron, in which the stimulus might be light intensity in a particular region of space. In the most typical case, information about the stimulus comes to a neuron most directly through excitatory synapses that use glutamate as a neurotransmitter. By estimating 'proximal' glutamate concentration through its glutamate sensors, the neuron indirectly estimates 'distal' stimulus intensity. As information flows from the external world to the neuron, there is a chain of inference or estimation that flows in the opposite direction. Each link in the chain is composed of molecular sensors, and they simultaneously pass information to their downstream neighbors and estimate the state of their upstream neighbors.

Besides ion channels that are gated by glutamate or other neurotransmitters, a neuron can express a great diversity of channels that open and close depending on membrane voltage. These channels receive information about glutamate concentration, and stimulus intensity, indirectly via membrane voltage. Thus they necessarily receive the information at least slightly later than the glutamate-gated ion channels. Furthermore, there are a great diversity of voltage-regulated ion channels, particularly potassium channels. Because these differ greatly in their kinetic properties, distinct subtypes carry information from distinct periods of the past. Thus it is useful to describe these channels as contributing "prior" information, and the excitatory channels, which are more directly linked to the external stimulus, as contributing "current" information. A neuron's estimate of glutamate concentration, and hence stimulus intensity, will therefore depend on both its past and current "observations."

This is illustrated by the case of a simplified neuron that expresses only two types of channels, excitatory glutamate-gated cation channels and inhibitory voltage-gated potassium channels (see figure 2 of Fiorillo, 2008). In response to a square-wave pulse of glutamate, the neuron is initially depolarized, but then gradually repolarizes as potassium channels open slowly. By estimating membrane voltage, the potassium channels indirectly estimate the fraction of open glutamate-gated channels, and therefore the concentration of glutamate as well. Probability distributions, conditional on either the population of glutamate-gated channels or the potassium channels, can be derived using Boltzmann distributions (equation 1), as described previously in greater detail (Fiorillo, 2008). Voltage-regulated potassium channels are just one of many examples of homeostatic mechanisms that stabilize membrane voltage. Homeostatic mechanisms (generally inhibitory) can be understood as using prior information to predict and counteract the effects of incoming "sensory" information (generally excitatory). A neurons output can therefore be viewed as a "prediction error." Prediction errors signal only "new" information, and are an efficient means of communication. The notion that neurons should communicate efficiently has so far been the primary contribution of information theory to neuroscience (e.g., Barlow, 1961; Rieke et al., 1997). Whereas the "efficient coding hypothesis" has traditionally been described from a xenocentric perspective, the term "prediction error" is explicitly from a neurocentric perspective (since the prediction is a property of the neuron). An important new aspect of the present account is that a neuron's prior information contributes to minimizing its uncertainty (making more accurate predictions), and the reduction of uncertainty is proposed to be the general computational goal of the nervous system. By contrast, although efficient communication contributes to this general goal, communication in itself is not the ultimate goal. A goal of the present work is to shift the emphasis of information theory, as applied to the nervous system, from communication to prediction.

It is important to note that the neurocentric approach proposed here uses probabilities solely to *describe* the biophysical information of a neuron. There is no physical step that must occur within the nervous system to "calculate" probabilities from information. Probabilities are a quantitative property of information in much the same way that mass is a quantitative property of matter. Likewise, information is an intrinsic property of matter and energy. Information follows the rules of physics, and Bayesian principles allow us to quantify information using probabilities.

5 The Groundwork for a General Theory of the Nervous System

A prerequisite for a general theory of the nervous system is to specify its general computational goal, and a primary virtue of the neurocentric approach is that it makes it relatively easy to state such a goal. The proposed goal is the reduction of uncertainty, which is simply the definition of information itself. I have described here how that goal can be achieved within single neurons by integrating information from multiple sensors. This alone provides little insight into the structure or function of the nervous system. However, if the goal is to minimize uncertainty, that suggests specific criteria for selecting a neuron's inputs (the specific ion channels and synapses that provide its information). The general theory therefore uses the computational goal of minimizing uncertainty in order to derive principles that should guide the selection of inputs to neurons, both synaptic and non-synaptic, and thereby shape the structure and function of the nervous system (Fiorillo, 2008). The fundamental argument made here is that once misconceptions concerning the nature of information have been clarified, the door will be open for a substantial acceleration in progress towards understanding and mimicking the intelligence of biological systems.

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What the *Escherichia Coli* Tells Neurons about Learning

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Abstract. The Escherichia coli is a bacterium that comfortingly lives in the human gut and one of the best known living organisms. The sensitivity of this cell to environmental changes is reflected in two kind of movements that can be observed in a swimming bacterium: "run" towards an attractant, for example food, and "tumbling", in which a new direction is chosen randomly for the next "run".

This simple bimodal behavior of the *E. coli* constitutes in itself a paradigm of adaptation in which roboticists and cognitive psychologists have found inspiration. We present a new approach to synaptic plasticity in the nervous system by scrutinizing *Escherichia coli*'s motility and the signaling pathways that mediate its adaptive behavior. The formidable knowledge achieved in the last decade on bacterial chemotaxis, serve as the basis for a theory of a simple form of learning called habituation, that is applicable to biological and other systems. In this paper we try to establish a new framework that helps to explain what signals mean to the organisms, how these signals are integrated in patterns of behavior, and how they are sustained by an internal model of the world. The concepts of adaptation, synaptic plasticity and learning will be revisited within a new perspective, providing a quantitative basis for the understanding of how brains cope with a changing environment.

Keywords: chemotaxis, integral control, internal model principle, Escherichia coli, homeostatic synaptic plasticity, habituation learning, perfect adaptation.

1 Introduction

We are living times of dramatic technological improvements. High throughput techniques have produced an extraordinary data abundance that is now being complemented with new in vivo techniques.

Construction of complex cellular models, including detailed descriptions at molecular scale, is an ongoing process moving at a strong pace. The challenge is however, not merely technological, but conceptual [26]. The behavior of a biological system can be studied at multiple levels, in deciding the level of detail that each component is described, we are making a strong commitment that should not be neglected.

The question we are addressing here is, How much knowledge of itself the *E. coli* or a neuron for that matter, needs in order to adapt to a changing environment? This epistemic problem is tackled twofold. First, we need to explore what is the capability of the *E. coli* of making new models of itself and the medium in which it moves; and second, how can we extrapolate the understanding on the organizational principles of the *E. coli* to the central nervous system of a mammal.

It must be said that by "knowledge of itself" we do not intend to tangle ourselves with speculative discussions about the introspective capacity of a single cell, rather our approach is in line with Fiorillo's neurocentric view, in which the information a neuron has about its world, may be quantified through biophysical parameters such as membrane potential [9], [10].

The paper is structured as follows. Section 2 emphasizes the necessity of realistic models grounded on empirical basis. Section 3 provides a basic understanding of *E. coli* adaptability at a molecular level. Behavioral aspects of the bacterium, and underlying mechanisms, such as homeostasis are sketched. Section 4 investigates adaptation in the *E. coli* within a quantitative framework, based on the computation of key properties like perfect adaptation. Furthermore, we introduce the idea that organisms are representational devices that subserve internal representations of the world [22].

The last part of the paper is devoted to expand concepts such as adaptation or internal model[15], to a more complex domain than bacterial chemotaxis i.e. nerve cells. Section 5 addresses, in a non speculative way, how much knowledge of itself has a biological system, by providing working definitions of knowledge as an internal model. In section 6 we borrow tools from Control Engineering. The Internal Model Principle, and in particular Integral Control, gives a mathematical basis for the study of *E. coli* adaptation, broading this result to synaptic plasticity in section 7. We conclude with conclusions and future works in 8.

2 Towards a New Approach in Modeling Adaptation

It is important to note that technical and biological systems differ in a fundamental way, while the former are built for a specific purpose the last is the product of thousand of years of evolution. The engineer is not (or should not be) a tinkerer [13], therefore technical systems, contrary to biological ones, are predominately linear, and this is because the mathematical tools accessible to the engineer are essentially linear. Furthermore, biological control systems may lack typical features present in engineering systems, such as the reference input, the error detector or the single input-single output architecture that makes amenable linear techniques like Laplace transforms [18].

E. coli is one of the simplest living things, and yet a complex system in the sense given by Trimmer in [24], where simple systems are formulated by a linear equation of second order or less, with constant coefficients. Those systems that do not meet these constraints are complex systems.

It is possible to model the movement of the *E. coli* as a control mechanism which drives the bacterium to one of the two possible set points or equilibria i.e. run and tumble. This approach subscribes a view of *E. coli* behavior as passively responding to a series of stimuli introduced in ideal laboratory conditions. The problem with this modeling strategy is that it does not inform us about the lengths of the run movements or the frequency of the tumblings.

A more realistic description of the bacterium should provide an analysis of the transients between the aforementioned run and tumble set points shown in figure 2. We need

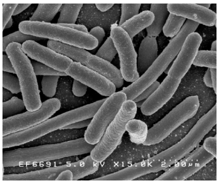

Fig. 1. *E. coli* microphotograph.

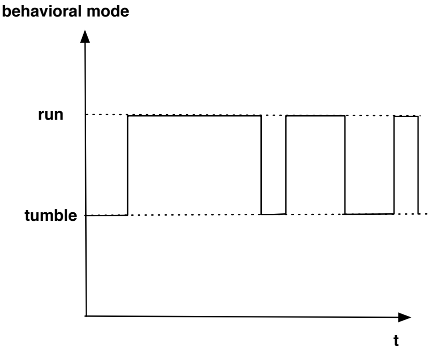

Fig. 2. The *E. coli* motility modeled as a system that alternates in its two possible states, *run mode* and *tumble* in the vertical axis, along time in the horizontal axis.

models able to explain how the extracellular signals are bounded to specific receptors in the cell's membrane and afterwards computed in the cellular milieu. The metabolic well-being of the cell, that is, its internal state, needs to be incorporated into our model.

In summary, we can say that in order to understand how the *E. coli*'s adaptation works, we need to acknowledge how the bacterium extracts information of the world, to encode it as signals that organize the system in a particular internal state.

3 *E. coli* Chemotaxis

In this section, we give a succinct description of the sensory and signaling machinery that direct the *E. coli* motion, for a more detailed account see [3], [21]. It may be worthy to start with a terminological remark. Molecular biologists use the term *pathway*, like in signaling pathway, as an abstraction to refer to a sequence of events involved in a specific process inside the cell, carried out by a network of molecules, mostly proteins, whose topology and dynamics have been explicitly described. Thus the *E. coli* chemosensory pathway is the basis of bacterial chemotaxis.

Pathways, in reality, are systems with complex network dynamics. Thus, the term pathway may be puzzling for the non specialist, because it entails a rather deterministic and linear vision, which is in direct opposition with the stochastic and non-linear nature of biochemical networks. Keeping this caveat in mind, we introduce the chemotaxis pathway which is one of the best well-known signaling pathways.

Bacterial chemotaxis is the movement towards or away from regions with concentrations of chemicals. For example, the bacterium *E. coli* swims toward substances such as amino acids (serine and aspartic acid), sugars (maltose, ribose, galactose, glucose), and away from potentially noxious chemicals, such as alcohols and fatty acids [4]. The chemotactic ability of the *E. coli* relies in its capacity to sense the rate of change of concentration of certain chemicals in its vicinity.

It is interesting to note that chemotaxis is an universal property of bacteria motility, which does not provide any evolutionary advantage per se, unless the movement is biased to produce a physiological response that is suited to a particular environment [27]. In order to acquire a real understanding of how the bacterium responds to a changing environment, we must capitalize the abundant empirical knowledge at single-cell level and, if possible, build predictive mathematical models grounded on quantitative data. The *E. coli* responds to the environment by a composition of two kinds of movements, *running* towards an attractant, and *tumbling*, in which a new direction is chosen randomly for the next running mode. In homogeneous environments, tumble events occur every second, so the *E. coli* moves randomly, while in environments with a non homogeneous concentration of chemicals, the frequency of tumbling is a function of the sensed gradients of attractants and repellents. There are two key mechanisms that underlie the movement of the bacterium; on the one hand, the binding ligand-receptor, and on the other hand, the homeostatic process by which the phosphorization of *CheA*[1] protein goes back to the pre-stimulus level. Let us see this in detail.

3.1 The Binding Ligand-Receptor

E. coli has five chemoreceptors, four of them are methyl-accepting proteins[2] (MCP) and the fifth is MCP-like protein. The receptors, in order to be effective, need to connect the cell with the environment, so the receptors are located through the membrane, having a periplasmatic section exposed to the environment, a thin section in the membrane, and a long tail immersed in the cytoplasm of the cell.

Ligands e.g: maltose, bind to the periplasmatic site, that is, the part of the receptor that is outside the cell. It might be said that the binding is not always 1:1 i.e. one kind of ligand to one kind of receptor, for example in the *E. coli*, one MCP (MCP *Tar*) can bind to two distinct ligands.

MCP receptors do not act in isolation but they form clusters. The clustering depends on the cytoplasmic proteins *CheA* and *CheB*. The clustering of MCP seems to play an important role in one of the most remarkable characteristics of the chemotaxis pathway, its high sensitivity: chemoreceptors are able to detect a change in a few molecules in simultaneity with a background concentration in the environment varying abruptly [23]. The binding of a ligand by a MCP cluster may affect other neighboring unbound receptors, thus the binding recognition process ligand-receptor, can not be understood as an isolated system with two matching parts, the ligand and the receptor [6].

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[1] *Che* stands for chemotaxis.

[2] A methyl groups is a $-CH_3$ group.

The number of methyl groups ($-CH_3$) in the receptor cluster (Figure 3), informs the cell about the perturbations, that is to say, the number of methyl groups is a measure of the rate of change of attractants or repellents outside the bacterium. Methylation acts as a compensator of the external signals entering to the cell. Dennis Bray [5] suggests that the methyl groups works as a memory that allows to trace the recent conditions of the environment in terms of attracting or repulsive substances. The more attractants are sensed the more likely is to have methyl groups carried by the receptor in the cell cytoplasm. There are 8 slots in the receptor for methyl groups, the number increases with the attractant concentration, so 0 methyl groups may indicate a response to a repellent.

3.2 Homeostasis in the *E. coli*

The other interesting phenomenon in bacterium motility is homeostasis by which the rate of phosphorilation in *CheA*, returns to the pre-stimulus state. As *CheB* is also phosphorylated by *CheA-P*, an increase in demethylation of the MCPs is produced, reducing *CheA* auto-phosphorization (even for low concentration of attractants). As a consequence, the rate of auto-phosphorization, together with the rate of direction changing in the motor flagella also decreases, returns to pre-stimulus level (Figure 3).

3.3 The Tumbling Mode

The tumbling mode is triggered by a decrease in the concentration of attractants, which produces a reduction in attractant binding to the MCPs, that in turn, elicits an increase in the auto-phosphorization rate of *CheA* protein, now called *CheA-P*. The phosphates are then transferred to the *CheY* protein, which regulates the way in which the bacterial motors turn. The phosphorylated form of *CheY*, *CheY-P*, binds to the flagellar motor, switching the rotation motor to clockwise so as to cause the bacterium to tumble.

3.4 The Running Mode

The run mode is symmetric to the tumble mode. As the concentration of attractants increase, the *CheA* auto-phosphorization is inhibited, which reduces the concentration of *CheY-P*, as a result, the frequency of motor switching is reduced. The bacterium swims towards a favorable region in the direction of a positive gradient, by rotating counterclockwise all the motor flagella.

In synthesis, the strategy followed by the *E. coli* may be easily stated as "if things are getting better do not change what you are doing, else change direction". It is interesting to note that *E. coli*'s behavior is fundamentally stochastic. The rationale for this must be found in the frequency of the tumbles i.e. the probability of a tumble decreases with the presence of chemoattractants, thus the bacterium moves in a favorable direction. When the environment is homogeneous, no privilege movement direction is observed in the *E. coli* since no beneficial nor detrimental chemical exists in the vicinity of the cell. Thus *E. coli*'s tumbling is produced by frequent aleatory changes in the direction of movement.

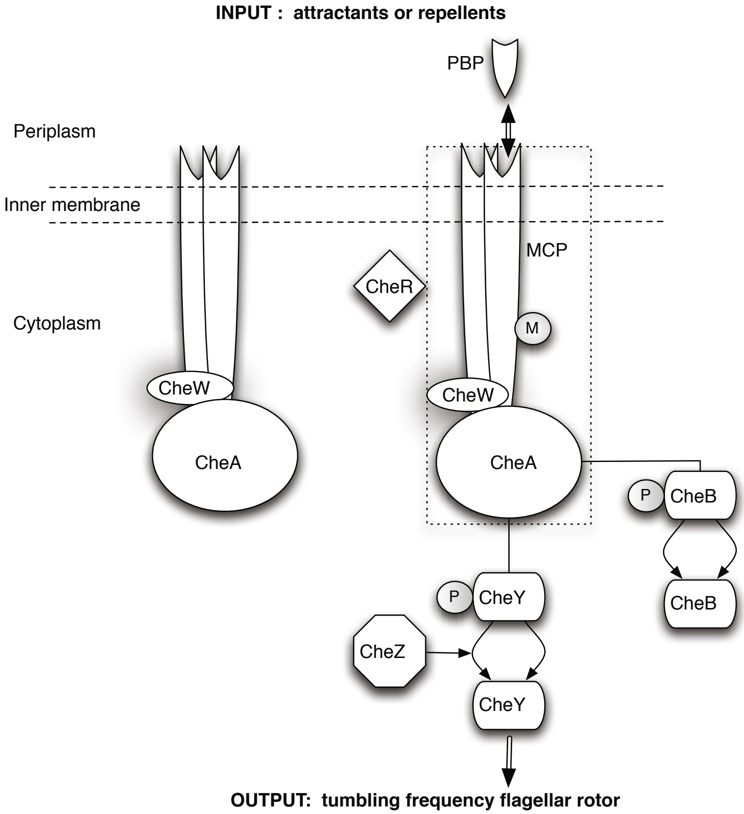


Fig. 3. Model system of *E. coli* chemotaxis. The figure shows two methyl-accepting proteins (MCP), one of which is interacting with one periplasmic binding protein (PBP), phosphoryl groups P, methyl groups M ($-CH_3$) and chemotaxis proteins CheA, CheB, CheR, CheW, CheY and CheZ. The receptor (dashed box) which is the system modeled in [2], is a protein complex composed of MCP, CheA and CheW. The kinetics inside the receptor is modeled by a set of coupled differential equations. The input is the ligand concentration and the output is the activity in the receptor, which is finally translated into bacterial movement through changes in the tumbling frequency in the flagellar rotor. A decrease in attractant concentration induces trans-autophosphorylation of CheA, which phosphorylates CheY, *CheY-P*, to bind to the flagellar motor to bring about a change in direction. Phosphorylated CheA also phosphorylates CheB which competes with CheR to control the number of methyl groups in the MCPs. As concentration of attractants increase, the *CheA* auto-phosphorization is inhibited, which together with phosphatase CheZ, reduce the concentration of *CheY-P*, as a result, the frequency of motor switching is reduced.

4 Adaptation in *E. coli*

Adaptation means different things depending on the context. For an ecologist, adaptation means the possession of forms and functions that help to explain how well an organism does what it does in a changing environment. In this paper, we are interested on a study of adaptation that does not rely on *survival* as the sole criteria of fitness. We need to provide a quantitative criteria of fitness, different to the anthropomorphic vision that assumes the idea of the system as a prosecutor of an "optimal fit" which has been established a priori by an external observer. Note the ressemblance with Expected Utility Theory in economics [20].

Definition 1. *Adaptation is the adjustment of a set of parameter values that permits continuing stability in the face of environmental changes.*

Adaptation in the *E. coli* is understood in relation to adaptation of a stimulus e.g. a chemoattractant, where methylation works as a force that compensates for the change in the tumbling frequency induced by the stimulus.

The addition of attractants causes a transient decrease in the activity of the cell, as a consequence, the methylation of receptors increase to compensate this activity reduction. It might be noted that methylation is a reversible process, therefore a removal of attractants will cause an increase in system activity, and consequently methylation will compensate for this effect.

Alon et al. [1] and Barkai and Leibler [2] have developed a quantified theory of bacterial adaptation based on the computation of a set of key parameters i.e. steady state tumbling frequency, perfect adaptation degree and adaptation time. When the membrane receptor is perturbed by an external ligand, methylation is triggered to retrieve the previous receptor activity value. This capacity of the system to compensate for external stimulation, in order to be ready for the next stimulus is adaptation at work.

Formally, the chemotactic behavior of the bacterium is adaptive when the output is equal to the pre stimulus state:

$$A(\delta) = A^{st}$$

where $A(\delta)$ is the activity function of the stimulus δ, and A^{st} is the steady state activity. For example, in a model of the *E. coli* chemotaxis, the output is the tumbling frequency and the input is the concentration of the ligand. We say that the bacterium has adapted in the face of a perturbation or external input, when the tumbling frequency returns to the pre stimulus value. Hence, $A(\delta) = A^{st}$, because the activity function A is independent of the external input δ.

4.1 Perfect Adaptation

By sensing and processing certain chemicals in the environment, the *E. coli* changes direction and position. This seemingly intentional movement is in reality a process of adaptation, that strives to maintain certain physiological conditions within acceptable limits. Hence, bacterium's adaptation pertains mainly to the homeostatic mechanisms by which the effect of the stimulus is gradually not taken into account despite is presence. The adaptation or homeostatic property in the *E. coli* refers to the adjustment of an output (tumbling frequency) to an external stimulus (the ligand, an attractant or a repellent).

Adaptation can be measured by its precision, which is ideally 1 (perfect adaptation).

$$precision = \frac{unstimulated\ tumbling\ frequency}{stimulated\ tumbling\ frequency}$$

Hence, perfect adaptation is a precise return to the activity level existing before the stimulus.

Terminology again may be confusing. For biologists, perfect adaptation occurs when the value of the steady state activity is independent of the ligand concentration. In dynamical systems theory, for a given linear system with a state vector state $q = (q_1, q_1, \ldots, q_n)$, an external stimulus u and output y, the equations of its dynamics are given by:

$$\begin{aligned} \frac{dq_1}{dt} &= A_{11}q_1 + \ldots + A_{1n}q_n + b_1 u \\ . &= .. \\ \frac{dq_n}{dt} &= A_{n1}q_1 + \ldots + A_{nn}q_n + b_n u \end{aligned}$$

This system has perfect adaptation when y is independent of the external stimulus u at steady state:

$$y = c_1 q_1 + \ldots + c_n q_n$$

4.2 Internal Models of the *E. coli*

Two sorts of mathematical models have been produced to model the adaptation property in the *E. coli*: models based on fine-tuning of parameters[16], and models of adaptation as an intrinsic property of the network[1]. While these two kinds models differ in the approach; both share a very fundamental characteristic, the internal structure of the system i.e. network of protein complexes, is precisely known.

However, the mere assumption of a wise parametric adjusting does not guarantee that the prediction of future states of the system is attained. This is mainly because in an unpredictable environment, the structure is not always valid; as a matter of fact, it may be drastically modified by the environment. This limitation in biological systems modeling becomes conspicuous with the use of metaphors.

For example, the key-and-lock metaphor still prevails to explain the selective binding between an extracellular molecule i.e. ligand, and the receptor site in a cell's membrane which targets the ligand specifically. Biologists call to this matching binding recognition.

We must acknowledge that these are toy models that make assumptions that are not completely realistic. If we want to build models as realistic as possible, we should account for the individual "character" of genetically identical cells. Furthermore, non linear characteristics, such as the crosstalk between receptors or the interaction between chemotactic and other signal systems, would introduce undesirable effects related to non computability.

But it is indeed possible and advisable to understand how the *E. coli* behaves and adapts, without being in possession of a complete description of the organism. This may be achieved by investigating which are the organizational principles that our model implements.

For it to be an engineering biology (or synthetic biology as vogue dictates today), it is necessary to be able to study the environment as signals that are mapped onto the organism's receptors, configuring a network where information is efficiently integrated and transmitted.

It is extremely important to emphasize that the *E. coli* is a representational device that subserves the formation of internal representation of the world through networks of proteins, notably *CheA* which informs the concentration of attractants in the neighboring of the cell, and *CheP*, which instructs the movement of the cell. Thus, the study of *E. coli* chemotaxis provides a solid step in this direction, because it is possible to map the concentration of attractants outside the cell onto the concentration of key signaling molecules such as *CheA*, *CheP* or *CheY* inside the cell.

5 How Much Knowledge of Itself Has a Biological System?

Before in this paper, in section 4.2, we addressed the important issue of how much knowledge of itself possesses the *E. coli*. According to Bray, [5], the internal representation of the bacterium is encoded in its networks of proteins.

Since our ultimate concern is to set the basis for a general theory of adaptation and learning, it is pertient to provide some working definitions of key concepts, such as knowledge and internal representation. Following Dudai in [8]:

Definition 2. *Knowledge is structured bodies of information that the* organism *has about the* world*, and capable of setting the organism's reactions to the* world.

It is important to precise that in this definition, *world* is both the environment and the internal state of the *organism.*

Definition 3. *Internal representation is a version of the world encoded in biological basis, typically a neural system. Internal representations are constituent of knowledge, they influence in the organism's behavior, and therefore are able to change the* world.

At least at conceptual level, it is easy to draw similarities in the way the *E. coli* and nerve cells adapt and process information. Both systems have internal models of their surrounding, built from networks of protein molecules. What is still to be shown is the precise way in which that connection can be materialized in a common framework. This will be discussed in section 6.

In order to understand the representational properties of neurons we need to unravel how they transduce, compute and transmit information. Neurons receive information from other neurons and/or the environment, integrate this information, and transmit it to other neurons or effector cells, for example in a muscle. Neurons signal to each other through specialized junctions called synapses.

Two kind of signals cohabit in neuronal information processing, electrical signals and chemical signals. Electrical signals are measured by the membrane potential produced by ionic currents across the membrane. The neuron's membrane receptors are gated ion channels. Based on the gating mechanisms, ion channels can be classified in voltage-gated or chemically-gated channels.

Local potential is a graded electrical signal that propagates passively in an attenuated way. Depending on its neuronal input, local potentials are called receptor potential or synaptic potential. The former is a local potential generated in sensory neurons and the last is generated in synapses. Local potentials are integrated by the cell, and when the summation depolarizes the neuron's membrane over a threshold, an action potential is elicited. Contrary to local potential, action potential is all-or-none signal, transmitted in a unattenuated way and maintained by voltage gated channels. The terms neural fire and neural spike mean both that the neuron generated an action potential.

An action potential conveys information as follows: it enters into a presynaptic terminal of a chemical synapse generating a release of neurotransmitters, which invade the synaptic cleft and bind to specific receptors in the postsynaptic terminal, which elicit a synaptic potential that eventually may trigger an action potential. Thus, a chemical synapse can be seen as a signal transduction system from chemical to electrical signals.

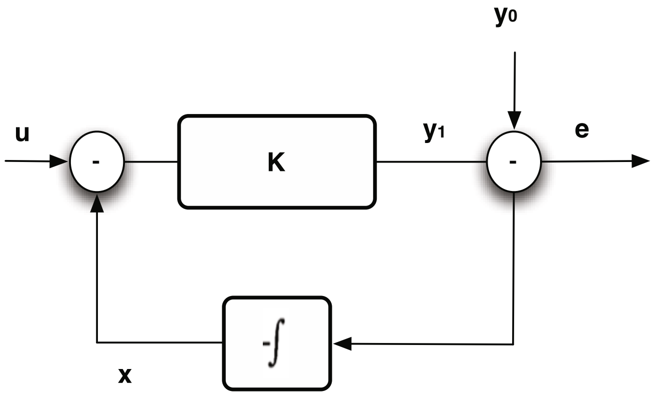
6 The Internal Model Principle

The aforementioned work of Barkai et al. [2] and Alon et al.[1], stated the robustness of perfect adaptation in bacterial chemotaxis. Yi et al.[28] generalized that result demonstrating that Barakai and Alon's model is a particular case of integral feedback control.

Integral control (IC) is used ubiquitously in engineering systems, ranging from simple thermostats, to the control of speed, altitude and heading in sophisticated airplanes. IC is a particular case of the Internal Model Principle (IMP) proposed by Francis and Wonham in 1976 [11]. IMP establishes that for asymptotic tracking of a signal, the controller must contain a model of that signal. This model of the exogenous input is called an internal model.

The *E. coli* adaptation is properly understood under the Internal Model Principle. Figure 4 shows a feedback loop that successfully implements a zero tracking error for a constant input. The integral control action is in the integral of the error that is feed back into the system. The input stimulus u is the concentration of chemoattractant, the output y is the concentration of active receptor complex. The reference signal y_0 is the pre-stimulus concentration of active receptor complex. The error is given by the difference between the actual output y_1 and the reference value, $e = y_1 - y_0$.

At steady state we have $e = 0$ for all input u. Thus, at steady state the *E. coli* activity i.e. tumbling frequency, is independent of the input i.e. ligand concentration. Therefore, the perfect adaptation is achieved when we have a zero tracking error in integral control action, that is to say, the output is independent of the input level in steady state. Feedback control theory is pertinent in the biological context if we acknowledge that "the physiology of biological systems can be reduced almost entirely to their homeostasis [12]". Homeostasis, the maintenance of constant physiological conditions, can not be fully understood without control system theory. The constancy of the internal state is achieved by negative feedback, and the internal state of the system is a representation of the *world* at a particular instant.



$$\begin{aligned} x(t) &= \int_0^t e(t)dt, \textit{then} \\ \dot{x} &= e\,,\ \textit{where} \\ e &= y_1 - y_0\,,\ \textit{being } y_0 \textit{ constant} \end{aligned}$$

Fig. 4. At steady state $\dot{x} = e = 0$ for all input u. In the *E. coli* case this means that the tumbling frequency of the bacterium is independent of the sensed attractants in its surroundings. In habituation learning in sensory neurons, the membrane potential is independent of the concentration of glutamate. For the *E coli*, the control signal u is the concentration of attractants in the bacterium's surrounding, y_1 is the tumbling frequency, y_0 is the tumbling frequency previous pre-stimulus and e is the difference between the actual tumbling frequency and the desired one. In habituation learning, u is concentration of glutamate in the synaptic cleft prompted to be binded in the membrane's receptors, y_1 is the membrane potential V_m, y_0 is the membrane potential pre-stimulus and e is the difference between the actual membrane potential and the desired one, y_0.

By no means should be this result undervalued or enclosed for the particular case of the *E. coli*. Integral control is both a necessary and sufficient condition for robust tracking of a specific steady-state value. One of the rationale of this paper is to bring this important result into physiological systems more complex than bacteria. In particular, we use it for modeling habituation learning in the nervous system.

7 Habituation Learning

Thanks to Kandel's work in the Aplysia, a mollusc with about 400 neurons, some of them visible to the naked eye, it is possible to distinguish three kinds of learning in this animal: habituation, sensitization and classical conditioning.

Habituation is the decrease in the behavioral response for a stimulus when the organism is exposed repeatedly to the same stimulus. At a cellular level, habituation leads to a reduction in effectiveness of synaptic transmission by sensory neurons.

Sensitization is characterized by an increase in the response when the animal is exposed to continual harmful stimulus, as a result, the animal learns to respond more vigorously to the coming harmful and also harmless stimulations.

Put in behavioral terms, both habituation and sensitization are an enhancement of reflex responses. Habituation tends to an unique equilibrium state of non response, while sensitization is a more complex behavior because it produces responses that do not converge to an equilibrium point. We focus here on the most basic form of implicit learning i.e. habituation.

In habituation learning, the organism learns to ignore a repetition of stimulus that is harmless. The effectiveness of synaptic transmission by sensory neurons that perceive the stimulus, is reduced by lowering the release of glutamate neurotransmitters. Thus, habitation is caused by a reduction in the release of glutamate from presynaptic neurons. It might be remarked that sensitivity of receptors in the postsynaptic terminal is not modified with habituation [14], which relies on glutamate concentration at the postsynaptic gates.

Figure 4 can be interpreted as the integral control scheme for habituation learning, which is the simplest type of implicit learning. The stimulus u is given by the synaptic input and the output is the membrane potential V_m. In the *E. coli* case, the internal model of the external signal ligand is the chemoattractant concentration; while in the neural case, the internal model is the concentration of glutamate that binds with specific receptors, eliciting the depolarization of the cell. Thus, depolarization is a deviation from the neuron's resting membrane potential towards its threshold potential.

The membrane potential at steady state V_m^{st} is independent of the input signal u (glutamate concentration), this result can be obtained because the neuron has a replicated model of the external signal, glutamate concentration. We say that the habituation learning capacity found in neurons is adaptive when

$$V_m^{st} = V_m$$

7.1 Homeostatic Synaptic Plasticity

Although all living cells have a difference of voltage across the membrane, in nerve cells, the membrane potential acts as an integrator of the neuronal input i.e. local potential. Synaptic potential depends on the release of neurotransmitters, for example glutamate in sensory neurons.

Plasticity is an experience-dependent modification of neuronal properties such as synaptic strength. It is widely believed that plasticity is at the core of learning and memory. Learning is a word with many different interpretations as it conveys a complex phenomenon that encompasses multiple of levels of analysis.

The neuron's stimulus is given by glutamate molecules that bind the membrane's receptor depolarizing the neuron. The concentration of glutamate constitutes an internal representation of the external stimulus. The output is the membrane potential generated by the integration of information in the neuron. The view of the brain as a decision making device is typically related with Helmholtz's motto "the brain is an inferential machine". In the beginnings of modern neurobiology, Sherrington perceived integration as the quintessential action of nervous system, which values consequences of different types of information to choose a proper response [19].

Homeostatic synaptic plasticity is a relatively young area of research that is dedicated to unveil the mechanisms that allow neurons and assemblies of neurons, to maintain a stable way of functioning in the face of perturbations and changes in synaptic strength [7],[17].

As it may be expected, homeostatic synaptic plasticity is sustained by negative feedback action that compensate for activity-dependent changes in synaptic strength through, for example, learning.

Habituation learning is indeed a form of homeostatic plasticity. For an extended review on the typology homeostatic plasticity see [25]. It is important to point out that given a change of synaptic properties, the identification of the plasticity mechanisms that underlie such modification are not straightforward. In summary, we propose here the internal model principle implemented in an integral control as the plasticity mechanism for the simplest form of implicit learning, habituation. A quantitative theory of learning and memory is a long way goal (Figure 5). More complex forms of learning such as explicit learning would require hierarchical structures of control that still need to be elucidated. However, the formulation of a common theoretical basis for adaptation in prokaryotic cells and plasticity in the neuronal system represents a solid milestone in this direction.

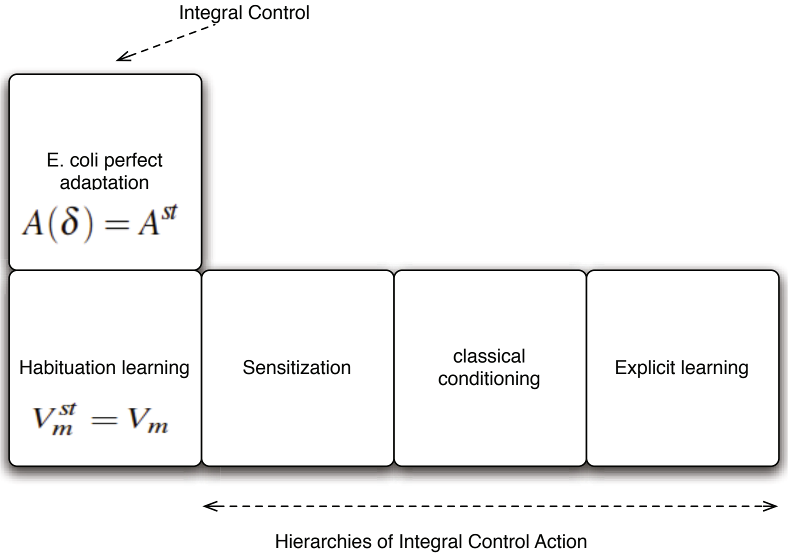


Fig. 5. Both *E. coli* and habituation learning can be modeled using Integral control. For more complex types of memory, the Integral Model Principle does not directly apply, perturbations are not necessarily constant control signals, though it is valid in the homeostasic mechanisms that characterized *E. coli* adaptation and habituation learning in neurons.

8 Discussion

Here we present, for the first time, an application of the Internal Model Principle used in control engineering to habituation learning in neuronal systems. By focusing on the domain of bacterial chemotaxis, we intend to translate quantitative models that are relevant in the domain of synaptic plasticity. We do this by capturing the general principles that apply to both domains. Our approach -i.e. going small in order to escalate to more complex domains through the formulation of general principles expressed in quantitative terms- is similar to Sidney Brenner's *middle-out* alternative to the customary rhetoric of bottom-up versus top-down.

Integral feedback control has been postulated as the strategy by which bacterial chemotaxis achieves robust adaptation, and in a more general way, underlies homeostatic mechanisms [28]. The integral control is one of the simplest controllers defined under the Internal Model Principle. We demonstrate that the IMP applies to habituation learning in neuronal systems. The membrane potential of a neuron integrates the world's stimuli received by the neuron through its ion channels. The knowledge that the neuron has of itself is gathered in the membrane voltage.

The control strategy proposed here has as regulated variable, the error, expressed as the neuron's output (membrane potential) *minus* the reference input (pre stimulus membrane potential), and as input the glutamate concentration. By feeding back into the system the time integral of the error which contains an internal model of the external stimuli, we are able to provide mathematical formulation of the homeostatic plasticity that mediates in habituation.

We are cognizant that the complexity of the brain will require of more powerful mathematical tools than those used here, to address other forms learning, like conditional learning or explicit learning. Nevertheless, this approach provides a quantitative framework that may open new and relevant insights for researchers in learning and memory.

Both adaptation in the *E. coli* and learning in neuronal systems are studied here as experience-dependent mechanisms of generation and modification of internal representations. We expect that important concepts in either technological and natural systems, such as adaptation or learning, which are used with multifarious connotations, will benefit from the quantitative stance developed here.

What is needed now is to design the tools and fabricate the concepts that account for the process of adaptation itself, that is, from the point of view of the organism.

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Galvanotaxis of the Plasmodium of *Physarum Polycephalum*

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Abstract. The traditional research method of the natural sciences chooses an element paying attention to the various elements in the natural world and analyzing their characteristics and components. To analyze the complicated structure of nature, one normally applies a highly precise device and the sophisticated expertise. This method will exclude other elements of the natural world, and will ignore mutual relations between elements that the network has. Such methods and results contribute to human profit immediately. On the other hand, by ignoring the function within the whole of the natural world, naturally we will face the environmental disruption threatening our survival. Thus modern technology resembles the person who is preoccupied with a specific thing in a forest, and loses his way. Because nature has a simpler aspect as a whole, it may not need the high quality technology for the understanding of nature as the whole. We have changed natural environments towards our profit for a long time. But, a protozoan (the lower animals) such as the myxomycetes let themselves adapt themselves to their environment by changing their lifestyle. Such a protozoan gives us valuable suggestions for our survival, and the new findings of a natural system provide a good opportunity to re-examine the scientific method. To understand nature as a whole, regardless of creatures and inanimate objects, it is necessary to understand how the systems of nature connect each other. Therefore, to obtain new findings on the mutual relations between environment and living creatures, in general, the ecosystem (or the behaviors of creatures) are investigated. The myxomycetes which have the time period of amoeba and a short life cycle, are considered best for observation of behaviors in environment.

In the plasmodium of *Physarum polycephalum*, we confirmed that galvanotaxis causes dilation of the tubular vein, the increment of resting potential, phase reversal of movement, and rapid flow of protoplasm streaming. In this paper, we show that the electric field strength can be used as an effective stimulus to motion control of a plasmodium on an agar-agar surface. (1) Galvanotaxic reinforcement: Our results show that the velocity of crawling increases in proportion to the DC electrical stimulus, up to a specific velocity. (2) Remaining galvanotaxis: A synthetic plasmodium composed of a experienced plasmodium which has been stimulated by the electric field strength and an inexperienced plasmodium which has not been stimulated, shows more rapid crawling than plasmodium which has not been stimulated. (3) Galvanotaxic application: In the experiment using a T-shaped path consisting of one path of feeble electric field strength and one with no electrical field, an experienced plasmodium, chooses almost always a path without the electrical field. On the other hand, the path chosen by an inexperienced plasmodium is always random. Our method has significant possibilities to find new findings for origin of memory and learning by a simple animal model, the plasmodium of *Physarum polycephalum*.

Keywords: *Physarum polycephalum*, galvanotaxis.

1 Introduction

To an organism, electrical stimulation produces various responses as well as the membrane potential [1]. In man, even if it is weak in strength, it activates to visual, auditory system. Therefore the electrical stimulation is applied to the diagnosis of eye disease such as pigmentary degeneration of the retina [2].

Galvanotaxis is well known in an amoebae and is used to escape from electric stimulation. From the investigation of Dictyostelium amoebae's electrotaxis, a recent paper suggests that electrotaxis and chemotaxis share similar signaling mechanisms. In this paper, researchers conclude that the pathways driving chemotaxis and electrotaxis intersect downstream of heterotrimeric G proteins to invoke cytoskeletal elements [3].

The presence of galvanotaxis, is well established when a constant current stimulation is given to the plasmodium of *Physarum polycephalum*.

While the plasmodium were showing avoidance behavior upon DC stimulation, in the tubular veins of the head and tail section, the number, diameter, and change of the protoplasmic streaming the inside were recorded.

The accompanied increase of the flowing quantity of the protoplasmic streaming, flow velocity, and the movement direction of the organism, and the expansion of the tubular veins of a leaf have also been confirmed [4,5,6].

In this study, we again used the plasmodium to investigate the changes in the velocity of crawling to the DC electrical stimulus frequency, and the remaining galvanotaxis of the synthetic plasmodium composed from a experienced plasmodium which has been stimulated by the electric field strength and an inexperienced plasmodium which has not been stimulated.

The purpose of this experiment is to investigate whether an intrinsic electric response level of organism can be changeable after it has received electrical stimulation. If the behavioral decision in an electrosensory system is confirmed experimentally, it is useful for new finding of the origin of memory and learning in the organism.

2 Method

1) Galvanotaxic reinforcement

A constant voltage power supply was used for experiments in the laboratory, or outdoors. Through a resistance of 200kΩ for prevention of overcurrent, 3V DC was applied to a plasmodium on the agar pool so that the current which flowed in an organism was 10μA. This is because it produced damage in the tubular veins when the current stimulation exceeds 1mA through a glass electrode [4]. The organisms whose weight was approx. 0.02 g, were raised on the agar nutrient medium.

In the experimental environment, an anode and a cathode were placed on both ends of the agar pool of size 1 x 1 cm. The surface of the agar pool was moistened with purified water (1 M Ω/100ml), and 3V DC was applied. A blob of oatmeal was placed over the cathode, whereas the organism was placed over the anode. 5 sets of the ager pool were used for experiment of the repeated stimulation. Ninety organisms were used.

When the organism arrives at a cathode, the organism is placed on the next agar pool with a pair of electrode. And 3V DC was applied again.

2) Remaining galvanotaxis

A new synthetic organism was composed from pairs of organisms. Both organisms whose weights were approx.0.01 g each, were used for experiment on the remaining galvanotaxis. One of them was an organism which had been stimulated one time at 3V DC. The other was an organism which had not been stimulated by an electric field.

3) The experiment using a T-shaped path

In the experiment using a T-shaped path having one path of feeble electric field strength and one of non-electrical field, the surface of the agar pool was moistened with purified water on the T-shaped path. Approx. 1μA DC current was applied on the right or the left path on T-shaped path. A blob of oatmeal was placed over both paths of T-shaped path, whereas the organism was placed in the front of T-shaped path, so that each organism can take a stimulated path or a non-stimulated path.

The experiment was conducted in two groups. One group contained thirty-one organisms which received electrical stimulation once at 3V DC. The other group is the same number of non stimulated organisms.

3 Results

1) Galvanotaxic reinforcement

Our results show that the plasmodium's velocity of crawling increases in proportion to the number of times it has been exposed to a DC electrical stimulus, up to a specific velocity as shown in Figure 1.

Figure 2 shows the membrane potential of typical organism. In the second stimulation of the organism, a higher resting potential following membrane potential is observed. Membrane potential differs at the recording site on the organism, and because of cyclic changeable potential. The increment of membrane potential, however, is recognized in general.

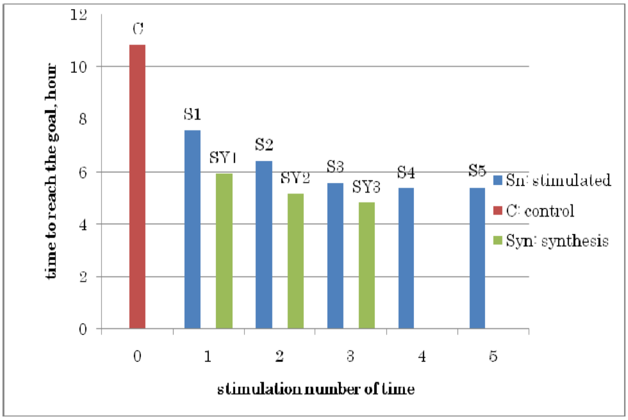

Fig. 1. The elapsed time of crawling from the onset of the stimulus. p<0.05 between control group C and one time stimulated group S1, S1 and S2, S2 and S3, S1 and synthesis group SY1, S2 and SY2, S3 and SY3. NS between S3 and S4, S4 and S5.

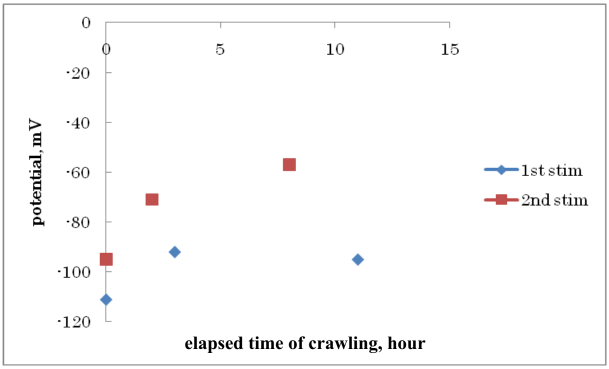

Fig. 2. Membrane potential on the head section of typical organism.

2) Remaining galvanotaxis

A synthetic plasmodium composed from an experienced plasmodium which has been stimulated by the electric field and an inexperienced plasmodium which has not been stimulated, shows more rapid crawling than a plasmodium which has not been stimulated.

3) The experiment using a T-shaped path

In the experiment using a T-shaped path having one path of feeble electric field strength and with no electrical field, an experienced plasmodium, chooses almost always a path of the nonelectrical field. On the other hand, the path chosen by an inexperienced plasmodium is always random. There is no relation between the position of the electrode and the choice of the path, each factor is independent respectively. (There is no significant difference.)

Table 1. The number of non stimulated organisms in the experiment using a T-shaped path at approx.1μA DC.

○ shows crawling away from the electrode.

● shows crawling towards the electrode.

Inexperienced. 71.0% Experienced 100% at approx.1μA DC. Both showed 100% correct rate at 4μA DC or more. On the Fisher's exact test of two-sided test at significance level 5%, 0.18 07>2α=0.1

	electrode position		
decision	left	right	total
○	12	10	22
●	3	6	9
total	15	16	31

4 Discussion

The reason for increment of the plasmodium's crawling velocity in proportion to the number of times is has been electrically stimulated, and the sensitivity of galvanotaxis of our composed plasmodium suggest that electrical stimulation gave to the organism a change in electrical features which reinforces galvanotaxis.

It is interesting that the organism continued still retains high electrical sensitivity even if electrical stimulation is stopped. The electric field strength may cause the change of electric features such as a conductivity, dielectric constant and time constant. As shown in previous research, furthermore, it causes mechanical changes such as the dilation of the tubular vein in the direction of the way to escape or making new network of the veins of the leaf by which the organism may minimize electrical damage [4].

The experiment using a T-shaped path suggests strongly that the experience of electrical stimulation changed the organism's behavior.

Our results can be useful to obtain new findings about basic knowledge of memory and learning for organism without brains.

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How Do Neural Systems Use Probabilistic Inference That Is Context-Sensitive to Create and Preserve Organized Complexity?

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Abstract. This paper claims that biological systems will more effectively create organized complexity if they use probabilistic inference that is context-sensitive. It argues that neural systems combine local reliability with flexible, holistic, context-sensitivity, and a theory, Coherent Infomax, showing, in principle, how this can be done is outlined. Ways in which that theory needs further development are noted, and its relation to Friston's theory of free energy reduction is discussed.

Keywords: self-organization, complexity, probabilistic inference, induction, neural systems, Coherent Infomax, context-sensitivity.

1 Unsolved Problems in Theoretical Neurobiology

Biological systems create and preserve organized complexity despite the ever present forces of noise and disorder. This self-organization occurs in open, holistic, far-from-equilibrium, non-linear systems with feedback, to which the classical paradigms of physics are not well-suited. Though usually implicit, probabilistic inference can be seen as being central to self-organization, and useful inference is only possible because the laws of physics are sufficiently reliable. The endless variety of individual circumstances and the prevalence of deterministic chaos and quantal indeterminacy make many things unpredictable, however; so, to thrive, biological systems must combine reliability with flexibility.

Erwin Schrödinger (1944) played an important role in the discovery of the genetic code by correctly estimating the balance between reliability and flexibility (e.g. mutation) in the case of genetics, and by showing, contrary to the opinion of many physicists at that time, that the required balance could be achieved at the molecular level. Analogous insights are now needed to guide our search for general principles of information coding and processing in neural systems. We need to know whether it is possible to state in general abstract terms what is coded by neural activity, how it is coded, and what use is to be made of that information.

Many forms of organized complexity have arisen in nature's long journey from uniformity to maximal disorder, but it is in neural systems that the importance of probabilistic inference is most obvious. Helmholtz correctly emphasized the centrality of unconscious inference to perception, and many examples of its use for contextual disambiguation can be given (e.g. Phillips, von der Malsburg and Singer 2010). Friston (2010) has now shown formally how such unconscious inference may also be central to reinforcement learning, motor control, and many other biological processes.

These arguments suggest several issues on which we need to make progress. What is organized complexity? What are the capabilities and constraints of various forms of inductive inference, e.g. classical versus Bayesian (Jaynes 1998), conscious versus unconscious (Engel and Singer 2008)? How is reliability combined with flexibility, i.e. how is information about reliable generalities combined with information about individual particularities? How is localism combined with holism? Do various neural systems or sub-systems perform inductive inference in different ways with differing degrees of accuracy or generality? Do biological capabilities for probabilistic inference evolve towards forms of inference with greater accuracy or generality? What learning do the inferences require, and how is that learning implemented at the synaptic level in neural systems? Information theory measures such as Shannon entropy and free-energy have been applied to these issues, but how can they be tested and what do they contribute to our understanding?

Better formalisation of these issues is clearly needed, so I will outline an elementary neurocomputational perspective that uses information theory measures to shed some light on them (Phillips, Kay and Smyth 1995; Kay, Phillips and Floreano 1998; Kay and Phillips 2010). A major advantage of this perspective is that it has wide-ranging interdisciplinary roots, and is related, often in considerable detail, to much empirical data from neuroanatomy, cellular and synaptic physiology, cognitive psychology, and psychopathology. I will also argue, however, that this perspective is still greatly in need of further development and testing.

2 Evidence for Local Reliability and Holistic Flexibility

Within neurobiology the contrast between the requirements of reliability and flexibility is reflected by two frequently opposed perspectives that have arisen from the neuroscience of the last century. First, there is the classical perspective, such as that of Hubel and Wiesel. This sees sensory features and semantic attributes as being signalled by single cells, or small local populations of cells, with well-specified receptive fields about which they transmit information. Though modifiable by experience, these codes are highly reliable. They do not change from moment to moment, and do not depend upon what is going on elsewhere. From this perspective feature detection, object recognition, and other higher cognitive processes, are thought to be achieved through a fixed or slowly adapting feedforward projection through a hierarchy of cortical areas.

In contrast, the second perspective emphasizes flexibility. From the early 1980s onwards, there has been a rapidly growing body of evidence showing that, even in sensory systems, neural activity is influenced by an ever-changing stimulus context that reaches far beyond the classical receptive field, and by high-level cognitive state variables such as attention. This has led many to conclude that the simple classical assumption of cells with reliable receptive-fields is no longer viable, and that information is conveyed only by the rich non-linear dynamics of very large and ever-changing populations of cells.

Our perspective combines these two views. It emphasizes dynamic contextual interactions, but claims that, instead of robbing the local signals of their reliability, they increase both their reliability and their relevance. Its central hypothesis is that there are two classes of synaptic interaction: primary driving inputs that specify the information content of the output signals transmitted by the local processor, and gain-controlling inputs that coordinate those computations so as to achieve current goals in current circumstances. This theory emphasises processes of contextual disambiguation and dynamic grouping that choose between alternative interpretations of the data. They do so by amplifying activity that is relevant to the current task and stimulus context, and by suppressing activity that is irrelevant. These coordinating interactions also group activity into coherent subsets, and combat noise by context-sensitive redundancy.

They are crucial to Gestalt perception, selective attention, working memory, strategic coordination, and perhaps also to reinforcement learning and motor control. The contextual coordinating inputs can be seen as learning to predict the activity driven by the primary inputs, and as using those predictions to emphasize and organize activity relevant to current tasks.

Contextual disambiguation and dynamic grouping require many locally specific coordinating interactions between all the detailed processes that compute the cognitive contents. This implies that, in the case of the mammalian cerebral cortex, coordinating interactions must occur within and between cortical regions, because it is only they that know the detailed cognitive contents. Our working assumption is that there is a special class of ubiquitous synaptic interactions within the cortex that selectively amplify and synchronise relevant activities. They are predominantly located on long-range lateral and descending connections and influence post-synaptic activity via various mechanisms, including NMDA receptors (Phillips and Silverstein 2003) and the control of synchronised disinhibition (Tiesinga, Fellous and Sejnowski 2008). They do not themselves provide primary drive to post-synaptic cells, but modulate the effects of those that do. We call them coordinating, or gain-controlling, interactions to distinguish them from the diffuse effects of the classical neuromodulators. There is now clear evidence for a variety of mechanisms that implement such gain-control (von der Malsburg, Phillips and Singer 2010; Silver 2010). Their variety and ubiquity provide evidence of their importance to neural function. One goal for formal studies within theoretical neurobiology is therefore to clarify the capabilities and limitations of such coordinating or gain-controlling mechanisms in more general and abstract terms.

In the cerebral cortex there is anatomical evidence for hierarchical data selection and organization, with extensive context-sensitivity at each stage. Douglas and Martin (2007) review much evidence suggesting that feedforward driving signals provide only about 5% of the input to the layer 2/3 pyramidal cells that transmit information through the system, with the remaining 95% being composed of various forms of contextual input. The small percentage of inputs that are driving may be telling us something crucial about constraints on the discovery of latent structure in data, i.e. it becomes much less feasible as the number of signals in the input to be summarised rises beyond a few hundred. The remaining 95% (several thousand inputs) then suggests that information from a much larger context can usefully guide that discovery. Adams and Cox (this Volume) argue that learning in neuronal systems requires highly accurate pairing of pre- and post-synaptic spikes, and that this faces unavoidable biophysical difficulties. Thus, this may be one of the constraints limiting the number of driving feedforward connections to no more than a few hundred.

These broad claims of close relations between particular local neuronal interactions and particular aspects of cognitive function are based upon much psychophysical, neurobiological, and clinical evidence, as reviewed in Phillips and Singer (1997), Phillips and Silverstein (2003), and von der Malsburg, Phillips and Singer (2010). Though there will not be room to review this evidence here it is of great importance because it suggests that formal clarification of the role of context-sensitivity in probabilistic inference would be worthwhile.

3 The Theory of Coherent Infomax

Our contribution to this effort has produced the theory of Coherent Infomax (Phillips Smyth and Kay 1995; Kay, Floreano and Phillips 1998; Kay and Phillips 2010). Only a brief outline is given here. For full formal presentations see the original publications. The theory of Coherent Infomax uses three-way mutual information and conditional mutual information to show how it is possible in principle for contextual inputs to have large effects on the transmission of information about the primary driving inputs, while transmitting little or no information about themselves, thus influencing the transmission of cognitive content, but without becoming confounded with it. Guided by neuroanatomy, the gross system architecture assumed is that of at most a few tens of hierarchical layers of processing, with very many specialized but interactive local processors at each stage. Feedforward connections between layers are driving, whereas lateral and feedback connections provide coordinating gain-control. Minimally, the function of local processors is to select and compress that information in their primary input that is relevant to the current task and situation, as indicated by the contextual input that modulates primary information transmission. This is formalized in information theoretic terms as an objective function describing the signal processing work to be done. In short, the goal is to maximise the information transmitted about the primary inputs subject to the constraints of substantial data reduction while emphasizing the three-way mutual information between output and primary and secondary inputs and minimizing the information transmitted specifically about the secondary inputs. To show how that objective could be met in neural systems, a biologically plausible activation function for idealized local neural processors was formulated to include the required gain-control, and a learning rule for modifying the synaptic strengths of the connections between these local processors was derived analytically from the objective function by a statistician, Jim Kay. What most impressed us about the consequent learning rule is that, although it was deduced formally from the objective function, assuming none of the physiological evidence concerning the dependence of synaptic plasticity on current and prior activity, it is broadly in agreement with that evidence. The theory of Coherent Infomax thus shows how it is possible for neural systems to perform probabilistic inference in a way that combines reliability with flexibility, and localism with holism.

4 Unsolved Problems in the Theory of Coherent Infomax

Despite its extensive roots in the relevant empirical sciences, however, there are still many ways in which this perspective requires improved conceptual development and empirical testing. One unresolved set of issues arises from what I think of as the impossibility of perfection. In the limit, coherence and information are opposed in that the total information within a system is reduced by correlations between its elements. Therefore, simultaneous maximisation of both considered separately is not possible. We assume that the objective is to increase the total information on which there is agreement, not the attainment of some final and complete optimum. Furthermore, applying the idealized Coherent Infomax objective to systems with many inputs and outputs is not computationally feasible unless simplifying approximations are used. Possible approximations were formally specified by Kay and Phillips (2010), but no attempt was made to explore either their applicability to realistic tasks or their biological plausibility.

A second unresolved problem concerns relations between Coherent Infomax and concepts of complexity. Proposed measures of organized or structured complexity try to combine order (organization/coherence) with disorder (entropy/information) as does Coherent Infomax, and they often do so using mutual information (Sporns 2007). These measures are designed to ascribe high complexity to systems of many elements that interact in such a way as to achieve effective integration but without imposing such uniformity that their joint entropy is low. The contextual interactions of Coherent Infomax seem well-designed to contribute to this because they coordinate activities while not becoming confounded with the information that those activities variously transmit. Furthermore, Coherent Infomax is highly compatible with the small-world network architectures conducive to high complexity on these measures. Therefore, it may be possible to formulate or modify Coherent Infomax so as to relate it explicitly to these measures of complexity, but nothing of that sort has yet been done.

The final unresolved issue concerns the relationship between Coherent Infomax and predictive coding. The current growth of interest in inference and prediction as possible keys to a fundamental understanding of neuronal systems is exemplified by the many groups that work on the ‘Bayesian brain’ and ‘predictive coding’. I will briefly discuss some relations of Coherent Infomax to the work of one of them, i.e. that proposing a unifying brain theory based on ideas from statistical physics and machine learning (Friston 2011) That theory interprets many aspects of neural structure and function as having evolved to reduce Helmholtz free-energy using a form of predictive coding in which ascending activities predicted by feedback descending from higher levels in the hierarchy are suppressed. In contrast to this, Coherent Infomax proposes that activities predicted by contextual input are amplified. Thus, prima facie, predictive coding theories and Coherent Infomax propose opposing effects of context. There are at least three grounds for thinking that these theories are not fundamentally opposed, however. First, both Friston's theory and ours imply that reduction of the difference between predicted and observed probability distributions is a major objective of neuronal dynamics. Furthermore, the reduction of free energy is central to Friston's theory, and in or about 1993 unpublished work by John Hertz (a statistical physicist) gave a proof that Coherent Infomax implies the reduction of free energy. That proof is now lost, but if valid, it shows a deep unity between the two theories. Second, Coherent Infomax emphasizes lateral connections between streams of processing dealing with distinct data-sets, whereas predictive coding is concerned exclusively with feedback connections from higher levels in the hierarchy. Coherent Infomax is most obviously relevant to the use of co-occurrence constraints between distinct streams of processing to select between alternative interpretations of ambiguous inputs, whereas predictive coding theories are concerned with the coding of information for transmission through a hierarchy. Thus, the two theories may be complementary, rather than opposed. Third, Spratling (2008) argued that predictive coding theories can be made formally equivalent to theories based on evidence for *amplifying* effects of top-down attentional inputs. He did so by reorganising the computations required and assuming that suppressive effects of prediction operate on intra-regional signals, not on inter-regional signals. His work therefore suggests that some form of predictive coding may also be formally equivalent to Coherent Infomax, but it is not yet known whether this is so or not.

Predictions may be amplifying in some cases and suppressive in others, so a more inclusive perspective that combines Coherent Infomax with Friston's theory of free-energy reduction may be possible. As the two theories emphasize many of the same details of neuroanatomy, neurophysiology, and psychopathology (Kay and Phillips 2010; Engel et al 2010), it may not be too difficult to create such a perspective. As Friston's theory emphasizes infomax, or redundancy reduction, as one component of his theory, it is important to note that Coherent Infomax is not simply a sub-type of infomax theory; it is infomax *plus* selective amplification of that information predicting activities elsewhere. It is thus our formalisation of another central component of Friston's theory, inference. Overall, therefore, though there are important differences between the two theories, they are in broad agreement. They can be seen as examples of a perspective on biological computation that might be greatly improved by expertise such as that in the INBIOSA initiative.

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Cells, Cell Abstractions, and Information Processing

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Abstract. Cells are the basic components from which living systems are composed. We describe an abstract version of a cell, and use it to discuss what cells really are doing, particularly in terms of information and information processing. Cells are characterised in terms of traffic across their boundary. We discuss the issues posed by an information-based view of this.

Keywords: Cell abstractions, Living systems, Cell membrane, Cell boundary, Stochastic reactions, Cell Information Processing.

1 Introduction: Living Systems and Cells

In the INBIOSA (`http://www.inbiosa.eu`) project we are trying to move beyond systems which are limited by being Turing machines, or at least are limited by current implementations of Turing machines. We are interested in determining whether we can develop systems which have more of the characteristics of living systems, and which are not purely programmed, or adaptive in a straightforward sense (as Bayesian Belief Systems, or traditional neural networks or reinforcement learning based systems are). We would like systems which are more autonomous, which can develop and pursue goals, and/or which have something recognisable by people as volition, drives or even intelligence. All of these desiderata come from the world of living systems, but there is essentially no agreement on how to determine whether a system actually is living (see [16] for some older but still relevant background, see [1], [2] for a review, see [10] for a philosophical view, and see [7] for a more recent view).

> "Today, curiously, living systems cannot be said to be anything more than dissipative structures informed internally by genetic information. There is not really anything substantially different from abiotic systems in them other than greater stability due to this internal information."(Stanley Salthe: private communication)

Whilst it is certainly true that being "dissipative structures informed internally by genetic information" is a characteristic of all living entities, it is possible to imagine automated systems which had these characteristics, but which one might not be willing to call alive. So while this characteristic is necessary, its sufficiency is more dubious. It is possible that this characteristic would be sufficient if we were to consider *synthetic* living systems: but then one would be in danger of defining living systems in this way (which is in essence what [7] suggests). If, on the other hand, we are considering living systems *as we know them*[1], then there may be need of a more prescriptive definition. We are aware that this is a large area, and we do not wish to be drawn into the detail of it: what we are looking for is something that we can *use*, not necessarily something that is entirely precise and able to fit all possible views of life. If we think in terms of independent living entities (ignoring viruses and prions, for example) then all are composed of one or more living cells. There are no non-living cellular entities (excepting recently dead entities: i.e. entities which retain the cellular structure which they had initially because they were alive). Cells are omnipresent in animals and plants (from the bacterium to the single celled amoeba to all plants to all classes of animals): indeed they are just about all that is omnipresent structurally (excluding the amino acids and ionic movements that underlie the actual material making up the cell, the mechanisms of energy production, and the DNA based core of genetics: but all of these are sub-cellular entities). It therefore seems appropriate to consider cells as archetypical living entities, and attempt to characterise them. Indeed, some proponents of synthetic biology also seem to see the cell as the basic building block [3].

Below, we consider some aspects of cells and how they operate in order to help to clarify living systems from non-living ones. The eventual aim of this project is to develop a mathematical/symbolic description of these areas, to move beyond words, in order that the tools of mathematics (such as Category theory [8]) can be applied, so that we may have a handle on systems which have the characteristics mentioned above.

2 Abstracting Cells

There are many levels at which one may model or describe living systems, from protein (molecular) interactions to large-scale population interactions: one difficult issue is choosing an appropriate level. Given the omnipresence of cells in living matter, it makes sense to include them as a specific model level, and it is this level that we consider here. What might such a model include, at an abstract level? What should it exclude?

What characterises cells is their closed-ness, that is, their boundary. They have an inside and an outside separated by a membrane. The membrane is thin, but not actually a mathematical surface: it is not homogenous, but includes localised capabilities for both active and passive transport of signals and material[2] from within to without the cell, and vice versa. Inside the cell there is a variety of machinery (and this varies from cell type to cell type), generally including genetic machinery used for protein manufacture, and possibly for manufacture of complete new cells. Outside the cell, there is firstly the immediate environment of the cell[3], then the rest of the Universe further away. Cells may abut other cells, or there may be space (extracellular medium, or whatever the cell is surrounded by - pond water, for example) between them. Cells are disjoint, and do not contain other cells (though they will contain other sub-cellular entities).

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[1] Clearly, this is a matter of debate. Does alive imply carbon-based or not? Here, we are considering actual (existing) life.

[2] We can consider material itself as a signal.

[3] With which the cell can interact directly.

We attempt to write this symbolically, in order to better define what we mean: then later we may consider how this relates to information processing and time in such systems.

We will write B for the cell boundary. In the usual 3-dimensional world, this boundary will be closed, or rather, both the inner surface and the outer surface of this (thin, but not 2-dimensional) B will be closed. We write B^+ and B^- for the outer and inner surface of the boundary (and these really are 2-dimensional surfaces). We write $\mathrm{in}(B)$ (really $\mathrm{in}(B^-)$) for the volume inside the cell, and $\mathrm{out}(B)$ (really $\mathrm{out}(B^+)$) for the world outside the cell (but in general, we will only be concerned with the area near to B^+). If B_1 and B_2 are the boundaries of two different cells, then $\mathrm{in}(B1) \cap \mathrm{in}(B) = \emptyset$.

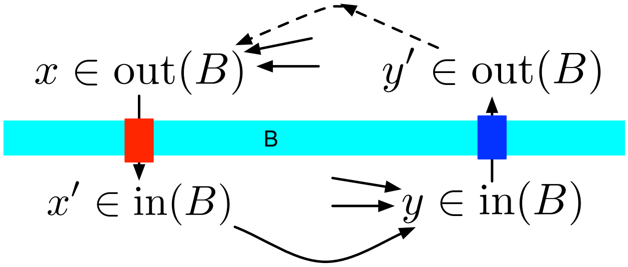

Fig. 1. Interaction between a cell and its environment. B is the cell membrane, and the area above B is outside of the cell, and below B is inside the cell. The blocks represent paths through the cell membrane.

Figure 1 illustrates the cell interacting with its environment: some entity x in the environment is either transferred to the inside of the cell (if x is, for example, an ion or small molecule), or reacts with a receptor embedded in B. x has some direct effect x' inside the cell: this might be that x has been transferred inside the cell, or that the effect of x at the receptor is x' inside the cell. In turn this (and most likely other factors as well) leads to some y inside the cell, and this is then transmitted either directly (that is, y is transferred from inside the cell to outside the cell, most likely if y is a protein or small molecule), or alternatively y has some effect y' outside the cell, through some effector probably embedded in the cell membrane. In turn, this action, probably along with others, has some effect which alters the local environment (shown as a dashed line), and so there is a cycle. A slightly different view of the same process is to say that the environment (as characterised by x) results in some change inside the cell (characterised by x') which in turn causes a change inside the cell which we label y (and which might simply be x' itself) which results in an action y': in this way we ascribe the cell what amounts to a perception/action cycle. The emphasis is on the cell's interactions, rather than on the cell's internal cycle of behaviour. This is a different view from that of Rosen and followers, [15], [14], [12]. The emphasis here is on input and output: the way in which the effect of the input changes is not described, so that changes (adaptation), stability and repair are not discussed. We view the basic operation of the cell as primary, and consider that these other aspects may be implemented on to of this basic level.

Clearly the cell boundary is not impervious to signals and matter: were it so, then the cell could not interact with the world outside the cell. How should this be characterised?

First, we consider direct transfer of material between the inside and the outside of the cell. B is not homogenous. It contains elements $p \in P$ that can allow movement (passive movement) of certain types of elements $e_p \in E_P$ of $\text{in}(B)$ through B to $\text{out}(B)$ and vice versa. It contains elements $d \in D$ that can cause movement (active transport) of certain types of element $e_d \in E_d$ from $\text{in}(B)$ through B to $\text{out}(B)$, or vice versa. Each p or d is located in B: the boundary B has a spatial extent, and the p and d are located at some position in B. Movement of the e_p or e_p takes time: there is a transit time $\tau = \tau_{e_p}$ or τ_{e_d} associated with the movement of elements whether passively or actively. Cells may also be in direct contact with other cells (which we can define by saying that $B_1^+ \cap B_2^+ \neq \emptyset$, so that the outside surfaces of the two cells B_1 and B_2 touch). In this case, given the colocation of suitable p or d in B_1 and B_2, material from $\text{in}(B_1)$ could be passed almost directly to $\text{in}(B_2)$, (or vice versa).

Of course, much of the interaction between the cell and its environment is less direct: so we need to characterise the hugely varied forms of interaction summarised as being receptor-based (for "input" to the cell) and effector based (for output from the cell). In general, some entity in $\text{out}(B)$ interacts with a receptor on the surface on the membrane (attached to B, or perhaps better $B+$). This results in some change (through some protein embedded in B) at $B-$, resulting in some further changes (perhaps cascades of reactions) in $\text{in}(B)$. This scheme runs in the opposite direction for effectors. The situation is similar to that in the paragraph above, except that the elements e_p or e_d are not transferred: instead, the action of the e arriving at the receptor (effector) is to produce (some time later) some e' at the other side of the membrane.

In both the case of transport from $B+$ to $B-$, and receptor mediated effects, we can consider the transfer as a signal from the environment to the cell.

So far we have described this system as a static entity, and then added movements of (so far undifferentiated, undescribed) elements of $\text{in}(B)$ or $\text{out}(B)$,and the effect of receptors and effectors. These are dynamic processes[4].

But what does the cell actually do? What is it about the cell that actually characterises the fact that it is alive?

The cell (which is itself likely to be in motion, relative to some aspects of its environment, (contained in $\text{out}(B)$)), traffics material (ions, perhaps proteins and other smaller molecules, or even larger particles: the e_p and e_d of the paragraph above) between its inside and its outside, and reacts to (and alters) its environment through these, and through its receptors and effectors. The cell uses its genetic material to organise the assembly of proteins inside the cell in response to internal conditions (mediated by internal biochemistry), which presumably are themselves affected by external conditions. These external conditions include the presence or absence of particular materials in $\text{out}(B)$ near to the cell membrane, but may include other factors too, such as temperature, light, etc. Moving material (apart from diffusion) and assembling proteins takes energy, so in

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[4] We note also that that the channels, receptors and effectors above may also change their characteristics in response to local conditions such as the presence of particular ion species, or the voltage across the cell membrane, or, indeed, other local conditions. Indeed, they may also move [18].

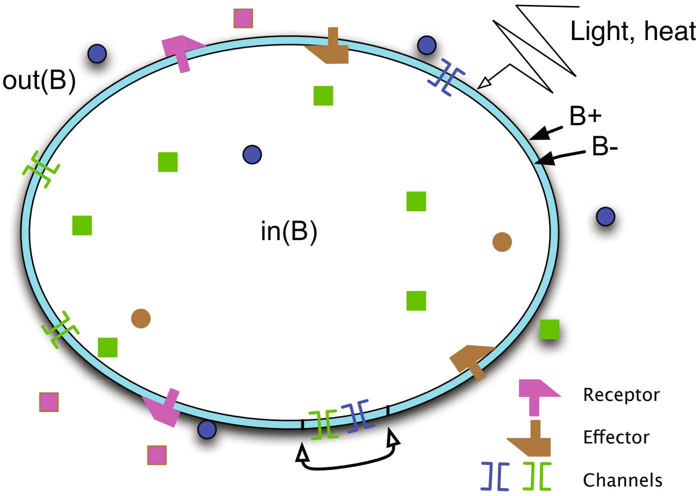

Fig. 2. Schematic of cell, with two varieties of channel (ion channel), and one variety each of receptor and effector. Small blocks represent material appropriate to channel or receptor of that colour.

some sense, the cell must take energy from its environment. But in addition to this (or rather, re-interpreting this differently), the cell organises its reaction to its surroundings in order to continue its existence effectively (see section 4).

How might we symbolically describe the internal behaviour of the cell?

It is difficult (and perhaps too early) to attempt this in a way that picks up the important aspects (as opposed to picking up all the aspects that are known about - this would imply a model that took all the systems biology of the cascades of reactions into account, and that would be a massive undertaking). What is clear is that the cascades of reactions can be considered to have trigger events, often caused by changes in out(B), detected by receptors, and/or movement of material across B, and that these then result in (changes to the) manufacture of proteins, over a period of time, and perhaps to some of these being transferred out of the cell (across B), or causing effectors to operate. Clearly, these can then affect other cells (either directly or through the intervening medium), possibly causing them to alter their behaviour.

Again there is an issue of causation and time: indeed, time is inherent in the concepts of causation and the term “cascade of reactions” implies a time-ordering. As matters stand, the cells are described as something like automata: particular receptors and effectors operate, and particular d or p allow particular e_p or e_d to transit B, and particular conformations of material, and perhaps other physical events cause the machinery of the cell to perform particular actions, operating particular effectors, and generating particular compounds that are then passed across B. It is a timed automaton: actions are not instantaneous, hence the cell performs a process that takes place over time.

In general, researchers interested in information processing in living systems have tried to differentiate between reactions and activities that relate to keeping cells alive, and those that might pertain to information processing: such a division makes sense from an engineering perspective, but may be meaningless from a biological perspective. Perhaps where the cells' primary function appears to be information processing (for example, neurons in the CNS of mammals), such a distinction might be possible, but even then, there is a balance between information processing activity and keeping the cell alive. But many cells in multicellular organisms have specialised functions (e.g. cardiomyocytes in heart tissue), and although one may analyse their function in an information processing way, this is not necessarily the most useful way to look at their operation. We note also that cells have a lifespan: cells can divide (though this is not considered here), and it is likely that the cell changes its behaviour in some ways over the course of its lifespan.

We note that what we have described is not quite a mathematical model for a cell: to turn it into such a model one would need to add actual timings, actual conditions: in other words to instantiate this outline descriptions with values and processes. What then is the status of this description? Essentially, it allows us to describe certain aspects of cells, without either having to resort to English, or having to define a precise model.

Can we take a process view of this system? One might consider

- the overall flow of material into and out of the cell through B, $\bigcup_{p\in P(B)} f_p \cup \bigcup_{d\in D(B)} f_d$, where f_p describes the flow of the e_p, and f_d describes the flow of the e_d
- the effect of activation of receptors
- the effect of activation of effectors
- the movement of the cell (of B, and of $\mathrm{in}(B)$).

Between these, one would have all the factors able to directly influence other cells: but this would ignore what was happening inside the cell itself. The overall movement and flow describe the cell at a level which could be incorporated into a higher level description (although there could be interactions possible but not included in this description).

Where does this leave interpretations of the activity of a cell in terms of information processing? In the same way that we ascribe informational values to electrical voltages and/or currents in digital and analogue computers, we can ascribe informational values to any aspect of cells (see section 4). Clearly, some are more appropriate than others. Some cells (most notably neurons and cardiomyocytes) have electrical potentials between $\mathrm{in}(B)$ and $\mathrm{out}(B)$, and these can vary both over time and over B[5]. Further these can modulate the operation of the receptors, effectors, and channels in B. For other cells (and indeed, for some neurons as well) other possibilities include relative ionic densities for various ionic species, movement of specific (usually small) molecules (e.g.neurotransmitters, neuromodulators), or possibly alterations in shape (perhaps mediated by Calcium ions at synapses in neurons) or even size.

Below, we consider one aspect of possible information processing, and how it might lead to outcomes that differ from those associated with digital information processing.

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[5] These are caused by the trafficking of charged ions across B.

3 Proteins and Stochasticity

The cell abstraction above makes no mention of actual interactions, or of actual reactions. Whilst appropriate from a purely abstract viewpoint, it may be necessary to consider the actual elements, primarily because they are themselves complex, and this complexity may not be easily specified, or straightforwardly combined (unlike gates used throughout digital electronics). Proteins are complex molecules: interactions between proteins (or even between proteins and relatively simple organic molecules, or even ions) are as a result also complex. This complexity may result in differences in the overall behaviour of the cells within which these reactions occur. As a result, simple abstractions may fail to capture the reality in ways that can be misleading.

Non-chemists usually think of chemical reactions in a simplistic way: a number of reactants combine to form a new compound, plus some other (waste) material. Given an appropriate temperature and pressure the reaction will take place. While this is true for small molecules (true up to a point: in fact most reactions work in both directions, but one usually much more than the other), for molecules like proteins, the situation is more complex. Most of the reactions in living systems are between (relatively) large molecules, and take place at active areas (sites) of these molecules. In order for the reaction to proceed, these active sites must come within a certain distance of each other. This will depend on the electrostatic forces around the molecule and on the overall and local conformation of the molecules involved. Since the conformation of the molecule is dependent on many factors (at least including temperature, and the presence and concentrations of ionised molecules and atoms in the aqueous solution where the reaction will take place), the extent to which a reaction will take place will also depend on these factors. Other factors may also be critical: for example, local catalysts (enzymes) that make the active site more accessible, or help to bring the reactants into near contact. There are also likely to be relatively small numbers of reacting molecules, making the stochasticity of the reaction higher [11]. This contrasts with the situation in digital (and even analogue) electronics, where a signal will always have the same effect, because the numbers of charge carriers is huge, and there is no issue equivalent to molecular conformation, or presence of local catalysts[6].

A second issue is the dynamic nature of proteins, even when they are not involved in reactions. Proteins are complex, and, according to a recent review [6] many proteins are in continuous motion. Something similar is referred to in Matsuno's work [13] where a single protein seems to function as a precisely timed oscillator and counter. This dynamic behaviour may be widespread, but is difficult to detect. This suggests that a reactant may have different effects depending on the precise time of its arrival.

These levels of complexity suggest that using a simple functional description for the activities inside the cell may be inappropriate, and may risk losing something that is important in the operation of the cell. There are multiple influences at work concurrently, multiple species of ions, enzymes and proteins all of whose concentrations

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[6] In general electronic systems are designed to ensure that this is the case. Recent work in the very deep sub-micron range of feature sizes does use transistors with very small numbers of charge carriers, see, for example the work of the nano-CMOS group at Electrical Engineering in Glasgow: however, there are real issues with how to use this type of technology when most electronics is reliant on systems behaving deterministically.

affect exactly which reactions occur in a subtle and complex way. Some of the simpler measurements that are often used to characterise the state of a cell (for example, local depolarisation) may be in danger of being misleading because they are the result of many different effects being summed, rather than describing the actual state of the cell.

4 Information Processing and Cells

Even after Shannon [17], the question of exactly what constitutes information remains elusive. In digital electronic systems, the range of possible signs is highly restricted (usually to strings of binary digits), and in digital computers, the issue is relatively easy. However, for analogue electrical signals, the situation is more difficult, and depends on coding techniques: it is straightforward where the coding technique is predefined, but if one is seeking to measure information content in an unknown signal, then it is (essentially) impossible. In cells, the signals are not (primarily) electronic: further, as discussed above, it is not immediately obvious what should be considered as a signal. In addition the cell is not (primarily) necessarily an information processing device: its aim is its continued existence, or perhaps its contribution to some multicellular organism, to the extent that it has an aim. Nonetheless information processing may assist it in this aim, but it is the semantics of the information - how it alters what is the most appropriate behaviour - that matters in terms that are visible externally. If the cell is carrying out something that we might consider to be information processing, we need to distinguish between input (signals) that arrive at the cell from outside, and internally generated signals that are part of the actual information processing itself.

What could be candidate input signals? Clearly candidate signals should have some effect at the cell: if they have no effect then they surely cannot be said to carry information to the cell. As we noted above, candidate signals may be the presence of particular species in out(B), or may take the form of light or other stimuli (electrical voltages, physical shock, etc.) arriving at B. So long as they have an effect they may (and probably do) carry information: but it is in no way clear how this might be quantified. Considering the discussion in section 3, it is clear that many different chemical and ionic concentrations and flows as well as external forces (light, physical shock) are all candidates to be information carriers. But how might these be be quantified? One could simply consider the concentration of each as a scalar, and treat them as independent signals, rather like a number of independent voltages, however, it is likely that their effects are not independent of each other, and that, and the continuous nature of the signals, makes information measurement extremely difficult.

A different view of information in living systems is taken by Friston and colleagues [9]. For them, living systems act to minimise free energy, in some sense modelling the world outside the animal internally. From the point of view of a cell, one might consider the effect of the cell's environment on the cell, (both in an energy transfer sense, and in terms of matter transferred across the cell boundary, or effects mediated by reactions which cross the cell boundary). Metaphorically, one might think of the cell boundary as a "lens" through which aspects of the cell's environment are mirrored/focussed into the inside of the cell. This (dynamically varying "lens") then enables the cell to react to its environment in an appropriate way: this is, in some sense, captured in figure 1.

Clearly, different cells have very different environments, and, indeed, different reactions to their environments. For a single celled organism, the reaction is about seeking energy sources: for a cell inside a multicellular organism, the local environment is very specialised (think of a kidney cell, or a liver cell), and the appropriate behaviour of the cell is very specific. Cells are necessarily blind to aspects of their environment which are not detected, so the ”lens” above is specific to certain aspects of the cell's environment.

5 What Is the Way Forward from Here?

We have produced a possibly usable basis for formal descriptions of a cell. But this does not cover the internal behaviour in terms of protein interactions, nor does it discuss the cell's behaviour directly in terms of information processing. Clearly, there is (at least one) level to be described below this cell level, and we have tried to make the case that this is critically important, because we believe that the way it works may affect the overall behaviour of the cell, and this means that the abstraction used to describe these interaction needs to capture the actual (and not just the idealised) behaviour. Can we associate Friston's free energy minimisation [9] with directing the events described in the earlier characterisation of cells? What does this principle mean for the way in which detected aspects of the environment result in actions taken through effectors or channels?

The issues of information measurement and Turing computation are, I suspect, intimately related. If the information content of the elements of the system were precisely defined in such a way as to be measurable (in the sense of [17]), then the system would clearly be a Turing machine, and would be emulatable straightforwardly by a computer, with all that it entails. Does the difficulty (and possible ambiguity) of information measurement affect the nature of possible computation?

One important way forward will be to take the relatively simple ideas described here, and find a way of embedding them within category theory [8]: then we might be able to add levels both below and above, but still be able to manipulate the overall structure. There is clearly also a need for operational semantics in this system as well. This could lead to something which might be worth calling Integral Biomathics.

Addendum

When I wrote this paper, I was not aware of the work of Cardelli [4][5]. His work develops a different but related model to that outlined in section 2. In it, the basic elements are membranes (sometimes called branes), and in [5] he develops a calculus enabling operations on these membranes including enveloping and vesicle formation in two dimensional membranes. In addition, in [4], he adds representations of proteins and other elements inside the (closed surface defined by the) membrane. This work is in the context of systems biology, considering how to produce a process calculus that is appropriate for describing cells. Neither Cardelli's model nor mine is an accurate reflection of all that happens in a cell: both are aimed at selecting an appropriate subset of the huge range of interactions on and within cells. The difficult question is whether either the model outlined here, or that of Cardelli (or indeed, any process calculus based model) is capable of capturing enough of the characteristics of cells to capture the difference between cell which is living and one which is not. This was not the aim of Cardelli, but is the eventual aim of INBIOSA.

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Part II

Mathematics and Computation

Editorial

This part consists of 5 papers, all proposing approaches to modeling living systems. These cover different kinds of hierarchies, natural computation, category theory and logic as a basis for self-organization, autopoiesis, and process-based agents.

The paper of Ron Cottam proposes a model for an organism primarily based on structural scale, characterized by the way in which scales are coupled together through complex fractal regions. Comparing this with a model from solid state physics (Kronig-Penney model for electron propagation in a crystal) which also presents a number of different energetic levels similarly separated by 'forbidden zones', the author proposes to develop better models of biological systems by crossover between these two very different representations: natural hierarchy and electron band structures.

Gordana Dodig-Crnkovic presents morphological computation (which emerged from robotics) for all natural computations, based on self-organization of information and the development of embodied cognition in living organisms. Info-computational naturalism describes nature as a succession of levels of organization of information; morphological computing on that information leads to new informational structures. Sensory stimulation is achieved by the interaction with the environment through constraints; generation of correlations in sensors allows reducing the complexity.

Andrée Ehresmann and Plamen Simeonov propose a project called WLIMES to combine Simeonov's Wandering Logic Intelligence (WLI) with the Memory Evolutive Systems (MES) developed by Ehresmann and Vanbremeersch. These two models are briefly recalled: WLI is an open, hierarchical and dynamically structured model for communication systems. MES provides a model, based on category theory, for multi-scale complex systems with a multi-agent self-organization. The idea is that WLIMES could make MES amenable to computations, while extending the scope of WLI to biological systems; the main problems on this road are explained.

The paper by Tatsuya Nomura presents a framework to formalize the distinction between organization and structure in autopoietic systems, by combining category theory and λ-calculus, using the equivalence between the category of Cartesian closed categories and that of typed λ-calculi. Cartesian closed categories on which completely closed systems, such as the (M,R)-systems of Robert Rosen, are defined form a specific subcategory in which an isomorphism exists between operands and operators.

The last paper by Anya Yermakova (an abstract of her Oxford thesis) is also inspired by logic. It describes a model for process-based multi-agent systems, with a view to applications to systems in molecular biology or biological systems. These agents are able to communicate and to execute concurrent processes while moving (as in bioambiant calculus). Information locally available to them is treated as their "knowledge", and the exchange of information between them as “dynamics of knowledge” maintained and gained upon process transition.

Towards Cross-Modeling between Life and Solid State Physics

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Abstract. We develop a hierarchical model for an organism which is primarily based on structural scale. This is then compared with the Kronig-Penney model for electron propagation in a crystal. Both models exhibit similar multi-level structure, where the levels are separated by complex or forbidden regions. We conclude that cross-modeling between natural hierarchy and electron band structures may help in formulating future models of biological systems.

Keywords: scale, hierarchy, hyperscale, life, Kronig-Penney.

1 Introduction

There have been many and varied attempts to provide models of living systems or organisms. Possibly the two most well-known are due to James Grier Miller (1978) and Robert Rosen (1991). Miller proposed that living systems form 8 levels of complexity, from biological cells up to supranational organizations, each depending on the same 20 essential subsystems in order to survive. Rosen developed his (M,R) representation of an organism by internalizing efficient cause. Unfortunately, neither of these successfully describes a multi-scalar organism: Miller's model takes no account of inter-scalar coupling, and Rosen's makes no attempt to deal with scale (Cottam et al., 2007).

In this paper we will develop a model of a living system – or organism – which is primarily based on structural scale. A major characteristic of the model is the way in which scales are coupled together through complex fractal regions, and this leads us in the direction of another different model. Arguably, the most developed model of a physical domain is that of solid state physics, through its application to the development of integrated circuits and computer processors. Fascinatingly, this model itself presents a number of different energetic levels similarly separated by 'forbidden zones'. Our central thesis is that it may be possible to develop better models of life by crossover between the two very different representations. An immediate objection which comes to mind is that the solid state physics of informatics applications is based on the long-range atomic order of perfect crystals, which is absent from living entities. However, many of the constituent chemicals which go to make up living tissue present an almost crystal-like appearance – for example the lipid pdmpg, or even DNA. We do not propose that simplistic solid state physical models can be directly applied to organisms, merely that it should be instructive to compare them with models of life.

2 Scale

Different systems or systemic sub-units exhibit different bandwidths in the way that they relate to their surroundings. In the theoretical extreme, these could range from sensitivity to *all* sizes to sensitivity to only *one* size (Figure 1(a), 1(b)). Practically, however, these extremes never exist, and real bandwidths range from large-but-finite to small-but-finite extents (Figure 1(c), 1(d)). Individual bandwidths start to become interesting when their owners are combined into more complicated systems.

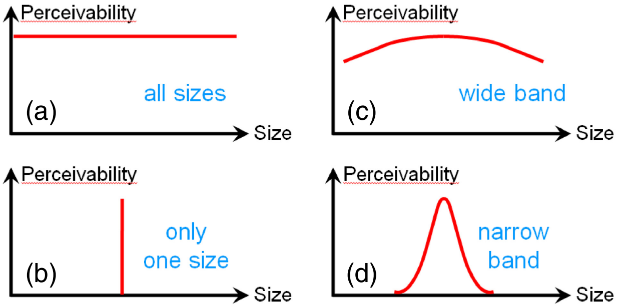

Fig. 1. System sub-unit bandwidths: (a) and (b) theoretical extremes; (c) and (d) realistic limits.

In the case of the theoretical extremes, if all sub-units possessed infinite sensitivities, then the individual sub-units would have no relevance at all (Figure 2(a)); and if all possessed sensitivities to just one size there would be no inter-unit coupling (Figure 2(b)).

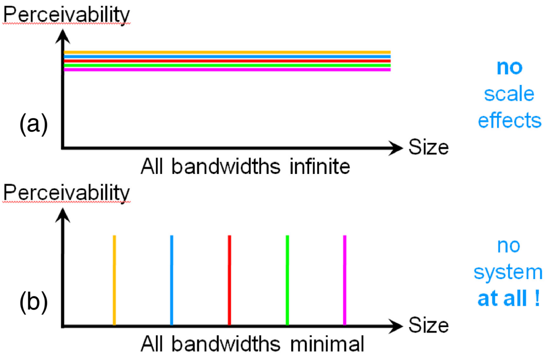

Fig. 2. Theoretical extremes of sub-unit bandwidth combinations.

More pragmatically, combining differently-‘scaled’ sub-units with wide bandwidths results in a global system which exhibits hardly any effects of scale – as in the case of a crystal (Figure 3(a)) – while combining sub-units with narrow but still overlapping bandwidths results in a system which exhibits complex inter-scalar properties – as in the case of an organism (Figure 3(b)).

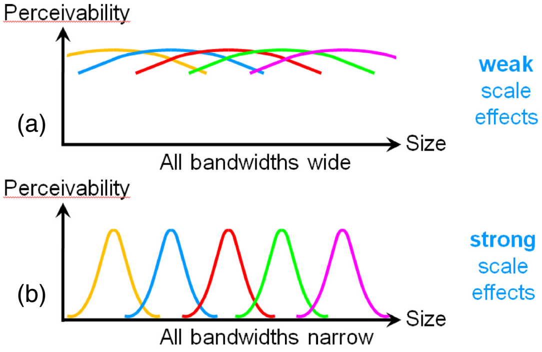

Fig. 3. Realistic limits of sub-unit bandwidth combinations

Given a system consisting of a number of different interacting scalar levels, then the ease or difficulty of transiting between any pair of adjacent levels depends on the similarity or diversity of their internal representations. Figure 4 presents an example of such a set of model-levels: those used to represent an electronic diode.

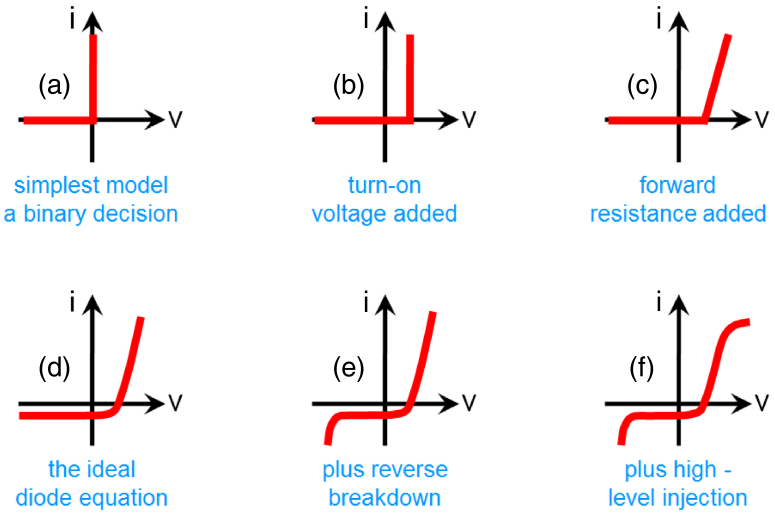

Fig. 4. A sequential set of models of an electronic diode.

The first, simplest model 4(a) corresponds to zero electronic current i for reverse (negative) voltage V, but a positive electronic current for forward (positive) voltage. The next, 4(b) adds in a zero-offset (the 'turn-on' voltage). Model 4(c) adds a linear slope to the forward current characteristic. All three of these – 4(a), 4(b) and 4(c) – are related piecewise linear models. The fourth model, 4(d) is radically different, being based on an exponential evaluation of electronic flow – the 'ideal diode equation'. Model five 4(e) adds in the result of 'reverse breakdown' of the diode, and model six 4(f) adds in the result of 'high-level injection'. None of these models is universally 'the best' – each of them relates best to a specific set of environmental conditions, mainly in terms of the applied voltage. This in itself is a valid generalization of all model sets for a specific parameter or phenomenon: a long-standing model is rarely 'wrong', but usually badly adapted to newly occurring or discovered environmental conditions. Transit between levels 4(a), 4(b) and 4(c) or between 4(d), 4(e) and 4(f) is comparatively easy, but certainly not between 4(c) and 4(d), where the models' derivations are completely different.

This question of inter-scalar transit is fundamental to the way multi-scalar systems operate. Each scalar level must be partially independent – or 'closed' – to maintain itself, while partially communicating with its neighbors – or 'open' – to maintain system unification. A good example of the problems involved in going from lower to higher scales of a system is the equation 1 + 1 = 2. This is far more complex than initially appears. The first thing we should notice is that there is no generally applicable manner of combining two entities to make one. The equation itself belongs in a completely abstract mathematical domain where its meaning and result are predefined. The problem is that between the left hand side and the right hand side of the equation there is a loss of degrees of freedom – a loss of information! In reality, one apple plus one apple does not give one bigger apple. And if it did, would that apple be two times the volume, or two times the width, or two times the height, or … This is a basic difficulty for the progressive evolution of multiple scales… at each level of development information is lost.

A place we expect to find scale, where in fact there is none, is in large complicated digital information processors. A computer has a physical nature, and as such there may/will be some aspects of spatial scale depending on the construction of its components. However, in its role as a digital information processor the individual processing gate operations are absolutely isolated from each other by the system clock, which ensures that all of the gates have settled down to their pre-ordained states before they are connected or re-connected for a short period. In essence, the only global properties of such an information processor *were* in the head of the computer designer or programmer, or *are* in the head of its user. Consequently, any attempt to create global-dependent phenomena in a digital computer – whether 'intelligence' or 'consciousness' – is doomed to failure.

In passing, this raises another, more general question: that of *information*. Information depends on interpretation. Habitually, the concept of information is closely tied to the work of Shannon (1948) on communication channels. Unfortunately, Shannon effectively maintains that information exists not only in 'the sender' and 'the receiver', but also within the intervening channel (Schroeder, 2011). This is unreasonable.

As we pointed out, information depends on interpretation – it is a combination of data and context, whose correlation is absent from the communication channel, where data and context are indistinguishable[1].

The principal function of a computer clock, therefore, is to isolate local from global. A result of this is that a computer cannot provide output until it has waited for the outputs of each and every one of its gates (it is no defense to maintain that many gates are eliminated by 'if-then' clauses; in terms of the current computation these gates do not exist!). Consequently, the bigger you make a processing structure, the slower the computer will be (for the same clock speed): lower 'levels' run faster than higher ones. This is fundamentally different from a biological multi-scalar system, where the bigger the scalar assembly, the faster it can run in responding to external stimuli: higher levels run faster than lower ones!

3 Hierarchy

Hierarchy is nominally "a human abstraction"[2]. Traditionally, only two types of hierarchy are recognized:

a *scalar* hierarchy, e.g. atoms – molecules – cells – organisms - …

a *specification* hierarchy, e.g. physics – chemistry – biology – society - …

However, natural systems are better represented by a *model* hierarchy, similar to that described in Figure 4, which resembles a specification hierarchy that has been constructed in terms of scale. Conventionally, the highest level of a hierarchy is supposed to be dominant, but in a model hierarchy this is not the case; any model level can be the most suitable in a specific context.

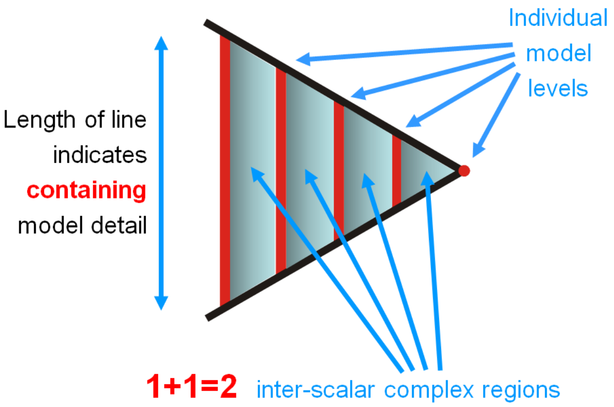

Fig. 5. A general representation of a natural multi-scalar hierarchy.

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[1] Clearly, in the case that both are transmitted as binary digits there is no distinction between them.

[2] A quotation from Stan Salthe.

To indicate this difference we will draw our hierarchy turned on its side (Figure 5), with the 'highest' level[3] at the right hand side. In Figure 5, each scalar level is represented by a vertical line, where the length of the line indicates how much information is needed to define that level. Between each pair of levels is a complex region which corresponds to the difficulty in generalizing the loss of degrees of freedom on transiting upscale[3].

The complexity we refer to here is not the Kolmogorov complexity related to digital systems, it is equivalent to Robert Rosen's definition:

> "*A system is simple if all its models are simulable. A system that is not simple, and that accordingly must have a nonsimulable model, is complex.*" (Rosen, 1991)

More generally, for our purposes, we can suggest that:

> *simple* implies 'easy to compute',
> *complicated* implies 'more of the same',
> *complex* implies 'only imprecisely computable, if that!'

The logistic plot of $x_{i+1} = -Kx_i\ (1-x_i)$ has the same form as this representation of a natural hierarchy (Figure 6), with scaled simple discrete solutions separated by regions of complexity[4]. This suggests that this general nature of scale sets and complex coupling may be more widespread than at first appears.

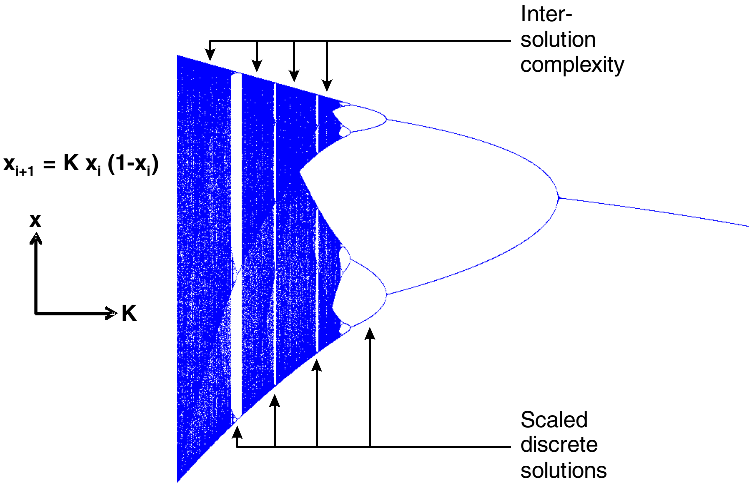

Fig. 6. The form of the logistic plot is similar to that of the natural hierarchy.

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[3] The 'higher' the level, the more descriptive information has been lost (c.f. 1+1=2).

[4] Note that here the complexity is not naturally Rosennean, it is created by temporal incomputability.

Natural multi-scalar systems, like organisms, are unified. However, unification cannot be imposed from outside – it is the result of inter-scalar correlations. It is important to note again that individual scalar levels are partially ‘enclosed’ – shut off from their neighbors – and therefore can only be approximately observed from outside. In essence, any specific level can ‘decide’ what it communicates and what it withholds (in the way that a biological cell does with respect to its neighbors).

The result of this cross-scalar-set correlation is a systemic identity referred to as *hyperscale* – an approximate reproduction of the scalar set but one which is transparent to inter-scalar transit (Figure 7). Hyperscale is the real nature of the system, whether it is observed from inside or from outside. To the extent that we can, we create a hyperscalar image of everything we encounter – even of ourselves! Any lack of ‘correct’ information is filled in subconsciously with un-validated images, convenient but outdated models, etc.[5]

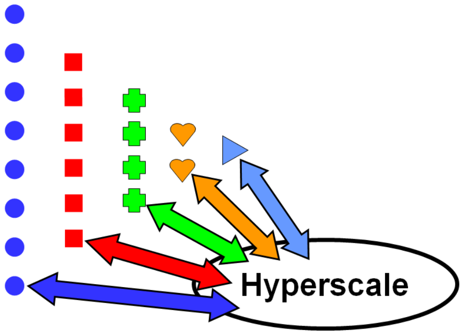

Fig. 7. Integration of the scales of a unified natural hierarchy into its *hyperscalar* identity.

The central premise of this paper is that the establishment of this kind of natural hierarchy is sufficient to create life. Such a hierarchical framework appears to be the basic building block of nature. Ergo, life is unavoidable. In searching for a mathematical formulation to represent biology this is an important guide; we should look for mathematical structures which naturally generate this kind of complexity-coupled multi-layer framework.

4 Electron Properties in the Solid State

We can refer to electrons in crystals either as particles or as waves.

In free space, the motion of electrons as particles can be characterized by

$$Energy\ E = \frac{1}{2}mv^2 \qquad \text{where } m \text{ is electron mass, and } v \text{ is its velocity}$$

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[5] For example, it is convenient when using satellite navigation (GPS) to re-assume that the earth is flat!

$$Momentum\ p = mv$$

$$Energy\ E = (1/2m)p^2$$

In a crystal, solution of Schrödinger's equation injects Dirac's constant $h/2\pi$:

$$Energy\ E = \left(h^2/8\pi^2 m^*\right)p^2$$

where m^* is the electron's effective mass[6]

This yields the parabola of *Energy E* plotted against *p* shown in Figure 8.

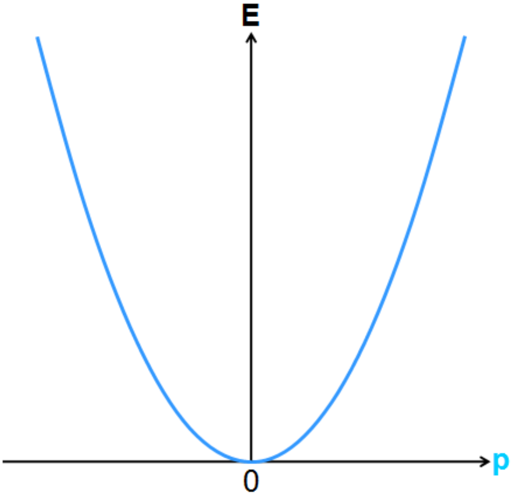

Fig. 8. Energy *E* versus momentum *p* for a particulate electron in a crystal

In a crystal with atomic separation *a*, and an electron characterized as a wave with wavelength λ, discontinuities in wave propagation will occur when $\lambda/2 = a$. Using the De Broglie relation $p = h/\lambda$ these will occur on the p-axis of Figure 8 at values of $n\pi$, where *n* is any integer.

Kronig and Penney (1930) proposed that the energy potential associated with each atom in a crystal, which causes these discontinuities, could be represented by a rectangular profile of width *w* and height V_0. Solutions for the electron wave propagation are then derived from the global equation

$$\cos ka = (R/\alpha a)\sin \alpha a + \cos \alpha a$$

where

$$k = 2\pi/\lambda$$

$$\alpha = (2\pi/h)\sqrt{2Em^*}$$

$$R = V_0 w(4\pi^2 m^* a/h^2)$$

---

[6] In a crystal, an electron appears to have a different mass from its free space value, called the effective mass m^*.

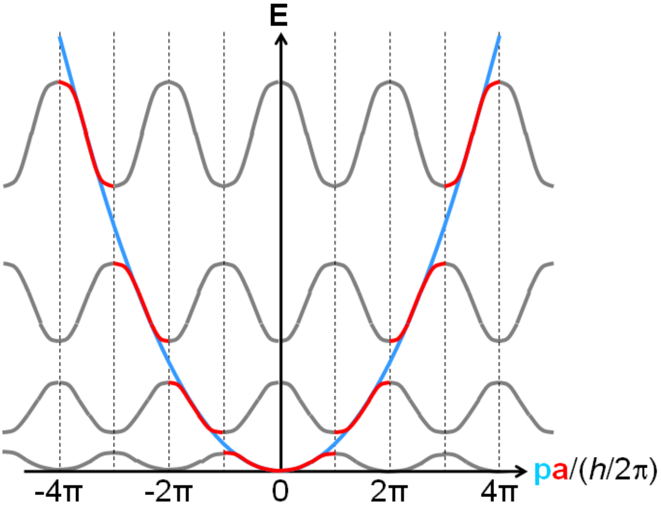

Fig. 9. Solutions of the Kronig-Penney equation. Valid portions are those closest to the parabola.

This yields the set of sinusoidal solutions shown superimposed on the parabola in Figure 9.

Restriction of the solutions to real values of sin/cos between -1 and 1 retains only the parts of the solutions which are closeto the parabola (Figure 10).

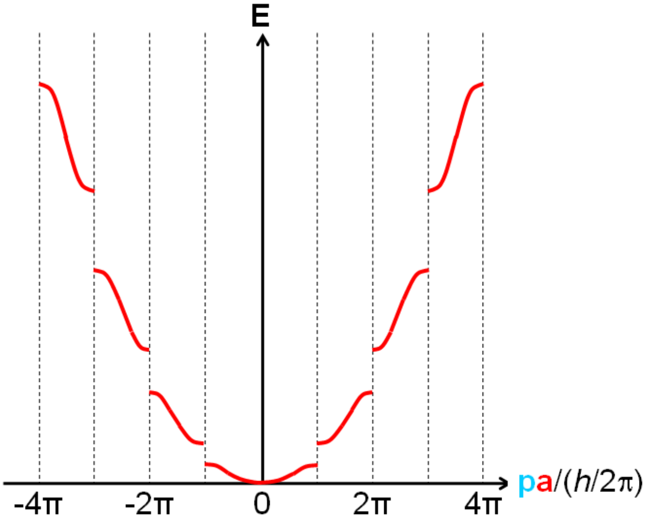

Fig. 10. Remaining *real* solutions to the Kronig-Penney equation

Regions of these solutions which are far from values of $n\pi$ in the plot coincide with the free-space parabola[7], but there are distortions from the parabola at values of $n\pi$. The repeated occurrence of discontinuities with $n\pi$ means that the individual sections of the plot can be folded in on themselves until everything lies between $-\pi$ and $+\pi$ (Figure 11). This gives us the normal way in which the electron *energy bands* are portrayed.

As indicated in Figure 11, we now have a set of permitted regions for electron occupancy which are separated by *forbidden gaps*: precisely the form we were looking for to represent the scale-set of a natural hierarchy.

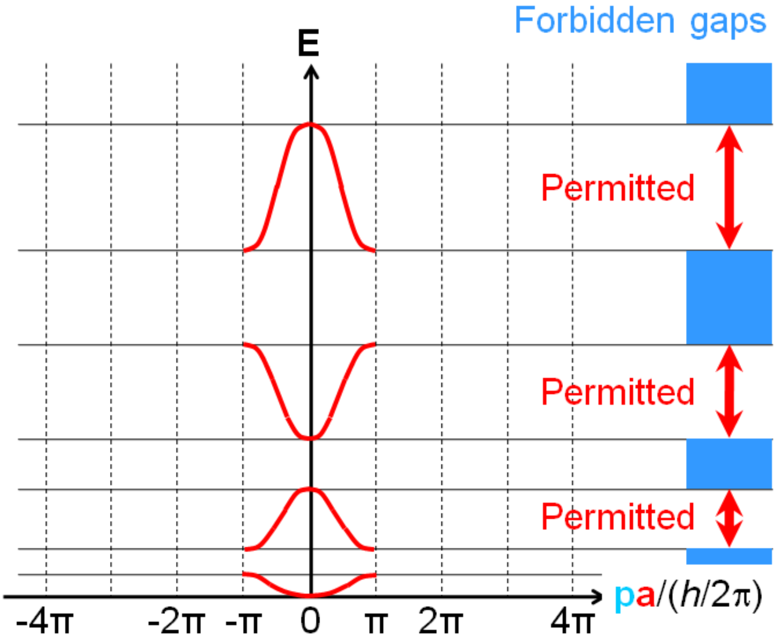

Fig. 11. Real solutions to the Kronig-Penney equation folded in to the region $-\pi$ to $+\pi$.

In addition, the folding in of the different energy bands to the central region closely resembles the generation of *hyperscale* in the multiscalar representation of a living system.

5 Conclusion

The mathematics of solid state physics does indeed present us with a possible mathematical route towards representing the scale-set of a natural hierarchy. As we commented earlier, a clear restriction is the lack of precise long-range order in a biological

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[7] … except for the modified value of electron mass m^*.

system when compared to a crystal, and it would be fatuous to suggest that the comparison between natural hierarchy and electron energy bands is sufficient to apply the mathematics we have presented directly to living systems. However, it may be that the fuzziness of biochemical and cellular order, which would correspond to a fuzziness in any comparison, indicates that the hierarchical model we have presented is itself far too precise. It remains to be seen whether cross-modeling between these two very different organizations may directly or indirectly lead to more successful models of biological systems.

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Info-computationalism and Morphological Computing of Informational Structure

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Abstract. Within the framework of info-computationalism, morphological computation is described as fundamental principle for all natural computation (information processing).

Keywords: Info-computationalism, Philosophy of Computing, Morphological Computing.

1 Foundations of a New Science of Computation

Present computational machinery evolved from mechanical calculators to electronic machines with vacuum tubes and then transistors, and to integrated circuits and eventually microprocessors. During this remarkable development of hardware towards ever smaller, faster and cheaper devices, the computational principles remained unchanged: an isolated machine calculating a function, executing an algorithm. Such machines were adequately represented by the Turing Machine model. However, computational machinery gradually started to change its character from isolated calculators to networked communicating devices. In the 1970s first networks were created with computers linked together via telecommunications. The emergence of networking involved a changed nature of computers and computing as operating systems and applications started to access and use the resources of each other, exchanging information.

Turing Machine model is sequential. As long as parallel processing, such as occurring in networks, is synchronous, it can be sequentialized, and thus Turing Machine model can be applied. However for networks with asynchronous processes Turing Machine is not appropriate. As (Sloman 1996) points out, concurrent and synchronized machines are equivalent to sequential machines, but some concurrent machines are asynchronous. (Dodig Crnkovic 2011)

One of the main arguments in favor of universal computing is the often repeated claim in Computer Science (based on Turing machine model of computation) that it is invariant on the details of implementation (hardware). Computational complexity classes, themselves based on Turing model of computation, are supposed to be substrate-independent general abstractions. However, it turned out that Turing Machine model depends essentially on the underlying assumption of classical physics:

The Turing machine is entirely classical, and does not allow for the possibility that paper might have different symbols written on it in different universes, and that those might interfere with one another. (Deutsch 1997)

This fascinating insight in the fundaments of computing leads us directly to the nascent field of Natural Computing, which sometimes is called Unconventional Computing or Physical Computing.

2 Natural Computation

According to the *Handbook of Natural Computing* (Rozenberg et al. 2011) Natural Computing is "the field of research that investigates both human-designed computing inspired by nature and computing taking place in nature." In particular, the book addresses:

Computational models inspired by the natural systems such as neural computation, evolutionary computation, cellular automata, swarm intelligence, artificial immune systems, artificial life systems, membrane computing and amorphous computing.

Computation performed by natural materials such as bioware in molecular computing or quantum-mechanical systems in case of quantum computing.

Study of computational nature of processes taking place in (living) nature, such as: self-assembly, developmental processes, biochemical reactions, brain processes, bionetworks and cellular processes.

Especially important in the context of Natural Computing is that knowledge is generated bi-directionally, through the interaction between computer science and the natural sciences. While the natural sciences are rapidly absorbing ideas, tools and methodologies of information processing, computer science is broadening the notion of computation, recognizing information processing found in nature as (natural) computation. (Rozenberg and Kari 2008) (Stepney et al. 2005) (Stepney et al. 2006)

This new concept of computation allows for nondeterministic complex computational systems with self-* properties. Here self-* stands for self-organization, self-configuration, self-optimization, self-healing, self-protection, self-explanation, and self(context)-awareness. Dodig Crnkovic in (Dodig Crnkovic and Müller 2009) argues that natural computation (understood as processes acting on informational structures) provides a basis within info-computational framework for a unified understanding of phenomena of embodied cognition, intelligence and knowledge generation.

While computing nature is an old idea, dating back to Zuse, and developed by number of other researchers (Fredkin, Wolfram, Chaitin, Lloyd) who argue that all of the physical world computes, the question may be asked: on what substrate does this computation goes on? Within the info-computational framework, the answer is: information. All computational processes in the Nature take place on informational structures (protoinformation).

3 Universe as Informational Structure

Von Baeyer (2003) suggests that information is to replace matter/energy as the primary constitutive principle of the universe. Wolfram supports the equivalence between the two descriptions:

Matter is merely our way of representing to ourselves things that are in fact some pattern of information, but we can also say that matter is the primary thing and that information is our representation of that. (Wolfram in Zenil 2011, p. 389).

The universe is "*nothing but processes in structural patterns all the way down*" (Ladyman, et al. 2007) p. 228. Understanding patterns as information, one may infer that information is a fundamental ontological category. What we know about the universe is what we get from sciences, as "special sciences track real patterns" (p. 242). Thus the realism of this approach is based on the claim that "successful scientific practice warrants networks of mappings as identified above between the formal and the material" (p. 121). The ontology is scale-relative, as we generate knowledge through interactions with the world (Dodig Crnkovic 2008) on different levels of abstraction (organization).

Information may be considered the most fundamental physical structure, as in Floridi's Informational Structural Realism (Floridi 2008). It is in permanent flow, in a process of transformation, as observed in physics. We know the world as a result of interaction and exploration:

Structural objects (clusters of data as relational entities) work epistemologically like constraining affordances: they allow or invite certain constructs (they are affordances for the information system that elaborates them) and resist or impede some others (they are constraints for the same system), depending on the interaction with, and the nature of, the information system that processes them. (Floridi 2008).

4 Info-computational Universe

Info-computationalism (Dodig Crnkovic 2006, 2009) is a unifying approach that brings together Informationalism (Informational Structural Realism) of Floridi (2008); Informational Realism of Sayre (1976) and (Ladyman, et al. 2007) – the informational universe - with the Naturalist Computationalism/ Pancomputationalism (Zuse, Fredkin, Wolfram, Chaitin, Lloyd) – the computing universe. Info-computationalist naturalism understands the dynamical interaction of informational structures as computational processes. (Dodig Crnkovic 2011) It includes digital and analogue, continuous and discrete as phenomena existing in the physical world on different levels of organization (Dodig Crnkovic and Müller 2009). Digital computing is a subset of a more general natural computing.

In what follows I will present the idea of *morphological computation* which is, as much of natural computation, different from the execution of an in advance given procedure in a deterministic mechanical way. The difference is in the computational mechanism based on *natural physical objects as hardware* which at the same time *acts as software or a program governing the behavior of a computational system.*

Physical laws govern processes which cause dynamical development of a physical system. Or in other words, computational processes are manifestation of physical laws. The new structure (data structure, informational structure) produced by computational processes is a new program in the next step of time development. Interestingly, morphological computation is not one of the topics of the Handbook of Natural Computing, even though the fundamental principles of morphological computing are underlying all of natural computing.

5 Morphological Computation

Recently, morphological computing emerged as a new idea in robotics, (Pfeifer 2011), (Pfeifer and Iida 2005), (Pfeifer and Gomez 2009) (Paul 2004). It has conceptually very important generalizable consequences with regard to info-computationalism.

From the beginning, based on the Cartesian tradition, robotics treated separately the body (machine) and its control**.** However, successively it became evident that *embodiment itself is essential for cognition*, *intelligence and generation of behavior*. In a most profound sense, embodiment is vital because cognition results from the interaction of brain, body, and environment. (Pfeifer 2011)

From an evolutionary perspective it is clear that the environment presents a physical source of biological body which through morphological computational processes leads to the establishment of morphogenesis (governing short time scale formation of an organism) and on long time scales governing evolution of species. Nervous system and brain evolves gradually through interactions (computational processes) of a living agent with the environment as a result of information self-structuring (Dodig Crnkovic 2008).

The environment provides a variety of *inputs*, at the same time as it imposes *constraints* which limit the space of possibilities, driving the computation to specific trajectories. This relationship is called *structural coupling* by (Maturana & Varela 1980) and described by (Quick and Dautenhahn 1999) as “non-destructive perturbations between a system and its environment, each having an effect on the dynamical trajectory of the other, and this in turn effecting the generation of and responses to subsequent perturbations.” (Clark 1997) p. 163 talks about "the presence of continuous mutually modulatory influences linking brain, body and world."

In morphological computing modeling of the agents behavior (such as locomotion and sensory-motor coordination) proceeds by abstracting the principles via information self-structuring and sensory-motor coordination, (Matsushita et al. 2005), (Lungarella et al. 2005) (Lungarella and Sporns 2005) (Pfeifer, Lungarella and Iida 2007). Brain control is *decentralized based on the sensory-motor coordination through the interaction with environment*. Some of the examples of the use of morphological computation (Pfeifer 2011) in robotics are: “Yokoi hand” which can grasp any shape, acting through self-regulation; “Passive dynamic walker” – the brainless robot who walks down the slope; for which the dynamics of the interaction with the environment is used for self-stabilization and "Insect walking" with no central control for leg-coordination but global communication through interaction with the environment.

6 Morphological Computing as Information Self-structuring

In morphological computation, generation of sensory stimulation is achieved by the interaction with the environment through constraints imposed by the morphology and materials. Through this interaction with the environment, generation of correlations in sensors (self-structuring of sensory data) is achieved by physical process. *The induction of correlations leads to reduction of complexity*. Interaction occurs across multiple time scales between body and control structure of an agent, and its environment. According to (Lungarella et al. 2005) "sensory input and motor activity are continuously and dynamically coupled with the surrounding environment." and "the ability of embodied agents to actively structure their sensory input and to generate statistical regularities represents a major functional rationale for the dynamic coupling between sensory and motor systems. *Statistical regularities in the multimodal sensory data relayed to the brain are critical for enabling appropriate developmental processes, perceptual categorization, adaptation, and learning*" (emphasis added). (Mirza et al. 2007) present an embodied, grounded individual sensorimotor interaction history, based on information theoretic metric space of sensorimotor experience, dynamically constructed as the robot acts in the environment. (Lungarella and Sporns 2005) give details of the study of the *coupling and interplay across multiple time scales between the brain, body, and environment*. Their findings are supported by the results of (Der 2011). It is important to notice that structures emerge on all levels of control:

> *Embodied interactions impose statistical structure not only on "raw pixels" within primary sensory channels, but also (and perhaps more powerfully so) on neural activity patterns far removed from the sensory periphery. We predict that embodied systems operating in a highly coordinated manner generate information and additional statistical regularities at all hierarchical levels of their control architectures, including but not limited to the immediate sensory input. (Lungarella and Sporns 2005)*

The above mechanism provides the basis for the evolutionary understanding of embodied cognition and knowledge generation. (Dodig Crnkovic 2008) In the process of self-organization of information, the states of the distant parts of the system are synchronized by *stigmergy* - indirect coordination between agents or actions. The trace left in the environment by an action increases the probability of the next action; so subsequent actions reinforce and build on each other, resulting in a coherent behavior.

The results on self-organization of information and the development of embodied cognition in living organisms have inspired the research program in *developmental robotics*. Learning is a continuous and incremental process and development proceeds through morphological change, growth and maturation. Boundary conditions and physical limitations play an important role in the development of an agent, as they cause reduction of the amount of information. Motor learning results in the reduction of space of possible movements and enables acquisition of motor skills through exploratory activity in the environment. It has been noticed that the greatest learning occurs in childhood when the most vigorous growth occurs. (Elman 1993) showed in training of networks to process complex sentences that neural processing limitations appear advantageous as they contribute to gradual learning. In a new born child initial low resolution vision successively increases, and coarse control becomes gradually more fine-grained (Pfeifer 2011) as learning proceeds. Only simple organisms are born in their final form, while for complex organisms, development seems necessary in order to successively achieve complexity, while avoiding chaos.

7 Info-computational Character of Morpohogenetic Computing

Morphological computation makes visible essential connections between an agent's body, (nervous) control and its environment. Through the embodied interaction with the environment, in particular through sensory-motor coordination, *information structure is induced in the sensory data, thus facilitating perception, learning and categorization*. The same principles of morphological computing (physical computing) and data self-organization apply to biology and robotics. Interesting to note is that in 1952 Alan Turing wrote a paper proposing a chemical model as the basis of the development of biological patterns such as the spots and stripes on animal skin, (Turing 1952). Turing morphogenesis did not originally claim that physical system producing patterns actually performed computation. Nevertheless, from the perspective of info-computationalism we can argue that *morphogenesis is a process of morphological computing*. Physical process – though not "computational" in the traditional sense, presents natural (unconventional), morphological computation. Essential element in this process is the interplay between the informational structure and the computational process - *information self-structuring* and *information integration*, both synchronic and diachronic, going on in different time and space scales.

Morphology is the central idea in understanding of the connection between computation (morphological/morphogenetical) and information. Materials represent morphology on the lower level of organization – the arrangements of molecular and atomic structures i.e., how protons, neutrons and electrons are arranged on the level below.

Info-computational naturalism describes nature as informational structure – a succession of levels of organization of information. Morphological computing on that informational structure leads to new informational structures via processes of self-organization of information. Evolution itself is a process of morphological computation on a long-term scale. It will be instructive within the info-computational framework to study processes of self organization of information in an agent (as well as in population of agents) able to re-structure themselves through interactions with the environment as a result of morphological (morphogenetic) computation.

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WLIMES, the Wandering LIMES: Towards a Theoretical Framework for Wandering Logic Intelligence Memory Evolutive Systems

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Abstract. This paper compares two complementary theories, Simeonov's Wandering Logic Intelligence and Ehresmann's & Vanbremeersch's Memory Evolutive Systems, in view of developing a common framework for the study of multi-scale complex systems such as living systems. It begins by a brief summary of WLI and MES, then analyzes their resemblances and differences. Finally, the article provides an outlook for a future research.

Keywords: Wandering logic intelligence, Memory evolutive systems, Hierarchy, Emergence, Self-organization, Autopoiesis, Genetic transcoding, Virtualization, Distribution, Non-locality, Category theory.

1 Introduction

This paper is divided in 3 parts:

(i) The first one gives a brief summary on the Wandering Logic Intelligence (WLI); a biology-inspired theoretical and practical framework for designing evolutionary communication architectures and their services and applications in terms of an always growing model of ever changing software and hardware. The WLI approach represents a next step of network virtualization and evolution of application- and user-aware networks as adaptive systems consolidating both network element and infrastructure flexibility. Now this approach is taken back to biology to model the operational semantics of complex emergent formations and processes.

(ii) The second part presents the main ideas at the basis of the Memory Evolutive Systems; a dynamic model for self-organized multi-scale complex systems such as living, cognitive or social systems; these systems have a hierarchy of components changing over time, and their dynamic is modulated by the cooperation/competition between a net of agents, the co-regulators, each operating locally with its own rhythm, function and logic. The model is based on a dynamic category theory which gives tools for representing the notion of hierarchy. It emphasizes 2 main properties of such systems: the Multiplicity

Principle, a kind of 'flexible redundancy' which is shown to be at the root of the emergence of higher complexity, robustness and flexibility; and the synchronicity laws that the co-regulators must respect and which generate cascades of failures/repairs at different levels.

(iii) The third part compares the above two theories and stresses their complementarity. It suggests how they could be merged into a common framework, the Wandering LIMES, which would add more structure on the WLI, and more quantifications to make the MES accessible to some sort of "computation".

2 The Wandering Logic Intelligence

The following paragraphs provide a summary of the WLI theory.

2.1 Overview

The *Wandering Network, WN* (Simeonov, 1998, 1999a, 2001) is a generalization for programmable and active networks based on a fomalism called the *Wandering Logic Intelligence*, *WLI* (Simeonov, 1999b, 2002a/b) and defined by:

- flexible, multi-modal specialization of network nodes as virtual subnetworks;
- mobility and virtualization of the net functions in hardware und software;
- self-organization as multi-feedback-based topology-on-demand.

The Wandering Network exhibits three essential characteristics:

1. it is a *hyper*active network which means that it is programmable and reconfigurable, incl. the network hardware up to the gate level;
2. it is a runtime extensible and exchangeable network in terms of both software and hardware components (a *wandering network)*;
3. it is an evolutionary network which realizes *adaptive* self-distribution and replication of sub-networks:
   - by guided or autonomous node and component mobility in terms of hardware;
   - by including network engineering information in the mobile code of the active packets and applying *genetic transcoding* mechanisms in the active mobile nodes.

In particular, network elements can contain several exchangeable modules capable of executing diverse network functions in parallel. These functions can be invoked, transported to or generated in the nodes upon delivery of mobile code containing programs about the node’s behaviour. An essential characteristic of the WLI approach is, however, the inherent ability to instantly spread out information about architectural changes among the nodes by encoding *executable re-constructon (genetic) instructions* within the transported active packets – as *“network” genes, N-genes.*

The *Wandering Logic Intelligence* (Simeonov, 1999b, 2002a/b) is a theory for modelling Wandering Networks. WLI generalizes active networks' capsules (Tennenhouse, et al., 1996; Kulkarni & Mindem, 1999) in *shuttles* as relatively autonomous mobile components including both programs and data possibly encoded in a language with (semantic) references to ships (active mobile network nodes, also called *netbots*) and other shuttles within the same or a different flow (protocol). Furthermore, the WLI model allows the creation of new capsules/shuttles (or the replication of "old" ones) in the intermediate netbots. In addition, a special class of shuttles, called jets are allowed to replicate themselves and to create, remove, or modify other capsules and resources in the network.

The essential contributions of the WLI model and the resulting Wandering Network are:

1. Role Change: The *role* of the network node within a particular virtual architecture can change during its operation. The new functionality is either resident on the node and waiting to be activated, i.e. it is not yet involved in the next step virtual scheme, or transferred to the destination node.
2. Parallel Roles: The execution of the parts of a distributed algorithm can be performed within the different roles of an active node's / ship's, configuration.
3. *Node Genesis ("N"-geneering):* encoding and embedding the structural information about a mobile node, the ship, and its environment into the executable part of the active packets, the shuttles (Simeonov, 2002c).
4. *Non-local Interdependence:* undeterministic distribution of system/network properties by means of active packets (shuttles) containing both code/commands and data.

Now, we propose to use WLI for modeling biological networks. In the following section we present the WLI design principles.

2.2 The WLI Principles

The goal of the *Viator* approach (Simeonov, 2002b) is to propose and demonstrate a simple and flexible mechanism for network evolution based on the emergence, change and movement of functional units within a given physical network infrastructure which recognizes its own boundaries. Such a network is known as *autopoietic system.*

The Wandering Network is based on the following WLI principles:

1. Dualistic Congruence (DC)
2. Self-Reference (SR)
3. Multidimensional Feedback (MF)
4. Pulsating Metamorphosis (PM)
5. Resource Usage and Availability (RUA)

The first four principles were defined in (Simeonov, 2002a/b), whereas the last one was added later in the HiPeer architecture (Wepiwé, & Simeonov, 2005-2006) which was based on the WARAAN algorithm (Simeonov, 2002a/c). The WLI program implementation is based on Lamport's Temporal Logic of Actions, TLA (Lamport, 1994) for generating C/C++ code.

2.2.1 The Dualistic Congruence Principle

The Wandering Logic model is based on: a) the dual nature of the *ployons*, the active (mobile) network component abstractions in their two manifestations, *ships/netbots* and *shuttles*, and b) on their congruence. The Dualistic Congrunce Principle (DCP) states that a ship's architecture reflects the shuttle's structure at some previous step and vice versa.

Thus, *ships* are both reconfigurable computing machines and active mobile nodes in terms of hardware and software. Shuttles transport software which can activate / replace ships and their components/aggregates.

A ship processing shuttles can change its state and re-configure its resources and connections *a posteriori* for further actions. In addition, it can adapt (itself) *a priori* to communications in such a way that it can anticipate and *best-match the structure of the shuttles at their arrival time.* Finally, a ship can also change the state of a shuttle.

*Shuttles***,** in turn, can be e.g. interpreted by a reconfigurable computing element inside a ship to build and/or invoke new functions. A shuttle approaching a ship can *re-configure itself* becoming a *morphing* packet to provide the desired interface and match a ship's requirements. This operation can be e.g. based on the destination address and on the class of the ship included in this address.

2.2.2 The Self-Reference Principle

Definition 1. The following characteristics identify a wandering network as *self-referring*:

- Each mobile node / ship knows best its own architecture and function, as well as *how* and *when* to display it to the external world. Ships are required to be *fair* and *cooperative* w. r .t. the information they display to the external world; otherwise they are excluded from the network community.
- Ships, are living entities: they can be born, live and die. Ships can also organize themselves into clusters based on one or more *feedback* mechanisms. Communication between the ships is realized through exchanging programs and data by means of *shuttles,* active packets, which may also contain encoded structural information about the ships or parts of the network itself. The structural information can be used to maintain the operation of the network as a whole, as well as to invoke desired or necessary changes in the infrastructure through service utilization and components' feedback.
- Each ship can acquire or *learn* some other function and extend its architecture by some additional functional components in software or hardware, as well as to become a (temporary) aggregation (a cluster) of other nodes with a joint architecture and functionality.

The *Self-Reference Principle (SRP)* addresses the *autopoiesis* and autonomy properties of the WN elements.

2.2.3 The Multidimensional Feedback Principle

The *feedback principle* in network engineering is well known in protocol design for applications such as traffic control. However, not all degrees of freedom have been exploited until now. A network offers much better opportunities to address e.g. traffic issues on a *per-service* basis than on per-devices alone. This actually corresponds to a dynamic change (re-configuration) of the network topology and resources in *multiple dimensions.* A Wandering Network provides a number of means for such a solution. Here is where the multiple dimensions come from. The number of such interoperating feedback dimentions is virtually unlimited.

2.2.4 The Pulsating Metamorphosis Principle

The generic process of network self-creation and self-organization is referred to as the *Pulsating Metamorphosis Principle (PMP).*

Definition 2. The *Pulsating Metamorphosis Principle* postulates that:

- There are two types of moving network functionality from the center to the periphery and vice versa inside a Wandering Network which are referred to as *pulsating metamorphosis*: horizontal, or inter-node, and vertical, or intra-node, transition.
- A net function can be based on one or more facts (events, experiences). The combination of net function and facts is called a *knowledge quantum* (*kq)* in the WLI model. Knowledge quanta are a new type of capsules which are distributed via shuttles in the Wandering Network. Net functions and facts can be recorded by, stored in and transmitted between the ships. They can be selectively processed inside the ships and distributed throughout the Wandering Network (WN) in an arbitrary manner.
- Facts have a certain *lifetime* in the Wandering Network. This lifetime depends from the clustering of facts inside the ships (knowledge base), as well as from their transmission intensity, or bandwidth (known as “weight”). As soon as a fact does not reach its frequency threshold, it is deleted to leave space for new facts. Since net functions are based on facts, their lifetime (and hence, the lifetime of the corresponding network constellations) depends on the facts. Which facts determine the presence of a particular function inside the Wandering Network is defined individually for each function. Through the exchange and generation of new facts, it is possible to modify functions in order to prolong their lifetime. The *kq* lifetime is defined by the lifetime of its network function. A modification of a net function is determined by a new set of knowledge quanta.
- Network elements can encode and decode their state in knowledge quanta. This mechanism is called *genetic transcoding.*
- A net function can emerge on its own (the *autopoiesis* principle) by getting in touch with other net functions (i.e. states and net constellations), facts, user interactions or other transmitted information. *The function defines the network and vice versa.* We call this new property *network resonance.*

The network resonance is the leading WLI characteristic and can be regarded as a kind of adaptive meta-policy for network development. With its help, clusters and constellations of network elements or their functions can be (self-)correlated, i.e. structurally coupled, and/or (self-)organized in groups, classes and patterns and stored in the cache of the single nodes/ships or in the (centralized) long term memory of the network, in order to be used later as a decision base or as a development program for particular processes in the network.

The above four principles define the overall concept framework of the Wandering Network, (Simeonov, 1998-2001).

2.2.5 The Resource Usage and Availability Principle (RUAP)

The Resource Usage and Availability Principle (RUAP) was defined and realized in the HiPeer architecture (Wepiwé, & Simeonov, 2005-2006). It simply states that the more the network resources are used, the more stable and reliable, i.e. the more strain-hardened the architecture becomes. This principle acts against the high plasticity of the other four principles and stimulates the development of reinforced structures and pathways. The latter capability is closely related to the AI concepts of pattern recognition, learning and self-awareness, thus representing an important advantage in evolutionary and cognitive networking which can be further developed towards truly intelligent, i.e. *conscious* network environments and infrastructures. RUA can have many different realizations in terms of naturalistic computation; HiPeer is only one of them.

3 The Memory Evolutive Systems Theory

The Memory Evolutive Systems (MES) give an integrative dynamic model for self-organized multi-scale evolutionary systems, such as biological, neuro-cognitive or social systems. Such systems are characterized by several kinds of multiplicities:

i. a tangled hierarchy of interconnected complexity levels varying over time;
ii. existence of multiform components (*Multiplicity Principle*) at the root of emergence and flexibility;
iii. a multi-agent multi-temporality self-organization, in which each agent (called *co-regulator*) has its own logic and operates stepwise at its own rhythm, though the discrete time-scales of the agents must synchronize in function of the global continuous 'time-clock' (*Synchronicity Laws*);
iv. a hierarchical central 'memory', both robust and flexible that allows for learning, self-repair and adaptation.

This model, developed by A. Ehresmann and J.-P. Vanbremeersch since 1987 (cf. the book of Ehresmann & Vanbremeersch 2007 for more details) is based on a 'dynamic' category theory integrating Time.

To account for the dynamic 'in progress', the system is not represented by a unique category (as in models giving a logic model of the invariant structure; e.g., Rosen, 1985 and his followers: Louie, 2009, Nomura 2012), but by an *Evolutive System* **K**, that is a family of 'configuration' categories K_t indexed by Time, and partial 'transition' functors between them.

3.1 Description of a MES. Multiplicity Principle and Its Consequences

3.1.1 MES as an Evolutive System K

The category K_t represents the configuration of the system at time *t*; its objects model the states of the components of the system existing at *t*, the morphisms (called *links*) channels through which information (or constraints...) can be transmitted between them. Each link has a *propagation delay* and can be *active* or *passive* depending if some information is transmitted or not through it around *t*. In the WLIMES project, this transmission will be effected by a *shuttle* in the WLI sense.

The transition from K_t to $K_{t'}$ connects the state of a component C or a link at *t* to its new state at *t'*, if it still exists at *t'*. This transition allows measuring the changes between 2 'snapshots' of the system but does not describe the continuous dynamic which has generated them.

3.1.2 The Hierarchy of Components

The components around a time *t* are divided into complexity levels, so that a component C of level n+1 acts as the aggregate of a pattern P of linked lower level components which it 'binds'. Thus C has the same functional role that its decomposition P acting collectively. Formally C is modeled by the categorical "*colimit"* of P (or inductive limit, Kan, 1958).

While a pattern has at most one colimit (up to isomorphisms), different patterns may have the same colimit. It allows explaining how a complex component C may preserve its *complex identity* (or "class identity" in the terms of Matsuno (2012)) while its composition varies; for instance the molecules of a cell are progressively replaced without affecting the complex identity of the cell. The rapidity of the change is measured by the *stability span* of C at *t*: it is the longest period *dt* such that C exists and admits a lower order decomposition which maintains its working conditions from *t* to *t*+*dt* not included (Ehresmann & Vanbremeersch, 1987). In particular the stability span of the cell has a magnitude order greater than that of its molecules, looked at separately.

Among the links from C to another component C', there are *n-simple links* which bind together a cluster of links between decompositions P of C and P' of C' of levels $\leq n$. These links just reflect properties already observable through lower level components of C and C'. However, there may also exist more *'complex'* links which 'emerge' at level n+1 thanks to the following characteristic of MES, explained below.

3.1.3 The Multiplicity Principle

The Multiplicity Principle, MP (Ehresmann & Vanbremeersch, 1996) models a kind of *flexible redundancy*, also called *degeneracy* in biology where it is

> " a ubiquitous biological property [...] a feature of complexity [...], both necessary for, and an inevitable outcome of, natural selection." (Edelman & Gally, 2001)

Formally MP asserts the existence of *multiform components* C which can operate, simultaneously or not, as aggregates of several lower level patterns P and Q possibly structurally non-equivalent and not connected by a cluster; and C can switch between them. Such switches will give robustness and flexibility to the system, in particular by allowing the formation of *n-complex links* which are composites of n-simple links binding non adjacent clusters. Though depending on the global structure of the levels $\leq n$, these links are not observable locally at these levels; they display properties emerging at the level $n+1$.

3.1.4 MP at the Root of Complexity

The level of a component C does not always reflect its 'real' complexity, which would correspond to the least number of binding processes necessary for re-constructing C from level 0 up (to be compared with Kolmogoroff-Chaitin 'complexity').

For that, we define the c*omplexity order* of C as the least length of a ramification down to level 0, a *ramification* being obtained by taking a lower level decomposition of C, then a lower level decomposition of each component P_i of P, and so on, down to components of level 0. A main theoretical result of this definition is the following

COMPLEXITY THEOREM (Ehresmann & Vanbremeersch, 1996). *MP is necessary for the existence of components of complexity order* > 1.

If MP is not satisfied, every component would be the aggregate of a pattern of components of level 0, as in a *pure reductionism.*

3.1.5 Complexification

The change of configuration from t to t' is due to operations of the following kinds: destruction of some components, decomposition of some complex components, addition of components, in particular by formation of a new component becoming the aggregate of an already existing pattern of linked components. It is modelled by the *complexification process* with respect to a *procedure* S having such objectives.

The complexification $K_{t'}$ of K_t with respect to S is explicitly constructed (Ehresmann & Vanbremeersch, 1987). It could be computed using the MGS language (Giavitto & Sprecher, 2008).

EMERGENCE THEOREM. *MP is preserved by iterated complexifications. It is necessary for the emergence over time of components of increasing complexity order. Moreover it intermingles the Aristotelian material, formal and efficient causes of the transitions.*

It follows that MP is a characteristic distinguishing "organisms" (such as MES) from "mechanisms" in the terms of (Rosen, 1985).

Remark. A procedure S can be interpreted as specifying a change of logic, which the complexification implements. Indeed, S leads to the construction of a mixed sketch, admitting the complexification as its prototype (constructed by A. & C. Ehresmann, 1972). Now it is known (Duval & Lair, 2002) that a mixed sketch can be interpreted as the diagrammatic presentation of a type of structure axiomatisable by a second order logic and the complexification gives a model of the corresponding theory. It can also be interpreted as the oriented object specification of an abstract type of data, thus opening the way for the complexification to be 'computable'.

3.2 Multi-scale Self-organisation of a MES and the Dynamics it Generates

The dynamics of a MES is modulated by the competition/cooperation between a heterarchical net of specialized functionally evolutive subsystems, the *co-regulators* (CRs). Each co-regulator has its own complexity, rhythm, logic, and a differential access to a central long-term *memory* which develops by learning and has robustness, flexibility and plasticity thanks to MP. The global logic/semantics of the system results from an interplay among the local logics/semantics of these co-regulators. The local constraints not respected by the resulting logic should be repaired later, perhaps causing cascades of events backfiring between levels.

3.2.1 One Step of a Co-Regulator (CR)

A Co-Regulator (CR) operates locally as a hybrid system, by a stepwise process at its own discrete timescale, one step extending between 2 successive instants of this timescale. The step decomposes in several more or less overlapping phases:

i. Formation of its *landscape at moment t* (modelled by a category L_t) with the partial incoming and/or remembered information transmitted to CR by active links.
ii. Selection (with the help of the memory) of a procedure S to respond (it should lead to the complexification AL of L_t by S).
iii. Sending commands to the effectors to realize S. It starts a dynamic process which unfolds during the continuous time of the step, possibly computable by differential equations, implicating the propagation delays and strengths of the links.
iv. The result is evaluated at the beginning *t'* of the next step by comparing AL to the new landscape. There is a *fractu*re for CR if the step is interrupted, or if the objectives of S are not met.

3.2.2 Temporal Constraints: The Synchronicity Laws

The step duration of CR beginning at moment *t* must be long enough so that CR may form its landscape, select a procedure S and send its commands to effectors. And during this time, the components in the landscape must preserve their overall internal organization up to the end of the step, in spite of the turnover of their lower order components. It follows that CR must respect the temporal constraints expressed by the following *Synchronicity Law*:

$$p(t) << d(t) << z(t)$$

where $p(t)$ is the mean propagation delay of the links intervening in the landscape at *t* and the commands of the procedure, $d(t)$ is the period of CR at *t* (= mean length of its close by preceding steps), and $z(t)$ is the smallest stability span of the components intervening in the landscape and the procedure (where “<<” means "of an order of magnitude lesser than").

The non-respect of one of these constraints is a main cause of dysfunction. A fracture not repaired soon enough causes a *dyschrony* of CR, and, if it persists, its repair may necessitate a change of period of CR, called *re-synchronization*.

3.2.3 The Interplay among Co-regulators

At the base of a MES, there is the "objective" continuous clock-time which helps coordinating the operations of the whole system. At a time *t*, the commands sent to effectors by the different co-regulators can be conflicting. Hence, there is a need of an equilibration process between them, possibly neglecting some of them.

This process, called the *interplay among the co-regulators*, leads to specify the operative procedure S° which will be really implemented on the system.

The interplay can take benefit of the degree of freedom given by the multiform components intervening in the various procedures; indeed they can operate through anyone of their lower level decompositions, with possible switches between them, allowing for a kind of selection to find the one most compatible with the other constraints.

Quantum processes can also have a role in this selection; it has been shown (Ehresmann & Vanbremeersch, 2002) that the existence of multiform components in biological systems takes its root in quantum processes occurring at the atomic level, and is extended to higher levels through successive complexifications.

3.2.4 Cascades of Dysfunction/Repair: Conclusion

The global logic specified by S° is a 'best compromise' between the different local logics specified by the various co-regulators; however it will cause more or less severe dysfunction to a co-regulator if its objectives are not realized, or if its synchronicity law cannot be respected.

A dysfunction of a co-regulator can backfire to others, with possibly severe consequences, such as loops of fracture/repair, possibly leading to the re-synchronisation of some co-regulator; or even a cascade of dysfunctions, itself leading to a cascade of re-synchronizations at various levels to avoid a "systemic disease".

Let us indicate some applications:

i. A physiologically inspired *Theory of aging* for a biological or a social organism through a cascade of re-synchronizations of co-regulators of increasing complexity (Ehresmann & Vanbremeersch, 1993).
ii. Efficient methods for ubiquitous complex events processing, in particular some methodology for anticipation in social systems such as large organizations, using switches between different realizations of multiform objects to generate complex scenarios.
iii. A main application is the model MENS for a neuro-cognitive-mental system (cf. Ehresmann, 2012, in this volume).

MES is a methodology in progress, still more qualitative than quantitative, and probably not amenable to 'usual' computations. This is where the idea for WLIMES, the Wandering LIMES (WLI + MES), project came from.

4 Can We Merge WLI and MES?

4.1 A Comparison of WLI and MES

WLI in is an evolving network architecture which is composed of dynamically reconfigurable network elements (netbots) which are generating and exchanging information about themselves and their surrounding environment (close neighborhood or 'local landscape') by means of active packets (shuttles) containing data and executable code for them. Shuttles are transporting various kinds of information (physical, algorithmic, topological, etc.).

A special kind of such local landscape information is the one about the formation of semi-stable patterns (spatial-temporal organization of entities and cyclic processes) incl. their discovery and communication mechanisms.

Co-regulators (CRs) in MES correspond to specialized subsystems of elements which are not necessarily disjoint, i.e. an element can belong to multiple CRs. Thus, CRs correspond to different (virtual) levels of structural and/or functional organization of the netbots. This organization is defined by the internal computation processes inside the netbot and by their external information delivered through the arriving shuttles.

While the components form an explicit hierarchy in MES, the CRs don't form a real hierarchy; their level comes from the level of their components, but a CR whose components are of level *n* does not aggregate CRs of lower levels. Netbots do not exhibit an explicit hierarchy. It is their landscapes at a given time which demonstrates a temporarily available internal composite hierarchy of structures and functions of their building elements interlinked with other elements and groups of them, in particular elements inside remote netbots. This composite hierarchy is changed stepwise (at the timescale of the CR) by that outcome of processing the shuttle information in combination with other internal and external exchange within the individual netbots and other components of the system. Herewith, the four WLI principles define the overall development of the network infrastructure.

The temporal and apparently undeterministic hierarchy of building different kinds of components, in particular elements inside the netbots and groups of them is guided by the 5th WLI principle, the Resource Usage and Availability Principle (RUA, cf. section 2.2.5), encouraging the development of stable structural-functional patterns of organization within and among the netbots. There might be different implementations of this principle such as differential logical distribution (Wepiwé, & Simeonov, 2005-2006). In P2P networks all the netbots are considered equivalent, unless a mechanism such as the Resource Usage and Availability Principle establishes a priority hierarchy. Some of them can have a biological character. In particular, in MES representing living systems, each CR has its own biological function.

Thus, the WLI architecture is complementary to a MES one. In a WLI, the mode of operation of the individual network elements (netbots) and their physical or virtual components depends on their processing/computation and on the result of interpretation/execution of the information/code contained in the arriving shuttles.

The transitions between netbots and their constituents execute a double function. On the one hand they illustrate such operations as addition, loss and binding of functional components inside a WLI closure or (sub)network. On the other hand, they represent unidirectional or bidirectional channels along which shuffles are transported. In MES, the links correspond to unique directed channels between the different components, which can be inter-levels (up or down) or intra-levels. The latter were implied in WLI in connection with the transmission of different types of shuttles.

One of the differences is that in MES there are also components (for instance in the memory, but not only there) which don't belong to CRs. The operations of a CR, such as the formation of its landscape, must also account for these other components. This is not the case with WLI yet.

The WN suggests a dynamic hierarchy within its multiple closures/(sub)networks. The netbots are cooperative; they negotiate their interplay/communication. They could be regarded as CRs in an emerging/development stage. Once the established channels between functional components/netbots become more frequently used, they can build semi-stable and permanent CRs and higher levels structural patterns of them. Hence, the CRs of a MES correspond to netbots or (virtual) clusters of them operating as units and always participating a WLI (sub)network; however the CRs are competitive and can be conflicting.

The reverse process is also possible. A WLI cluster/node can cease to operate/exist as a result of the interpretation/processing the information contained in incoming shuttles. Thus, a degradation/'aging' and even death of some parts of the wandering network is possible, thus enabling their replacement with new functional structures and links/channels between them. In the same manner operates the regeneration of same former dead areas of the network, once they involve living components, i.e. those at the edges of the network which maintain at least one connection to another netbot and capable to process its shuttles. The realization of such repair mechanisms depends on the particular 'regeneration' policies; the latter are matter of future investigation. In a MES both components and CRs may disappear either completely or through replacement by others, and new ones can be created (by aggregation of patterns) through the complexification process.

The memory in MES is centralized, with each CR having its own differential access to it, whereas in WLI it is distributed among the netbots, their components and the exchanged shuttles.

WLI's first duality principle suggests a duality between shuttles and netbots at the "arrival time" which means that the internal configuration/architecture and functionality of the netbot before the arrival of the shuttle changes in that manner after its arrival that it matches the structural and functional configuration (executable code) of the arriving shuttle after processing its information content. In other words, the shuttle causes changes in the netbot.

To which extent these changes result from evaluating and considering previous accumulation of such shuttle information and/or triggering/switching, integration/superposition or exclusion/differentiation between different types of signals, is left to the particular implementation of the mode of operation (operational semantics) of the WLI. This includes the selection of and the interplay between the 4+1 WLI principles.

In MES, there is a kind of duality between the situation at the beginning *t* and at the end *t'* of a step of the CR, caused by the information gathered in the landscape at *t* (through incoming 'shuttles'), and the selection of a procedure to respond by the CR.

On the other hand, the netbot also causes changes in the shuttle while processing it, thus influencing changes in other netbots receiving that shuttle at a later moment. This can be regarded as another incarnation of the dualistic congruence principle. In MES, the commands of the procedure selected by a CR transmit information (through 'shuttles') to other CRs, for instance to effector CRs such as the effectors of a 'muscular' command.

In summary, a WLI realization implies a multiplicity of evolving gates which operate in a highly undeterministic way. By definition the WLI nodes/gates cooperate to enable a self-stabilizing network architecture. However, they can also compete for some resource/function by involving some special reservation policies that can be transmitted by means of shuttles

The intelligence/plasticity of the system at the moment *t* is the instant result/response of the interplay between its constituting elements (components, netbots and interworking clusters of them). In MES the interplay is through the procedures of the different CRs at a given time, and its flexibility comes from the multiplicity principle allowing to process each command along its most adapted ramification.

4.2 Complementarities between MES and WLI

We found the following complementarities between our approaches.

(i) **Patterns.** CRs are initially defined as patterns of components; these patterns may bind ('aggregate') into high-level components, but it is not always the case. The reachability tree of the netbot corresponds to its abstract connectivity landscape (localization). A netbot's 'landscape' at a moment *t* contains only the connectivity/links active at this moment. In WLI information about this abstract landscape is spread out by means of shuttles; in MES the case is different, because the categories vary over time. The new information can be 'seen' through the transition functors by looking to what is new and what gets lost. A CR uses the information at a moment *t* by the fact that it is 'here'. This difference comes out of the fact that WLI is a system which varies, while MES is described by the family of its successive configurations, and the 'transitions' between them. The formation and recognition of structural spatio-temporal organization patterns in WLI is operational; it is part of the specific implementation which can be realized e.g. by labeled shuttles carrying archetypal n-genes, r-genes and t-genes to be identified in the processing netbots.

(ii) **Rhythms.** In MES each CR has its own rhythm; the interplay among the temporalities of different CRs has an important role in the interplay among CRs, for instance leading to a 'dialectics' between CRs of different complexity and short/long period; it is also important for the mechanisms of failure/repair which may backfire between CRs. It is not clear yet how such rhythms can be implemented in WLI.

(iii) **Distributed vs. Centralized Memory.** The memory in WLI is distributed inside the netbots and shuttles, while in MES there is a central memory to which each CR has a differential access. The distributed nature of the memory in WLI is operative, allowing the fast propagation of local and non-local system changes, whereas the centralized one in MES is both robust and flexible, allowing for adaptation to changing environmental conditions. .

(iv) **Hierarchy.** In MES the hierarchy is exquisitely described: a high-level component binding at least one pattern of lower ones. This allows the existence of multiform components (MP). In WLI the hierarchy is implicitly described by entailment relations between the building components inside the netbots and outside of them with other components in other netbots in terms of virtual closures/overlays. This is the mechanism in which a single netbot component can participate in different network overlay configurations. In MES this hierarchy concerns all the components. The CRs are sub-systems which inherit the complexity of their components, but they don't form a strict hierarchy. A higher CR may control different lower CRs, but not always and not strictly, depending on the MES.

(v) **Link Activation.** One of the problems with MES is that there is no explanation of how links are 'activated' at a given time/event (except for MENS). Therefore, we are intending to use shuttles representing information carried out by the links when they become activated. Shuttles are particularly interesting in 3 cases regarding the operational semantics of MES:

1. In the formation of the landscape of a CR at moment *t*: only the perspectives for the CR of links activated by a shuttle arriving about the moment *t* are retained in the landscape;
2. In the selection of a procedure, either by a CR or in the interplay among CRs, where the respective strengths of the payloads of the shuttles activating different admissible procedures (coming from the memory) will play a role.
3. In the commands of a procedure to its effectors, in particular during the interplay among CRs to form an operating procedure. Thus, shuffles will be at the base of the 'progressive' dynamics in MES.

(vi) **WLI Principles.**

1. The 'duality principle' of WLI reduces to a 'partial duality' in MES: on the one hand, the construction of the landscape of a CR at moment *t*, and the selection of its procedure depend on the information received by the CR through the shuttles which it ‘unpacks’; on the other hand, the realization of this procedure consists in 'packing' into shuttles the commands of the procedure to effector CRs.
2. The 'self reference' principle in WLI relates to the autonomy/autopoiesis, also valid for MES. However, in WLI it supposes that netbots always cooperate,

whereas in MES there is a possibility of conflicts between CRs which are at the basis of the interplay among CRs, thus allowing for the ubiquity, plasticity though robustness (and non predictability) of MES. As stated above, it is possible to develop mechanisms in WLI used by shuttles that stimulate competition among CRs. Thus, both policies, cooperation and competition among CRs, become possible.

3. The 'multiple dimensions' principle in WLI would be stronger in MES, since we have the various temporalities of the CRs and their differing logics (hence, the risk of competition and fractures). Furthermore, the development of the memory by learning/experience plays an essential role in MES, in particular in more complex MES (e.g. the application MENS to a neuro-cognitive system) where a sub-system called the *Archetypal Core* can develop to function out as an internal model of the system/self. This operational semantics can be also developed in terms of specific WLI implementations.
4. The 'pulsating metamorphosis' principle in WLI was initially related to the possibility of upscaling and downscaling the wandering network in terms of functional-structural elements (shuttles, netbots, their components and clusters). It could correspond to the double dynamics in MES: local (via CRs) vs. global (via their interplay). This appears to be also in relation with the development and use of memory. A further elaboration of the details of this principle in the MES context is necessary to optimally capture and exploit the synergies between WLI and MES. TLA (Lamport, 1994), which is the implementation base of WLI, combines the logic of actions with a temporal logic. It seems to be suitable to represent the 'hybridity' or dual nature of the CRs using: a) the logic of actions via commands of procedures, and b) a temporal logic via their realization during the next step of their effector CRs. Then the interplay among CRs adds a global logic on top of the different interacting temporalities and local logics. This model is implied in WLI for higher levels of organization of the wandering network (e.g. self-reflecting and 'conscious' networks), but not explicitly stated. Therefore, the specific realization in terms of MES needs to be further elaborated.
5. The 'resource usage and availability' principle in WLI is a guidance directive for the formation of semi-stable and permanent network configurations based on the modes of their exploitation. It could have a number of implementations, incl. e.g. the realization of specific policies for competition among CRs transported by 'marked' shuttles. The particular application of this principle in MES context should be further investigated.

(vii) **MES Principles.**

1. The 'Multiplicity/degeneracy Principle' (MP) in MES which ensures that different patterns, possibly not structurally equivalent nor even well connected, can be functionally equivalent. As explained in Section 3.2 it is at the root of the emergence of higher complexity, robustness and flexibility.
2. The 'synchronicity laws' which must be respected by each co-regulator, at the root of ubiquitous complex events (cf. Section 3.2.2)

(vii) **Safety and Liveness.** These properties are important in the context of computing and networking systems to guarantee their robustness in case of failures. They were essential for the original WLI application domain. However, in multi-scale complex systems modeled in MES, there is both the risk of fractures and the possibility of developing repair mechanisms (e.g. by re-synchronization of some CRs).

It is not yet clear how to embed the safety and liveness properties in biological context. Further investigations are required to answer this question.

5 Conclusions and Outlook

This analysis shows that WLI and MES present important complementarities:

WLI

- provides a formal means for the specification and verification of the generic temporal properties of netbots and shuttles;
- supports the reflexive dynamic adaptation of both mobile code (software) and node architecture (software and hardware);
- provides the formal means for specification and verification of dynamic properties in ad-hoc mobile networks;
- assists the formal transformation of the systems' properties into mobile code.

These capabilities allow the WLI usage in modeling the operational semantics of complex biosyntheic systems.

MES proposes a developing methodology in a well-structured frame emphasizing important properties of multi-scale, and multi-agent multi-temporality systems (Multiplicity Principle, Synchronicity Laws) at the basis of the emergence of complexity, self-repair, learning and adaptation; however it remains mostly qualitative.

Our WLIMES project proposes to develop a theoretical frame englobing these two theories, so that each one benefits from the stronger aspects of the other. The target would be to obtain a dynamic model for complex systems, in particular for living systems, demonstrating most properties of both systems, and accessible to some kind of 'computation'.

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A Proposal for Combination of Category Theory and λ–Calculus in Formalization of Autopoiesis

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Abstract. There have recently been some computational or mathematical formalization studies on closedness of living systems such as autopoiesis and (M,R) systems. In particular, some have mentioned relationships between cartesian closed categories and λ–calculus. Following this line, the paper proposes a framework to formalize autopoiesis by combining category theory and λ–calculus more strictly, by introducing an equivalence between the category of cartesian closed categories and that of λ–calculi while providing a formalization of the distinction between organization and structure in autopoietic systems.

Keywords: Autopoiesis, category theory, λ-calculus, operational closure, Cartesian closed category, organization, structure.

1 Introduction

Autopoiesis gives a framework in which a system exists as an organism through physical and chemical processes, based on the assumption that organisms are machinery [8,9]. This system is organized as a network of processes of production of components, where these components continuously regenerate and realize the network that produces them, and constitute the system as a distinguishable unity in the domain in which they exist. However, the system description of autopoiesis includes circular closedness of relationships between components, and it is hard to interpret the definition from the perspective of the existing computational and dynamical systems. For solving this difficulty, some formal models have been proposed to represent its characteristics. McMullin [10] has studied a computational model of autopoiesis as 2-D biological cells. Bourgine and Stewart [1] proposed a mathematical formalization of autopoiesis as random dynamical systems, and explored the relationships between autopoiesis and cognitive systems. Egbert and Di Paolo [4] proposed an artificial chemistry model to represent autopoiesis.

Moreover, some research works have mentioned the similarity of autopoiesis with metabolism-repair ((M,R)) systems, which are an abstract mathematical model of biological cells proposed by Rosen [14], from the perspective of closedness of the systems. Letelier et al., [7] reviewed (M,R) systems and provided them with an algebraic example which suggested the relationship with autopoiesis. Chemero and Turvey [3] proposed a system formalization based on hyperset theory and found a similarity between (M,R) systems and autopoiesis on closedness.

The author also proposed some mathematical models of autopoiesis while connecting between closedness of autopoiesis and (M,R) systems, based on category theory [12,13]. On the other hand, recently, Mossio, Longo, and Stewart [11] showed that closedness of (M,R) systems can be formalized within λ–calculus by using category theory, that is, some properties of Cartesian closed categories corresponding to λ–calculus. Moreover, Cárdenas et al., [2] critically discussed their work. In the sense that a Cartesian closed category is used in the model of autopoiesis by the author, these studies lead to a common framework for discussing relationships between closedness of autopoiesis and its implementation within computational formal systems.

For encouraging the discussion about closedness of autopoiesis and its computational formalization, in particular, about closedness in organizations and dynamics in structures, this paper proposes a framework of a research program by a combination of category theory and λ–calculus, based on the models previously proposed.

2 Completely Closed Systems: Revisited

The author proposed "completely closed systems" under entailment between components in a category with specific properties and a distinction between organization of components and structure among elements by introducing functors between the categories [12,13]. As mentioned in the previous section, the systems are defined within a cartesian closed category [6].

We assume that an abstract category $\mathscr{C}$ has a final object 1 and product object $A \times B$ for any pair of objects A and B. The category of all sets is an example of this category. Moreover, we describe the set of morphisms from A to B as $H_{\mathscr{C}}(A,B)$ for any pair of objects A and B. A element of $H_{\mathscr{C}}(1,X)$ is called a morphic point on X. For a morphism $f \in H_{\mathscr{C}}(X,X)$ and a morphic point x on X, x is called a fixed point of f iff $f \circ x = x$ ($\circ$ means concatenation of morphisms) [15]. Morphic points and fixed points are respectively abstraction of elements of a set and fixed points of maps in the category of sets.

The fact that the components reproduce themselves in a system implies that the components are not only operands but also operators. The easiest method for realizing this implication is the assumption of the existence of an isomorphism from the space of operands to the space of operators [5].

When there exists the power object Y^X for objects X and Y (that is, the functor $\cdot \times X$ on $\mathscr{C}$ has the right adjoint functor $\cdot^X$ for X), note that there is a natural one–to–one correspondence between $H_{\mathscr{C}}(Z \times X, Y)$ and $H_{\mathscr{C}}(Z, Y^X)$ for any objects X, Y, Z satisfying the diagram in the upper figure of figure 1. Thus, there is a natural one–to–one correspondence between morphic points on Y^X and morphisms from X to Y satisfying the diagram in the lower figure of figure 1. This property is the condition for which $\mathscr{C}$ is a cartesian closed category.

Now, we assume an object X with powers and an isomorphism $f : X \simeq X^X$ in $\mathscr{C}$. Then, there uniquely exists a morphic point p on $(X^X)^X$ corresponding to f in the above sense, that is , $p' = f$. Since the morphism from X^X to $(X^X)^X$ entailed by the functor $\cdot^X$, f^X, is also isomorphic, there uniquely exists a morphic point q on X^X such that $f^X \circ q = p$. We can consider that p and q entail each other by f^X. Furthermore, there

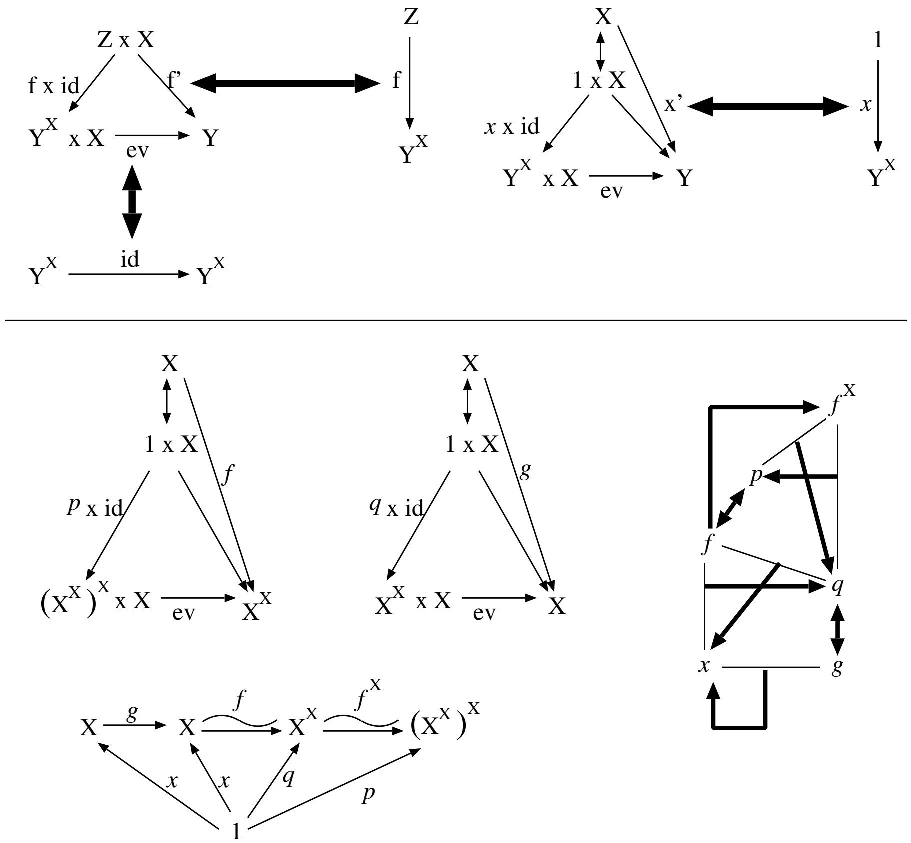

Fig. 1. The Diagrams of a Completely Closed System and the Entailment Relations based on Natural One–To–One Correspondence

uniquely exists a morphic point x on X such that $f \circ x = q$ because f is isomorphic. Since we can consider that x and q entail each other by f, and f and p entail each other by the natural correspondence, the system consisting of x, q, p, f, and f^X is completely closed under entailment. Moreover, if x is a fixed point of $g : X \to X$ naturally corresponding to q, that is, $g \circ x = x$, we can consider that x entails itself by g. The lower figure of Figure 1 shows the diagrams of this completely closed system and the entailment relations.

3 Distinction between Organization and Structure: A Combination with λ–Calculus

In [12,13], the author proposed a model of distinction of structures and organizations in autopoiesis. If circular relations between components and their production process network are closed under entailment, this closedness may be hard to formalize in a general category such as state spaces. On the other hand, the structure of an autopoietic system must be realized in a state space as a physical one (as shown in the upper figure

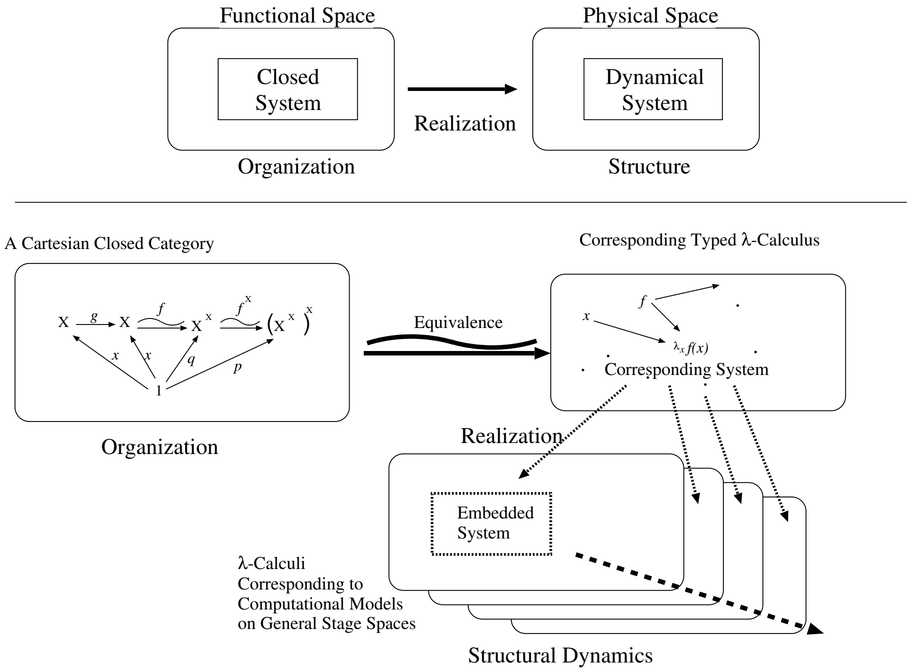

Fig. 2. Aspect of Autopoiesis based on Distinction between Organization and Structure, and Its Category Theoretical Formalization

of Figure 2)[1]. In the model, the organization is formalized in a specific category, that is, as a completely closed system in a Cartesian closed category. Then, the structure is formalized in the category of general state spaces, and realization from the organization to the structure is represented by a functor between the categories.

However, this framework does not argue for any concrete definition of the category of structure or functors. Moreover, the model consists of a family of Cartesian closed categories which include completely closed systems representing the same organization, and one general state space. The model can represent a structural dynamics on a state space based on the organization. However, it cannot include higher dynamics in which the state space itself changes, as, for example, occurs in metamorphoses of life systems. To overcome these problems, the paper proposes the introduction of categorical equivalence between cartesian closed categories and typed λ–calculi into the distinction between organization and structure in the model of autopoiesis.

According to Lambek and Scott [6], a cartesian closed category generates a category of typed λ–calculus, a category of typed λ–calculus generates a cartesian closed category, and the functors by these generations induce the equivalent relation between the category of cartesian closed categories and that of typed λ–calculi. The framework to be proposed in the paper consists of the following items (shown in the lower figure of Figure 2):

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[1] This distinction is mentioned in Maturana and Varela's original literature [9].

1. A completely closed system as an organization is formalized in a cartesian closed category.
2. There exists a system in the typed λ–calculus corresponding to the completely closed system.
3. Realization is formalized by embedding the system in the typed λ–calculus into a more general λ–calculus corresponding to a computational model in a state space.
4. In order that components of the embedded system are repeatedly entailed within the organization, another general λ–calculus is found and the original system is repeatedly embedded into it.

4 Discussion

The framework proposed in the paper differs from the study of Mossio et al., [11], which showed a possible formalization of closedness of (M,R) systems on λ–calculus. Although autopoiesis requires distinction between organization and structure, the form of (M,R) systems does not include the explicit distinction between closed organizations and structures realized in state spaces, and these concepts are confused [13]. Although Mossio et al., [11] used some properties of cartesian closed category, closedness of (M,R) systems is discussed only on the category of structure. In the proposed framework, closedness of a system is dealt with on cartesian closed categories, and then the corresponding structure is discussed.

The framework proposed in the paper has an advantage. Cartesian closed categories on which completely closed systems are defined are a specific subcategory in which an isomorphism exists between operands and operators. By considering the relationship between this specific category and the corresponding subcategory in the category of typed λ–calculi, what type of computational model is needed to realize systems with operational closure, (that is, what class of computation is required for formalization of operational closure) can be investigated. More strictly, we can investigate whether the form of λ–calculus corresponding to a completely closed system can be embedded into general λ–calculi corresponding to computational models on general state spaces, and whether operationally closed systems can be formalized as computational models, by this investigation.

The framework in the paper is currently at the stage of a proposal. It is most important to clarify the form of closed organization in typed λ–calculus based on mathematically strict relationships between Cartesian closed categories and typed λ–calculi, and the form of embedding from the specific typed λ–calculus to general λ–calculi. Moreover, it should be extended to more general systems with operational closure.

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A Dynamic-Epistemic Logic for Mobile Structured Agents

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Abstract. Multi-agent systems have been studied in various contexts of both application and theory. We take Dynamic Epistemic Logic (DEL), one of the formalisms designed to reason about such systems, as the foundation of the language we will build.

BioAmbient calculus is an extension of π-calculus, developed largely for applications to biomolecular systems. It deals with ambients and their ability to communicate and to execute concurrent processes while moving.

In this paper we combine the formalism of Dynamic Epistemic Logic together with the formalism of BioAmbient Calculus in order to reason about knowledge maintained and gained upon process transitions. The motivation lies in developing a language that captures locally available information through assignment of knowledge, with potential application to biological systems as well as social, virtual, and others.

We replace the ambients of BioAmbient Calculus with agents, to which we attribute knowledge, and explore the parallels of this treatment. The resulting logic describes the information flow governing mobile structured agents, organized hierarchically, whose architecture (and local information) may change due to actions such as *communication*, *merging* (of two agents), *entering* (of an agent into the inner structure of another agent) and *exiting* (of an agent from the structure of another). We show how the main axioms of DEL must be altered to accommodate the informational effects of the agents' dynamic architecture.

Keywords: dynamic epistemic logic, mobile agents, structured agents, multi-agent system, subagent, indistinguishability of states, knowledge (logic), bioambient.

1 Introduction

We develop a formalism $\mathscr{PADEL}$ suited for talking about various multi-agent systems. In particular, we discuss previous and potential applications to systems of molecular biology, though the language is not limited to this. We develop the notion of an *agent*, which can refer to an entire system or a subsystem thereof, all seen as *informational* (and *information-acquiring*) systems. Information locally available to a given system is treated as *knowledge* and the flow and exchange of information between systems as *dynamics of knowledge* in a multi-agent setting. For all of the above, we rely on a formalism derived from Dynamic Epistemic Logic and BioAmbient Calculus.

We assume the following things about the architecture of these agents: First, the number of agents (and thus subagents) is always finite. Second, they are nested in a dynamic tree structure (with no loops).

In addition to typical communication actions, such as sending and receiving information or public announcements, we consider three specific actions which involve mobility: entering, exiting, and merging. The formalisation and the specific rules for the latter are inspired largely by Luca Cardelli's developments in BioAmbient Calculus[1], which aims to formalize information flow in systems of molecular biology.

2 The Formalism and Motivation of $\mathscr{PADEL}$

At a given state, an agent is to be defined by an assignment of concurrent processes, and in a given process there can occur agents, capabilities, or other non-agent, non-capability processes.

2.1 Basic Definitions

Let $\mathscr{A}$ be a finite set of agents and $\mathscr{A}c$ a finite set of atomic actions.

$$\text{An agent } A \in \mathscr{A} \text{ occurs in a process } P\text{, or } A \sqsubseteq P\text{, iff } \begin{cases} A \sqsubseteq A \\ A \sqsubseteq P \Rightarrow A \sqsubseteq P \mid Q \\ A \sqsubseteq P \Rightarrow A \sqsubseteq Q \mid P \\ A \sqsubseteq P \Rightarrow A \sqsubseteq a.P \end{cases} \quad \text{where}$$

$P \mid Q$ denotes two processes running in parallel and $a.P$ denotes an action capability a, which, if executed, will initiate a process P.

We define $\sqsubseteq^+$ as the transitive closure of $\sqsubseteq$:

$A \sqsubseteq^+ P \;\Leftrightarrow\; \exists$ a chain $P_0, P_1, \ldots, P_n$ of processes s.t. $n > 0$, $A = P_0$, $P = P_n$, and $P_{i-1} \sqsubseteq P_i$, for all $i \leq n$.

$$\text{An agent } A \in \mathscr{A} \text{ is a \textit{subagent} of } P\text{, or } A < P\text{, iff } \begin{cases} A < A \mid P \\ A < P \mid A \\ A < P \Rightarrow A < P \mid Q \\ A < P \Rightarrow A < Q \mid P \end{cases}$$

Definition. A *state* s is an assignment of Processes to Agents, $s : Agents \to Processes$, such that for every two distinct agents $A, B \in \mathscr{A}$ and for any agent $C \in \mathscr{A}$:

$$C \sqsubseteq s(A), C \sqsubseteq s(B) \Rightarrow A = B \text{ and } A \not\sqsubseteq^+ s(A) \tag{1}$$

That is, agent C cannot simultaneously occur in a process assigned to two different agents and an agent cannot occur in a process assigned to itself.

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[1] See [10] and [11].

For a given state s and two agents A,B, we define $A <_s B \overset{def}{=} A < s(B)$. We read $A <_s B$ "A is a subagent of (agent) B in state s."

Consequences

$$A <_s B \Rightarrow A \sqsubseteq s(B). \tag{2}$$

From (1) and (2), it follows also that:

$$C <_s A, C <_s B \Rightarrow A = B \tag{3}$$

In other words, assignments $s(A)$ and $s(B)$ for different agents $A \neq B$ must contain no agents in common.

Definition. We define $<_s^+$ as the transitive closure of $<_s$, and call it the *iterative* subagent relation at state s, while referring to $<_s$ as the $one-step$ subagent relation.

$A <_s^+ B \Leftrightarrow \exists$ a finite chain $A_0, A_1, ..., A_n$
s.t. $n > 0$, $A = A_0$, $B = A_n$, and $A_{i-1} <_s A_i$, for all $i \leq n$.

Consequence 3 in turn disallows loops in the tree of agents:

Proposition [Tree Property] For $A \neq B$:

$$C <_s^+ A,\ C <_s^+ B \ \Rightarrow\ A <_s^+ B \vee B <_s^+ A. \tag{4}$$

Proof. We prove this by induction on the length of the chain. By the hypothesis, there must exist two chains, where $A \neq B$:

$C = X_1 <_s X_2 <_s ...X_{i-1} <_s X_i <_s X_{i+1} <_s ... <_s X_n = A$ and
$C = Y_1 <_s Y_2 <_s ...Y_{i-1} <_s Y_i <_s Y_{i+1} <_s ... <_s Y_m = B$.

Without loss of generality, suppose $n \leq m$ (the case for $m < n$ is similar).

Then, by (3), $X_2 = Y_2$, and again by (3), $X_3 = Y_3$, and so on until $X_n = Y_n$, $\Rightarrow$ $A = Y_n$.

Now, if $n = m$, then $A = Y_m = B$, contradicting the fact that A and B were assumed to be distinct.

If $n < m$, then $A = Y_n <_s Y_{n+1} <_s ... <_s Y_m = B$ and we have shown that $A <_s^+ B$. □

Given a finite set $\mathscr{A}$ of agents, denoted by $A, B, C, A_1, ..., A_n$, and given a finite set $\mathscr{A}c$ of atomic actions, denoted by $a, a_i, \overline{a}$, we combine the syntax of BioAmbient Process Algebra and DEL, adding only the atomic sentence $A <^+ B$, and define the sentences of propositional logic together with the $one-step$ subagent relation. φ, ψ are formulae and p are propositional sentences in the language:

Table 1. Syntax and Definitions

Assume A, B, C are distinct agents. Then:

$\mathrm{P} ::= \mathbf{0} \mid A \mid (P \mid P) \mid \Sigma_i a_i.P_i$
$\varphi ::= A <^{+} B \mid \neg\varphi \mid \varphi \wedge \varphi \mid K_A \varphi \mid DK_{A_1,\dots,A_n} \varphi \mid [\alpha]\varphi$
$\alpha \in \{(a_A, \overline{a}_B)\}$
$\underline{a, a_i, \overline{a} \in \{\varphi?,\ \varphi!,\ enter,\ accept,\ exit,\ expel,\ merge+,\ merge-\}}$

$$\begin{aligned}
\varphi \vee \psi &\overset{def}{:=} \neg(\neg\varphi \wedge \neg\psi) \\
\varphi \Rightarrow \psi &\overset{def}{:=} \neg(\varphi \vee \psi) \\
\varphi \Leftrightarrow \psi &\overset{def}{:=} (\varphi \Rightarrow \psi) \wedge (\psi \Rightarrow \varphi) \\
A < C &\overset{def}{:=} A <^{+} C \ \wedge \ \textstyle\bigwedge_{B \in \mathscr{A}} \neg(A <^{+} B \ \wedge \ B <^{+} C) \\
< \alpha > \varphi &\overset{def}{:=} \neg[\alpha]\neg\varphi \\
\top &\overset{def}{:=} p \vee \neg p, \text{ for some fixed } p \\
\bot &\overset{def}{:=} p \wedge \neg p, \text{ for some fixed } p
\end{aligned}$$

2.2 Actions

The set $\mathscr{A}c$ of atomic actions is finite. Similar to the notions of *executability*, or *precondition*, in DEL, agent A must have the capability $a.P$ included in the processes assigned to it at the initial state in order for a_A to take place (agent A executing action a).

The capabilities each agent is assigned at a given state are expressed as a nondeterministic sum of atomic actions $\sum_i a_i.P_i$, each of which is attached to the process that would initiate as a result of A performing a given atomic action.

2.2.1 State Transitions

Following the Bioambient improvement on Ambient Calculus, we only allow suitable action *pairs* to induce state transitions. A cell has to accept a virus that is trying to enter, just like an announcement must be heard in order for it to affect an agent's knowledge.

We define actions α as dual pairs of atomic actions, which form a finite set $i\mathscr{A}c$:

$$\alpha = (a, \overline{a}) \in \mathscr{A}c \text{ x } \mathscr{A}c = i\mathscr{A}c.$$

We use $B :_s \alpha$ to denote agent B's participation in action α at state s. For $\alpha = (a_A, \overline{a_C})$:

$$B :_s \alpha \overset{def}{=} A \leq_s^{+} B \ \vee \ C \leq_s^{+} B \text{ and } \exists s' \text{ s.t. } s \xrightarrow{\alpha} s'$$

We define four types of actions, of which three involve a $one-step$ superagent E whose state assignment is crucial to the executability of the action (see Figure 1).

For any agents A, C, E that are distinct:
$\alpha_I = (\varphi?_A, \varphi!_C)$,
$\alpha_{II} = (enter_A, accept_C, E)$,
$\alpha_{III} = (exit_A, expel_C, E)$,
$\alpha_{IV} = (merge{+}_A, merge{-}_C, E)$

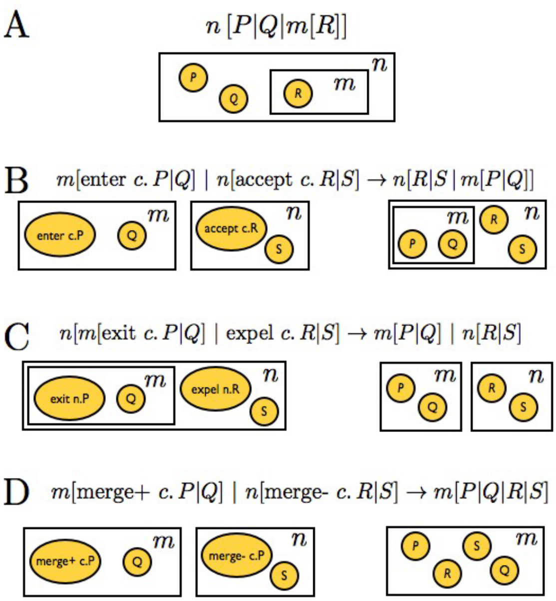


Fig. 1. Motivated by work of Luca Cardelli (see [9]-[11]), this figure depicts the application of this language to molecular biology. B, C, and D show the change in structure of processes and subprocesses as a result of acting on dual capabilities (Types II, III, IV, respectively), separated by no more than two ”membranes.” In $\mathscr{PADEL}$, we can think of each ”membrane” with all its contents as a unique agent.

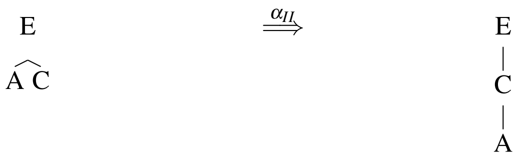
We now define the state transitions for the four different types of actions.

Type I. For $\alpha_I = (a_A, \overline{a}_C)$, where $(a, \overline{a}) = (\varphi?, \varphi!)$:

$s \xrightarrow{\alpha_I} s'$ iff
$\exists\, a, a_i, P, P_i, Q$ such that $s(A) = \sum_i a_i.P_i + a.P \mid Q$,
$\exists\, \overline{a}, c_j, R, R_j, S$ such that $s(C) = \sum_j c_j.R_j + \overline{a}.R \mid S$,
$s'(A) = P \mid Q,\ s'(C) = R \mid S,\ s'(X) = s(X),$ for all $X \neq A, C$.
This is the only type of action that does not change the structure of the tree of agents.

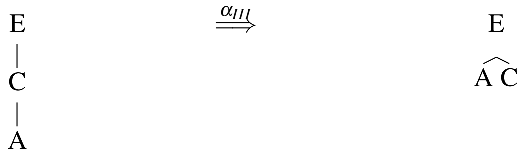
Type II. For $\alpha_{II} = (a_A, \overline{a}_C, E)$ where $a = enter$, $\overline{a} = accept$:

$s \xrightarrow{\alpha_{II}} s'$ iff
$\exists\, a, a_i, P, P_i, Q$ such that $s(A) = \sum_i a_i.P_i + a.P \mid Q$,
$\exists\, \overline{a}, c_j, R, R_j, S$ such that $s(C) = \sum_j c_i.R_j + \overline{a}.R \mid S$,
$\exists\, \Gamma$, *a process*, such that $s(E) = A \mid C \mid \Gamma$, and
$s'(A) = P \mid Q,\ s'(C) = A \mid R \mid S,\ s'(E) = C \mid \Gamma,\ s'(X) = s(X),$ for all $X \neq A, C, E$.
After α_{II} state transition, agent C is assigned a new agent, while agent E – the initial superagent of both C and A – is stripped of the $one-step$ subagent A:



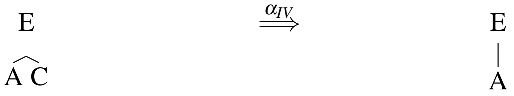
Type III. For $\alpha_{III} = (a_A, \overline{a}_C, E)$ where $a = exit$, $\overline{a} = expel$:

$s \xrightarrow{\alpha_{III}} s'$ iff
$\exists\ a, a_i, P, P_i, Q$ such that $s(A) = \sum_i a_i.P_i + a.P \mid Q$,
$\exists\ \overline{a}, c_j, R, R_j, S$ such that $s(C) = \sum_j c_i.R_j + \overline{a}.R \mid A \mid S$,
$\exists\ \Gamma$, *a process*, such that $s(E) = C \mid \Gamma$, and
$s'(A) = P \mid Q$, $s'(C) = R \mid S$, $s'(E) = C \mid A \mid \Gamma$, $s'(X) = s(X)$, for all $X \neq A, C, E$.
After α_{III} this state transition, the effect is exactly opposite to that of transitions by actions of Type II:



Type IV. α_{IV}, defined as $(a_A, \overline{a}_C, E)$ where $a = merge+$, $\overline{a} = merge-$:

$s \xrightarrow{\alpha_{IV}} s'$ iff
$\exists\ a, a_i, P, P_i, Q$ such that $s(A) = \sum_i a_i.P_i + a.P \mid Q$,
$\exists\ \overline{a}, c_j, R, R_j, S$ such that $s(C) = \sum_j c_i.R_j + \overline{a}.R \mid S$,
$\exists\ \Gamma$, *a process*, such that $s(E) = A \mid C \mid \Gamma$, and
$s'(A) = P \mid Q \mid R \mid S$, $s'(C) = \mathbf{0}$, $s'(E) = A \mid \Gamma$, $s'(X) = s(X)$, for all $X \neq A, C, E$.



The following validities follow immediately from the definitions, where, as in DEL, $< \alpha_i > \top$ denotes executability of α_i, and $[\alpha_i]\varphi$ denotes a statement φ that holds true after action α_i:

Table 2. Consequences of Action Definitions

Assume A, C, E are distinct agents. Then:

$< \alpha_{II} > \top\ \Rightarrow\ A < E \wedge C < E$
$< \alpha_{III} > \top\ \Rightarrow\ A < C \wedge C < E$
$< \alpha_{IV} > \top\ \Rightarrow\ A < E \wedge C < E$
$[\alpha_{II}]A < C$
$[\alpha_{III}]A < E$
$[\alpha_{IV}]\neg C < E$

2.3 Indistinguishability Relations on States and Actions

As in Epistemic Logic (EL), we define indistinguishability of two states for a particular agent A, denoted by $\sim_A$, in order to reason about knowledge.

Definition. [Indistinguishability of states] $s \sim_A s'$ iff $s(X) = s'(X)$, for all $X \leq_s^+ A$.

That is, two states are equivalent for agent A if and only if they are indistinguishabe for A and all of its subagents, as assigned at state s. Two states can be indistinguishable for a group of agents $B_1, ..., B_n$ if none of them can distinguish between these states:

Definition. [Group Indistinguishability of states] $s \sim_{B_1,...,B_n} s'$ iff $s(X) = s'(X)$, for all $X \leq_s^+ B_i$, for all $1 \leq i \leq n$.

We define indistinguishability of actions:

Definition. [Equivalence of actions] Here s represents any state in the history.

$$\alpha \overset{A}{\sim}_s \alpha' \Leftrightarrow \begin{cases} either\ A :_s \alpha \text{ and } \alpha = \alpha' \\ or\ \neg A :_s \alpha\ and\ \neg A :_s \alpha' \end{cases}$$

If A is a participant in α, then it would certainly be able to differentiate between taking part in two different actions α and α', unless they were actually the same. On the other hand, if A does not participate in either α ot α', then both actions appear equivalent to A. This implies that A is a subagent of both agents executing α.

3 Semantics

We will evaluate logical formulas on *histories*, which are sequences of states and actions (representing possible histories of a system). However, in order to define the semantics for epistemic and dynamic modalities, we need to define appropriate (epistemic) indistinguishability relations and (dynamic) transition relations on histories, by lifting to histories the corresponding state relations.

3.1 Relations on Histories

To ensure that our knowledge is accumulative, as in DEL, we must expand the language to include Perfect Recall and extend equivalence relations to state transitions and to previous states. For this we define histories and develop axioms based on histories rather than states.

We define a *history* h as a sequence of alternating states and actions:

$$h = (s_0, \alpha_0, s_1, \alpha_1, ..., s_{n-1}, \alpha_{n-1}, s_n)\ s.t.$$
$$s_i \xrightarrow{\alpha_i} s_{i+1} \text{ for all } i < n.$$

- $(h, \alpha, t) := (s_0, \alpha_0, s_1, \alpha_1, ..., s_{n-1}, \alpha_{n-1}, s_n, \alpha, t)$ iff $s_n \xrightarrow{\alpha} t$
- $|h|$ denotes the size of the history, equal to the number of state-action pairs in the history, not counting the final state
- $last(h) = s_n$. We use the convention of $h \models \varphi$ iff $last(h) \models \varphi$, read "history h satisfies statement φ if and only if the last state in history h satisfies statement φ"

We extend the notion of state indistinguishability to history indistinguishability for an agent A.

Definition. [Equivalence of histories]
Let $h = (s_0, \alpha_0, s_1, \alpha_1, ..., s_i, \alpha_i, ..., \alpha_{n-1}, s_n)$ and
let $h' = (s'_0, \alpha'_0, s'_1, \alpha'_1, ..., s'_i, \alpha'_i, ..., \alpha'_{n-1}, s'_n)$, then

$$h \overset{A}{\sim} h' \Leftrightarrow \forall i \in \{0,1,2,....n\} : \ |h| = |h'| \text{ and } s_i \overset{A}{\sim} s'_i \text{ and } \alpha_i \overset{A}{\sim}_{s_i} \alpha'_i$$

Definition. [History transition]
For two histories h, h',
$h \overset{\alpha}{\to} h'$ iff $\exists t \ s.t. \ h' = (h, \alpha, t)$.

Proposition. [Perfect Recall] This follows from the definitions above and ensures uniqueness of history transitions.
$h' \sim_C h'', h' = (h_1, \alpha, s'), h'' = (h_2, \beta, s'') \ \Rightarrow \ |h_1| = |h_2|, h_1 \sim_C h_2, \alpha \sim_C \beta.$

Proposition. Indistinguishable histories for an agent remain indistinguishable for its subagents in the last state:
$h \sim_C h', \ A <^+_{last(h)} C \ \Rightarrow \ h \sim_A h'$

Proof. $s_i(X) = s'_i(X)$, for all i, for all $X \leq^+ C$ implies the same for $X \leq^+ A$ since A is a subagent of C.

Now, for each $\alpha_i \sim_C \alpha'_i$ in the histories, if C is not a participant of α and they appear to be the same, then by definition of participation the same holds for A since it is a subagent.

If $C :_{s_i} \alpha$, then $\alpha_i = \alpha'_i$. In this case, regardless of whether or not A participates in α, the two appear the same to it. □

The definition for equivalence of histories for a group of agents is similar:

$$h \sim_{B_1,...,B_n} h' \overset{def}{:=} h \sim_{B_1} h' \cap \ ... \ \cap h \sim_{B_n} h' \tag{5}$$

3.2 Semantics

The semantics of our language is embodied by a satisfaction relation $\models$ between histories and logical formulas, which is defined by the inductive clauses in Table 3. The definition is by induction on formulas. For $A, B, B_1, ..., B_n$, distinct, $\in \mathscr{A}$:

Table 3. Semantics

$h \models A <^+ B$	iff $A <^+_{last(h)} B$
$h \models \neg\varphi$	iff $h \not\models \varphi$
$h \models \varphi \wedge \psi$	iff $h \models \varphi$ and $h \models \psi$
$h \models K_A \varphi$	iff $\forall (h' \sim_A h) : h' \models \varphi$
$h \models DK_{B_1,...,B_n} \varphi$	iff $\forall (h' \sim_{B_1,...,B_n} h) : \ h' \models \varphi$
$h \models [\alpha]\varphi$	iff $\forall h \overset{\alpha}{\to} h' : \ h' \models \varphi$

4 Proof System

We use axioms and rules of inference from propositional logic and those of DEL[2], together with those specific to our formalism. In addition, we outline reduction laws, with select proofs. In this section, $A, B, C, X, Y, B_1, \ldots, B_n, A_1, \ldots, A_n$ are agents $\in \mathscr{A}$.

Table 4. Axioms of Knowledge

$\vdash DK_A\varphi$	$\Leftrightarrow K_A\varphi$	G1
$\vdash K_A\varphi$	$\Rightarrow DK_{A,B_1,\ldots,B_n}\varphi$	KtoDK
$\vdash A <^+ C$	$\Rightarrow K_C(A <^+ C)$	KOwn
$\vdash A <^+ C \wedge C <^+ B$	$\Rightarrow DK_{B,A_1,\ldots,A_n}(A <^+ C)$	DKOwn
$B_1,\ldots,B_n <^+ A \wedge DK_{B_1,\ldots,B_n}\varphi$	$\Rightarrow K_A\varphi$	KfromDK

Proof. [KOwn] The right hand side of the statement is equivalent to $\forall h'(h \sim_C h' \Rightarrow h' \models A <^+ C)$. By the definition of equivalence, we have that $\forall i,\ s_i(X) = s'_i(X)$, for all $X \leq^+ C$, which implies that state assignments, for all states in histories h, h' will be the same for C and its subagents.

But then $last(h)(X) = last(h')(X)$ will also hold true for $X = C$ and $X = A$ and all agents in between them, thus satisfying $h' \models A <^+ C$. □

Axioms R, Trans, and Tree reveal the loop-less tree structure of agents.

Axiom R. $\vdash \neg A <^+ A$

Axiom Trans. $\vdash A <^+ B \wedge B <^+ C \Rightarrow A <^+ C$

Axiom Tree. $\vdash (X <^+ A \wedge X <^+ B) \Rightarrow (A <^+ B \vee B <^+ A)$

Proof. [Axiom Tree] For $s = last(h)$, the statement is semantically equivalent to $X <^+_s A$ and $X <^+_s B$, for some state s. But then by (4), we guarantee that $B <^+_s A$ or $A <^+_s B$, which is semantically equivalent to the desired result. □

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[2] These include the Necessitation and the Modus Ponens rules of inference, as well as KT45 axioms and all tautologies of propositional logic. See [14] for more description.

We now explore reduction laws involving the dynamic modality.

Partial Functionality Axiom. $[\alpha]\neg\varphi \Leftrightarrow (<\alpha>\top \Rightarrow \neg[\alpha]\varphi)$

That is, the transition induced by α, if it exists, goes to a unique next state: if $h \xrightarrow{\alpha} h'$ and $h \xrightarrow{\alpha} h''$, then $h' = h''$. This ensures uniqueness of transition.

Table 5. Preservation of Facts Axioms[a]

$[\alpha_I]\varphi$	$\Leftrightarrow$	$(<\alpha_I>\top \Rightarrow \varphi)$	PF1
For $X \neq A$:			
$[\alpha_{II}]X < Y$	$\Leftrightarrow$	$(<\alpha_{II}>\top \Rightarrow X < Y)$	PF2a
For $Y \neq E, C$:			
$[\alpha_{II}]A < Y$	$\Leftrightarrow$	$(<\alpha_{II}>\top \Rightarrow A < Y)$	PF2b
For $X \neq A$:			
$[\alpha_{III}]X < Y$	$\Leftrightarrow$	$(<\alpha_{III}>\top \Rightarrow X < Y)$	PF3a
For $Y \neq E, C$:			
$[\alpha_{III}]A < Y$	$\Leftrightarrow$	$(<\alpha_{III}>\top \Rightarrow A < Y)$	PF3b
$(X < C)$	$\Rightarrow$	$[\alpha_{IV}](X < A)$	PF4a
For $X \neq C$:			
$\neg(X < A) \Rightarrow ([\alpha_{IV}]X < Y$	$\Leftrightarrow$	$(<\alpha_{IV}>\top \Rightarrow X < Y))$	PF4b

[a] Note that the Consequences outlined in Table 2 also belong to this category of reduction laws.

The Preservation of Facts axiom of DEL demands several versions for the different types of actions (see Table 5).

Proof. [PF4a] We unwrap the definition for Type IV action, found in 2.2.1, where $s = last(h)$. It follows:

If $X < C$ at $last(h)$, then $X \sqsubseteq S$ (occurs in process S).
Since $s'(X) = s(X)$, for all $X \neq A, C, E$, then X still occurs in S at s'.
Since $s'(A)$ is assigned process S, where X occurs, then X must be a subagents of A at s'. □

Similarly, the Action-Knolwedge reduction laws are expanded for specificity (see Table 6).

Table 6. Action-Knowledge Axioms

For $X = A, C$:	$[\alpha_I]K_X\varphi$	$\Leftrightarrow (< \alpha_I > \top \Rightarrow K_X[\alpha_I]\varphi)$	AcKn1a
$(A <^+ X \vee C <^+ X) \Rightarrow$	$[\alpha_I]K_X\varphi$	$\Leftrightarrow (< \alpha_I > \top \Rightarrow K_X[\alpha_I]\varphi)$	AcKn1b
$C <^+ X \Rightarrow$	$[\alpha_{II}]K_C\varphi$	$\Leftrightarrow (< \alpha_{II} > \top \Rightarrow DK_{A,C}[\alpha_{II}]\varphi)$	AcKn2a
	$[\alpha_{II}]K_X\varphi$	$\Leftrightarrow (< \alpha_{II} > \top \Rightarrow K_X[\alpha_{II}]\varphi)$	AcKn2b
	$[\alpha_{II}]K_A\varphi$	$\Leftrightarrow (< \alpha_{II} > \top \Rightarrow K_A[\alpha_{II}]\varphi)$	AcKn2c
For $X = A, C$:	$[\alpha_{III}]K_X\varphi$	$\Leftrightarrow (< \alpha_{III} > \top \Rightarrow K_X[\alpha_{III}]\varphi)$	AcKn3a
$A <^+ X \Rightarrow$	$[\alpha_{III}]K_X\varphi$	$\Leftrightarrow (< \alpha_{III} > \top \Rightarrow K_X[\alpha_{III}]\varphi)$	AcKn3b
$A <^+ X \Rightarrow$	$[\alpha_{IV}]K_A\varphi$	$\Leftrightarrow (< \alpha_{IV} > \top \Rightarrow DK_{A,C}[\alpha_{IV}]\varphi)$	AcKn4a
	$[\alpha_{IV}]K_X\varphi$	$\Leftrightarrow (< \alpha_{IV} > \top \Rightarrow K_X[\alpha_{IV}]\varphi)$	AcKn4b
$(X <^+ A \wedge X <^+ C) \Rightarrow$	$[\alpha]K_X\varphi$	$\Leftrightarrow \bigwedge_{\beta \in i\mathscr{A}c^+, \beta \sim_X \alpha}(< \alpha > \top \Rightarrow [\beta]\varphi)$	AcKnNP

Note that the final rule in Table 6 is for non-participants of any action α. All proofs are achieved by a counterfactual argument of "chasing the diagram," though we omit them here.

Theorem. The proof system for $\mathscr{PADEL}$ is sound.

Proof. In order to show soundness, all axioms in the system must be valid. For all axioms presented in gray boxes, validity was either proved in the text or it follows from the semantic definitions. □

Theorem [Model-checking] The model-checking problem for $\mathscr{PADEL}$ is decidable on finite models.

Proof. Given a model M with a countable set of histories h and formula φ, the axioms and rules of inference are sufficient to decide whether or not φ is satisfiable at M, h, since we have provided axioms for all syntactic combinations of terms φ can have. □

Corrollaries. The following are semantically valid consequences of axioms and rules of inference:

- $\vdash A < B \Rightarrow A <^+ B$
- $\vdash X < A \Rightarrow \neg X < B$
- $\vdash A <^+ C \wedge C <^+ B_1, \ldots, B_n \Rightarrow DK_{B_1,\ldots,B_n}(A <^+ C)$
- $\vdash A <^+ C \wedge C <^+ B \Rightarrow K_B(A <^+ C)$
- $\vdash B_1, \ldots, B_n <^+ A \wedge DK_{B_1,\ldots,B_n,A}\varphi \Rightarrow K_A\varphi$
- $(X <^+ A) \Rightarrow [\alpha_{III}]\neg(X <^+ C)$

5 Conclusion

We have thus developed a sound, decidable language $\mathscr{PADEL}$ based on a nested tree structure of a finite number of agents, which are defined by concurrent processes, subagents and capabilities. Furthermore, we developed the notion of knowledge and distributed knowledge for agents based on

1. the currect *state* of an agent, which captures its current $one-step$ subagents and its current capabilities for future interactions
2. the current *state* of all of its $iterative$ subagents. This encodes a principle of monotonicity of information: all information carried by a subagent is available to any of its superagents
3. the memory of an agent, encoded in a history that each agent perceives differently. Following the premises of DEL, information is never lost and contradictory knowledge is never acquired.

The presented axiomatization allows one to reason about knowledge and change in knowledge of agents executing actions, as well as their subagents and superagents. Further applications to biological systems remain to be explored, in particular seeking to define "knowledge," as described by indistinguishabilities, for a given biological unit. It also remains to investigate whether the system is complete.

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Part III

Models and Applications

Editorial

This part consists of six rather different papers. Four of them discuss the emergence of life and mind, natural or artificial intelligence, hierarchical organization while the other two are more experimental, proposing models of communication in a swarm and relations between species and their environment.

Paul Adams and Kingsley Cox defend the thesis that the chemical/genetic/mathematical framework developed to explain the emergence of life can be 'transposed' into a neural/psychological/mathematical framework explaining the emergence of mind. In particular both rely on the extraordinary levels of accuracy of the relevant lower-level processes. In parallel to the accuracy of base-copying, the authors propose a similar accuracy of synaptic detection of spike-pairing thanks to a “Hebbian proofreading”, with a cortical proofreading circuit for super-accurate learning.

John Cummins proposes a new framework for the emergence in humans of a flexible, high-level general intelligence capable of anticipating the future: an adaptation of the stress response may have enabled a new and flexible balance of accurate and incorrect assessments of the animal’s control over the environment and reduced the load of stress to within adaptive parameters. It relies on a conjectural model of information processing in the non-human primate brain, showing where and how “buffer intelligence” could have later arisen and been exploited in early hominids.

The paper by Gunji, Murakami, Niizato, Sonoda and Adamatzky studies the alternation of passively active and actively passive attitudes of communication in a society-like system. It constructs a model for a swarm based behaviour only on mutual anticipation: each individual knows where the neighbors can go, and can estimate locally popular sites to which some transitions may converge. The "Mutual Anticipation" model represents the swarm as a graph and the mutual anticipation structure as a fixed point with respect to equivalence classes on it. It shows that redundant connections can contribute to a robust and dynamic swarming behavior.

Gerard Jagers op Akkerhuis introduces the "Operator Hierarchy" theory as a fundamental, theoretical, multilevel methodology for analysing natural organization. In this theory, the word “operator” generically represents physical particles and organisms. The operator theory may act as a backbone for modelling approaches by offering general principles indicating how hierarchical levels of organization emerge along three dimensions: from interactions between operators, from complexity increases within operators, and from complexity increases leading to higher level operators.

Joyce and Herrmann investigate the mechanisms underlying the broad diversity of species in the natural world. Using a 2-dimensional variant of a classical model, they describe a model to capture competition for resources among species, represented as a specific point in a 2-dimensional phenotype space, each dimension corresponding to a quantitative trait that influences resource preferences. They examine the structure of the distributions of species, and explore how the functions defining competition and carrying capacity interact to give rise to these structures.

Craig Lindley is concerned with the development of engineered systems having properties of autonomy and intelligence. He discusses the limitations of artificial intelligence and suggests that a paradigm of engineered synthetic intelligence should replace AI, in particular because of problems with the knowledge acquisition bottleneck and the difficulty of associating symbols understood by a machine. He also suggests that the contemporary discourse concerning intelligent robotics reflects an outmoded industrial foundation that must be superseded as engineering progresses more deeply into molecular and biological modes.

From Life to Mind: 2 Prosaic Miracles?

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Abstract. The origin of life from matter and the subsequent emergence of mind were fundamental events. Our work is based on the idea that the chemical/genetic/mathematical framework developed over the last 150 years to explain the first is conceptually similar to the neural/psychological/mathematical framework needed to understand the second. First we outline the first, seemingly adequate, framework and then we explain some related, unusual and controversial, ideas that offer a “translation” into neural terms. The core idea is that the extraordinary, mysterious and qualitatively unique features of “life” and “mind” arise because of extraordinary (though completely explicable) levels of accuracy of the relevant elementary processes (base-copying and synaptic strengthening). The living and the mental might hinge on prosaic, though accurate, lower-level machinery.

Keywords: Hebbian Proofreading, Crosstalk, Neocortex, Mind, Neural Sex.

1 Chemical Machinery of Darwinian Evolution

The key transitions[1] that led to complex life were (1) Onset of Darwinian evolution in the RNA world; (2) emergence of the dna/protein world and prokaryotic life (3) sexual, eukaryotic, evolution.

(1) Spontaneous formation of an RNA sequence that could act as a high-fidelity selfreplicase. The length of this sequence must have been under the per-base copying error rate (Eigen threshold), allowing onset of Darwinian evolution, in a phase transition. But search was restricted to compact sequence spaces.
(2) Searchable sequence space vastly enlarged (> 4^8 fold) as a result of replicase fidelity improvements, notably proofreading. But the Eigen threshold prevented more complex forms of organization than prokaryotes. The problem is that near-neutral mutations cannot accumulate in a finite population for long enough to combine with other individually near-neutral mutations with which they are synergistic, because the mutation rate must be below the Eigen threshold. Instead, selection in slowly changing environments favors low mutation[2].
(3) Advent of eukaryotes and sex allowed the threshold to be surpassed[2].

The crucial factor for life is proofreading, which lowers the copying error rate by ~10^4, though other smaller factors also play roles. Proofreading copies bases twice, and only if the 2 attempts agree is replication allowed.

2 Neural Machinery of Learning for Understanding

In our view causal learning (a neural equivalent of Darwinian adaptation) is the key to intelligence and mind. We learn to (partly) understand the world, and infer underlying causes (objects, ideas etc) from sensations, by adjusting vast networks of synaptic connections in response to local spiking traffic across those connections, as well as more global signals. Networks learn to track possible hidden causes given the current inputs, based on past statistics, and gradually narrow the range of likely causes. Repeated past temporal pairing of input and output spikes at specific connections leads, slowly, to more frequent future pairing and ultimately to improved inference and understanding. However, different from most approaches, we focus on crucial details of the relevant synaptic hardware. We believe that the accuracy of synaptic detection of such spike-pairing plays a fundamental role in the sophisticated learning underlying cognition in much the same way that accurate base-pairing drives Darwinian evolution. In this view, the essential problem confronting the brain is to ensure that pairing-based adjustment is connection-specific, despite extremely high synapse density. Mind could only emerge, in a type of phase-transition, if synapse adjustment were extraordinarily specific, and such specificity would be attainable only using specialized neural circuitry found throughout the neocortex and associated thalamus.

We studied this novel thesis in the simplest possible general model of the synaptic learning of weights that allow underlying causes to be extracted from neural inputs ($\mathbf{x}$). We assume, for simplicity, that causes (the independently fluctuating components of $\mathbf{s}$) are veiled by linear mixing: $\mathbf{x} = \mathbf{Ms}$, where $\mathbf{M}$ is an n by n matrix. To extract a cause, one must learn a row of $\mathbf{M}^{-1}$. Fortunately this can be easily done using (completely-accurate) nonlinear Hebbian, spike-pairing based, learning, which is driven by the higher-order correlations between inputs generated by the mixing of causes, which must have nonGauss distributions. Hebbian learning is driven by recently described synaptic processes, such as localized calcium entry through spike-pair activated NMDA receptors. Such machinery has 2 conflicting requirements: a synapse must *transmit* current to the spike-trigger region of the neuron, but calcium etc. must be *confined* to the synapse. This conflict implies that the Hebbian spike-pair detection cannot be completely synapse-specific. A similar “read/write dilemma” arises in DNA replication: Crick-Watson basepairing must be strong (to give accuracy) but weak (to allow replica separation). We[3] therefore modified the standard Hebbian rule to incorporate inevitable inaccuracy (via a matrix $\mathbf{E}$ which specifies how different connections slightly affect each other). In the simplest most plausible case, this matrix has equal small offdiagonal elements $e/n << 1$ that reflect inaccuracy.

The key result of this bifurcation analysis (to which T. Elliott has crucially contributed[4]) is that there is a maximal value of e, e_c, allowing reliable learning of causes; e_c approaches zero as n increases. This result is similar to that underlying the Eigen error catastrophe, and implies that sophisticated learning (i.e. of causes, driven by higher-order correlations between numerous inputs) is only possible given extraordinary Hebbian accuracy. Above this crosstalk threshold, correct learning (which corresponds to “understanding”) can only be achieved if one starts very close to the correct solution (e.g. via luck, genetics or supervision); if weights start equal or random, learning is driven only by the combined influence of **E** and (causally-uninformative) pairwise correlations. To reliably learn from higher order correlations, and gain individual insight into novel problems, crosstalk must be very low, and in some cases (especially for large n) even negligible.

While this analysis is rooted in machine learning (the problem of assigning meaning to observations), it is also rooted in recent ideas about the underlying detailed neural mechanisms. Progress in understanding learning, the neocortex and mind has been retarded by the almost complete isolation of 3 relevant fields: machine learning; synapse biophysics; circuit/system neuroscience. Dramatic progress in biology ensued by bringing together molecular, genetic and ecological levels of description. Understanding the world requires analyzing the structure of the higher-than-pairwise correlations that it generates: these are the clues that can reveal underlying causal structure. Structure in higher-order correlations can be revealed by nonlinear Hebbian learning (or variants thereof), but only when it is extremely accurate. In this view the simplest observation about brains is the most relevant: they have a lot of synapses! Highly specific synapse adjustment would allow circuits to develop powerful representations capturing underlying realities hidden by the apparently random flux of experience: truth from trash; meaning from observation. These trillions of synapses must each be regulated by the tiny aspect of the world they see: the impulse traffic across them. Extracting meaning from data thus resembles efficiently evolving DNA sequences, bit by bit.

3 Cerebral Proofreading

The general view that high accuracy is needed for the sorts of elementary "local" processes underlying neural network learning is not revolutionary; most theorists assume that synapses can reliably do this. Experimenters know that they cannot, but they assume instead that the theories have adequate slack. Darwin knew that organisms reproduce, but he did not know how; what it essentially requires is copying the entire genome, with a per base error rate approaching 10^{-10}. The "miracle" of life lies in that extraordinary number, achieved by a combination of processes, of which molecular proofreading is the most important. We propose that the miracle of mind is similarly, and rather prosaically, achieved, by a "neural proofreading" operation that is unique to the neocortex, the brain structure that first appears in mammals, and reaches its acme in humans.

Hebbian learning boils down to detecting paired, pre- and post-synaptic, spikes, manifesting as a *local* (e.g. calcium) signal. The reason why this crucial synaptic process (very rarely) makes mistakes is that signals can diffuse from neighboring synapses that belong to different connections experiencing different impulse traffic. This problem is *biophysically* inevitable but it can be greatly alleviated by a proofreading operation: one needs a second independent, extrasynaptic, measure of the relevant spike-pairing, which has to "approve" the first, synaptic measure. Because the 2 measures are independent, their error rates multiply. This principle drives accurate basepairing, and ultimately, life.

The problem of implementing this necessary “Hebbian proofreading” operation may have been solved by the special characteristic circuitry and physiology of the neocortex (and the associated thalamus; see Figure). We believe[5] that each thalamocortical connection, primarily responsible for the tuned responses of cortical neurons, is equipped with a “proofreading neuron”, which gets copies of input and output spikes arriving at that connection. This proofreader would be a corticothalamic neuron in layer 6. If it also detects a “coincidence” (a spike-pair) it swiftly sends signals to both the input and output side of the relevant synapses comprising the connection. This double-signal then confirms that the synaptically-detected coincidence was valid, in a procedure that is closely analogous to that operating during DNA proofreading. This analogy arises because proofreading is the only effective strategy for overcoming physical limitations.

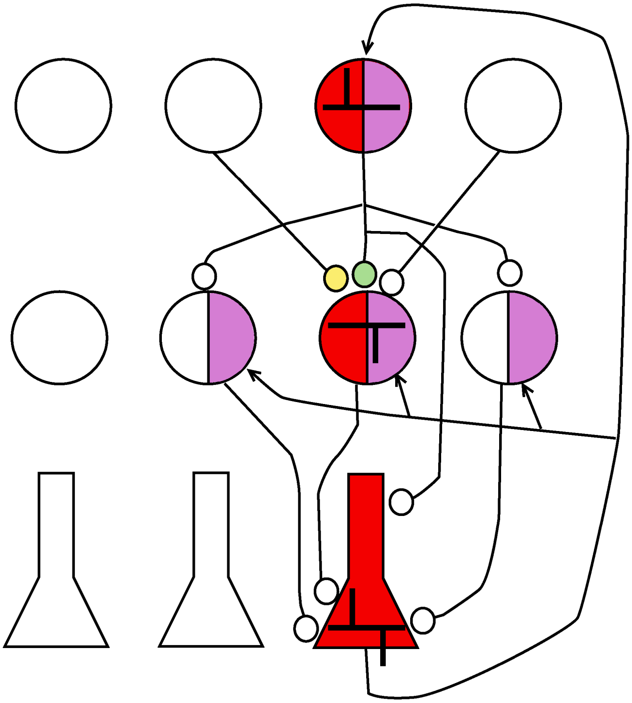

Figure. Cortical proofreading circuit for superaccurate learning (postsynaptic error version). A circuit that would allow a single cortical layer 6 cell (bottom row, red) to proofread many connections, all formed by the same presynaptic thalamic “relay” cell (top row, colored). However, the connections formed onto a particular layer 4 cell (middle row) by different relay cells each get there own layer 6 proofreader, only one of which is shown in detail here. One of a set of relay cells fires (denoted by the left red semicircle), as does one of set of layer 4 target cells (red, middle row). The timing of the relevant paired spikes is shown by the vertical lines within the circles; presynaptic spike up, and postsynaptic spike down. In this case, the pre-spike is closely followed by a post-spike (a “pairing” or “coincidence”), which triggers the generation of a second messenger within the relevant postsynaptic spine. The spine itself is not shown, and the small circles show synapses, without specific reference to boutons or spines. The coincidence occurring at one of the connections is marked by green, and this produces crosstalk ("false pairing"), because of postsynaptic messenger spread to another synapse, made by a different relay cell on the same target cell, shown in yellow. The neurons shown in the bottom row are coincidence-detecting "proofreading" neurons in layer 6; the relevant proofreading neuron (colored), which detects coincidences between a specific partner relay neuron and any of the thalamorecipient neurons on which it currently synapses, fires in response to this coincidence (the firing is shown as red color, and the coincidence detecting function is shown schematically within the cell body). Such pre-post coincidence-detection can be implemented if the relay cell makes weak distal synapses on the proofreader, and the target cells makes proximal synapses, as shown. Both types of inputs must fire, in sequence, to trigger proofreader firing, which then feeds back both to the whole set of neurons targeted by the relay being proofread by the given layer 6 cell, and to its "partner" relay cell; this feedback is modulatory (arrows). This modulatory feedback briefly (~100 msec) "half-enables" (purple semicircles) the expression of the coincidence-induced plasticity change (held in "draft" or temporary form) both presynaptically and postsynaptically. However, although the relevant output cell is half-enabled, the relevant relay cell (that contributing the synapse receiving the crosstalk) is not, and therefore the erroneous "false pairing" induced by spillover from the activated synapse is not expressed as a strength change. Note that the colored proofreader shown here can perform a similar operation at any of the connections (only 3 are shown) made by its thalamic partner (also colored). For example, if paired spikes occurred in this thalamic cell and its rightmost layer 4 target, the proofreader would enable that connection (but not false pairings erroneously induced at other connections on that rightmost cell). But if a spurious coincidence occurs at that same connection shortly afterwards, it would be falsely approved, because of inevitable proofreading delays and persistences. This "distributed crosstalk" makes proofreading imperfect, especially with large numbers of inputs. If most connections are merely potential, such errors are reduced, at the expense of slower learning. These circuits must be continuously updated by separate sleep-like offline learning to track ongoing online rewiring (e.g. conversion of potential to actual connections). A different but closely related circuit, using anticoincidence, would be needed to handle presynaptic errors, and we think these are the dominant type, and that this second form of proofreading is the one that is actually used. Since presynaptic errors are probably associated with anticoincidence detection, the connections onto layer 6 proofreading neurons must be reversed (input from 4 is distal, and input from relays is proximal, as observed).

4 Proofreading Machinery

Because there are far more thalamocortical connections than layer 6 corticothalamic cells, proofreading must be done in a distributed fashion: each proofreader services all the connections made by a given thalamic (or thalamorecipient) cell (see Figure). This can work well because the close spiking-pairings that drive learning are quite rare, and become rarer as learning proceeds and weak connections are eliminated. Merely potential connections, prior to dendritic spine insertion at close axodendritic approaches, do not require proofreading. There are 2 interesting consequences. First, sophisticated learning will be very slow (since potential connections cannot immediately learn). Second, proofreading neurons must be continuously rewired to match current connectivity created by recent learning. Both input and output connections must be rewired; this may be the purpose of the alternating slow-wave and paradoxical phases of sleep.

This view shifts the balance in the study of mind from machine learning or psychological principles to the associated neural hardware, which is where neuroscience makes the most distinctive contribution. We focus on the tremendously difficult problem of implementing basic learning rules at quadrillion-element scales, and less on clever "AI" algorithms built around assumed perfect rules. Rather than complex rules that work despite hardware imperfections, nature uses simple rules but complex hardware. The figure diagrams the proposed neocortical "proofreading" hardware that would allow extremely accurate adjustment of a particular thalamocortical (top 2 layers) synapse (marked in green) in response to pre-post spike-pairing (red colors and vertical black lines) despite inevitable postsynaptic chemical spread to an inappropriate synapse (yellow). A layer 6 neuron (bottom layer) detects the coincident pairing (pre-post spikes and red color) and fully enables potentiating plasticity only at the appropriate synapse. Note that although approval is also delivered to other synapses (formed on the flanking layer 4 cells), these do not register the triggering coincidence event. A similar, complementary, arrangement (not shown) could be used to proofread "anticoincidences", reflecting close post-pre spike pairing underlying long-term depression, and we think this alternate arrangement is that actually used.

5 From Mammals to Humans: Neural Sex

In this account, all mammals, possessing a neocortex, could learn to understand aspects of their world. Such ability ("insight") is the hallmark of intelligence, and would be uniquely conferred by neocortical proofreading. However, it seems only humans can do this systematically. The problem is of course that the necessary slowness of learning, which as explained stems from the inevitability of synaptic crosstalk (even though greatly mitigated by neocortical proofreading) means that little deep understanding can be achieved in an individual lifespan, given the limited sampling of necessary high-order statistics. Clearly human culture and language somehow overcome this difficulty. While novel insight fragments could be generated in individual brains by the process described above (incredibly accurate learning driven by higher-order correlations), they cannot accumulate without culture and language. Our new account of cortical learning leads to an unexpected parallel between this rather conventional view of culture and language, and recent understanding of the role of sex in Darwinian evolution[2]. Only eukaryotes have the necessary machinery to engage in true sexual reproduction, which is essentially, like language, a species- agreed protocol for the exchange of (genetic) information. Crucially, it appears that sex alleviates the Eigen error threshold. Thus the human per generation mutation rate is around 10^{-8}, tenfold higher than the genome length, which is in turn ten times greater than the reciprocal per-base error rate. This high level, mostly due to successful sperm-delivery by older men, is far above the error threshold. But sexual recombination blunts Muller's ratchet, which would otherwise lead to mutational meltdown. Bacteria, without sex, are forced to live well below their error threshold, and never evolved complex forms.

Most human learning is not based on individual discovery (driven by subtle correlations in an apparently random input data stream, requiring extreme synaptic accuracy, as just described) but by much more robust, banal, supervised learning insights of others. Language/culture converts the very difficult, slow, process of individual discovery to the rather trivial problem of copying available solutions; as noted above, analysis shows that if one can initially get close to the correct solution, a quite high degree of crosstalk allows one to perfect this, based on experience. More concretely, sex allows various alleles, individually near-neutral, to accumulate in a population, and provides a way they can be systematically and synergistically be combined, either negatively (and eliminated) or positively (and spread). This is achieved without an intolerable increase in the mutation rate (which is the only way that near-neutral alleles can accumulate in an asexual population). Likewise, humans can individually discover new idea fragments (such as those outlined in this paper) but only the collective process of combination and appraisal called Science allows their diffusion. Much of the human massive cortical expansion underpins the protocols that allow such "brain-sex", but this requires the core, generic underlying neocortical proofreading process, in much the same way that sex is underpinned by mutation, and requires elaborate special machinery.

6 Summary

Although this work covers many technical details at various levels and fields of analysis, our thesis is simple, naïve and we hope powerful: the mysterious and quasimiraculous states of matter we call "Life" and "Mind" are the result of the intensive repetition of elementary selective amplification processes such as base-copying and synapse-strengthening. The outcome of such straightforward processes is remarkable because the selectivity is extraordinarily high: in the case of base-copying no constant in physics has a lower error. But extraordinary selectivity requires extraordinary machinery. For DNA, that machinery involves an elaborate protein complex whose key component is a proofreading step that enormously boosts accuracy. Our contribution to this emerging picture, which explains unexpected "effects" in terms of elemental "causes", has 2 parts. First, we (and others) show mathematically that learning from higher order correlations, probably necessary for any form of understanding (and thus "mind"), breaks down, in a fixed-point bifurcation, unless synaptic adjustment accuracy is extremely high. Second, we propose that the unique elaborate circuitry of the neocortex (which seems to at least facilitate intelligence) performs the proofreading operation necessary for such accuracy. Intriguingly, both these ideas have strong parallels in Darwinian evolution, suggesting that life and mind are closely related phenomena. But these ideas lie firmly within the existing scientific framework: we are NOT proposing new and outlandish principles. Instead, we believe that very careful analysis of the implications of current ideas and facts, has and can lead to significant progress. Mind would be extraordinary because it uses extraordinary, though understandable, machinery.

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Do the Origins of Biological General Intelligence Lie in an Adaptation of the Stress Response?

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Abstract. Research into natural and artificial intelligence can overlook that natural intelligence capable of anticipating the future has a potential cost, mediated by cognitive factors involved in the stress response, leading to high allostatic load (‘wear and tear’). This theoretical paper suggests that nature may have partly resolved the problem by using the same mechanism—an adaptation of the stress response enabling a new and flexible balance of accurate and inaccurate assessments of the animal’s control over the environment---to (a) generate flexible, high-level general intelligence in humans and (b) reduce allostatic load to within adaptive parameters. This new form of intelligence, probably appearing in early hominins, acts as a buffer between the animal and its environment. A tentative framework for information processing around the primate brain is proposed, showing where and how such ‘buffer intelligence’ could have arisen and been exploited in early hominins. This appears to be a development of a function undertaken in non-human primates by the neural correlates of consciousness, an area of the non-human primate brain where there is no, or very little, intelligence. There is a brief discussion of whether this principle might enable the spread of a capacity for intelligence throughout a complex adaptive system, with flexible linguistic syntax in humans as an example.

Keywords: Stress, Cost of intelligence, Allostatic load, Assessment of control, Chaos, Buffer intelligence, Consciousness, Language, Syntax.

1 Introduction

This theoretical paper offers a possible signpost towards understanding the origins and structure of flexible, high-level general intelligence in humans.

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The ultimate goal of any living organism is to preserve its structural integrity long enough to promote its genetic material successfully into the environment. Processes aimed solely at achieving proximate goals such as survival, nutrition, reproduction and shelter, etc. occur within the overarching context of this ultimate evolutionary goal. Proximate goals (including those pursued by ‘intelligence’), although contributing to the ultimate goal, are not necessarily identical to the ultimate goal. Achieving the ultimate goal involves factors that may affect how different proximate processes operate and are integrated with each other. The result may be a complex balance of costs and benefits. This paper examines the balance of costs and benefits in the relationship between intelligence, the stress response and allostatic load.

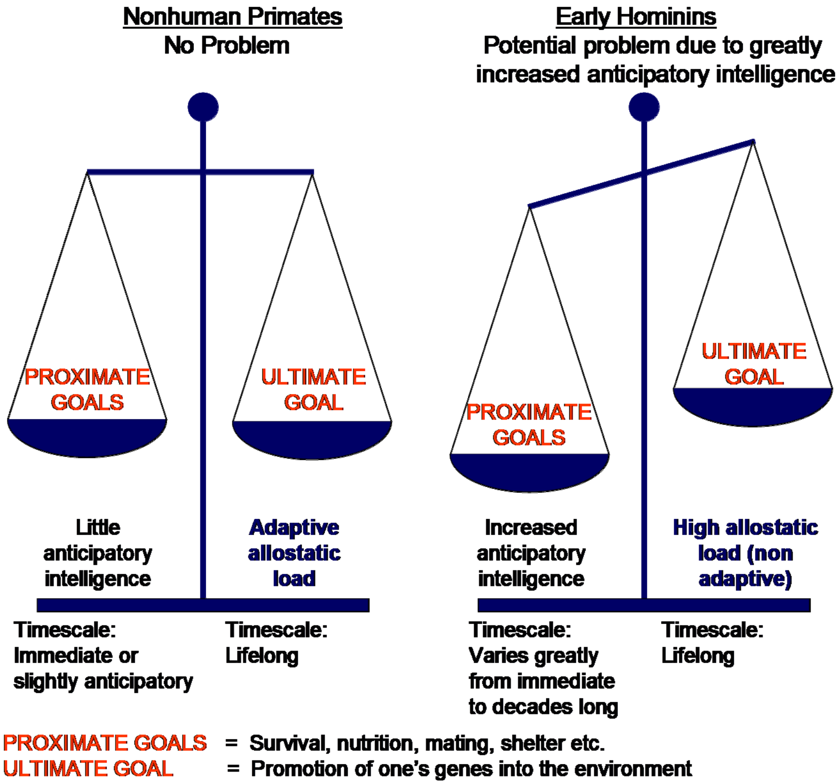

Fig. 1. Potential Problem In early hominins, the ‘weight’ of increased anticipatory intelligence could cause increased allostatic load that impacts adversely on the ultimate goal of reproductive success. The result is a non-adaptive imbalance between proximate and ultimate goals

Research into natural and artificial intelligence can overlook that natural intelligence capable of anticipating the future has a potential ‘downstream’ cost, mediated by the stress response, in the form of high allostatic load. In brief, allostatic load is the damage caused to the animal by over activation of the stress system. As intelligence increases, an animal lives less ‘in the moment’ and can prospect about future outcomes, leading to cognitively-mediated stress and high allostatic load. This can impact adversely on health, longevity and reproductive fitness, leading in turn to an evolutionary bottleneck, as illustrated in Fig.1.

Nature may have partly resolved the problem by varying the primate stress system. The argument will be that a random genetic change raised a threshold in the brain of late –state activation of the physiological stress response. Feedback from this raised threshold created a flexible and adaptive balance of accurate and inaccurate assessments of the animal's control of its environment. This same mechanism is (a) the origin of flexible, high-level human intelligence and (b) responsible for reducing the potential cost of stress response-mediated high allostatic load to within adaptive parameters. Human intelligence is not optimised to make accurate assessments of control in pursuit of proximate goals but to contribute towards the ultimate goal. This adaptive balance of accurate and inaccurate assessments of control acts as a buffer between the animal and its environment. Section 2 discusses the possibility of introducing purposeful flexibility into a brain, Section 3 expands on the evolutionary reasons why this might have occurred, and Section 4 proposes a framework for information processing around the primate brain, showing how such 'buffer intelligence' could have arisen in early hominins.

2 Accuracy of Control and the Generation of Purposeful Flexibility

Accuracy of assessments of control in the primate stress system may offer a way to understand flexible high-level general intelligence, defined as an ability to respond adaptively to challenges, whether novel or similar to ones previously experienced, and flexible anticipation and modelling of a wide range of future scenarios of varying likelihood and the ability to choose (or where necessary create) and execute adaptive responses thereto. The key word is 'adaptive', which can only be defined by reference to the ultimate goal, not preconceived ideas of accuracy or 'efficiency' in performance of proximate tasks.

The cognitive architectures reviewed by Duch and colleagues [1], the large scale brain simulations discussed by de Garis and colleagues [2], and the biologically inspired cognitive architectures discussed by Goertzel and colleagues [3] assume that achieving accuracy of assessments of control over the external environment is a wholly beneficial goal. Within artificial systems, accuracy of assessment of control may have to be partly traded for other benefits such as speed or economy of resources, but it remains an ideal.

A problem in artificial general intelligence is how to introduce purposeful flexibility into a system. The limitations of an artificial system are apparent when it encounters a novel situation. If it encounters an uncertain situation, a learning-based, Bayesian–inspired system [4] may operate in accordance with Bayesian statistics to infer the conditional probability of an event P occurring, given that Q has occurred, therefore allowing the system to respond optimally under known uncertainty. This may suffice in an environment with 'known unknowns', but if a genuinely novel situation arises such a system will not be able to optimise its response or learning about the environment and, indeed, *may not survive the initial encounter*. Whether it does survive will depend partly on luck. This is because Bayesian predictions based on a model cannot create new arbitrarily complex models out of smaller units [5]. A learning–based system without flexibility will therefore always tend to gravitate towards the most likely response based on what has occurred previously; it will have difficulty generating a functional response to a novel environmental challenge, or modelling novel scenarios and responses internally.

The problem and some possible solutions are outlined in Fig.2. This shows a memory / learning-based, probabilistic system operating especially at the level of sensory-motor coordination, anticipating the future based on the past. For this limited system to respond creatively to novel situations and model novel scenarios and possible responses internally, it must be integrated with a capacity to generate purposeful flexibility if it is to be described as having flexible, high-level general intelligence. Possible sources of purposeful flexibility include logic, randomness, 'chaotic itinerancy', and the focus of this paper, a variation of the stress response that harnesses accurate and inaccurate assessments of control to generate purposeful flexibility.

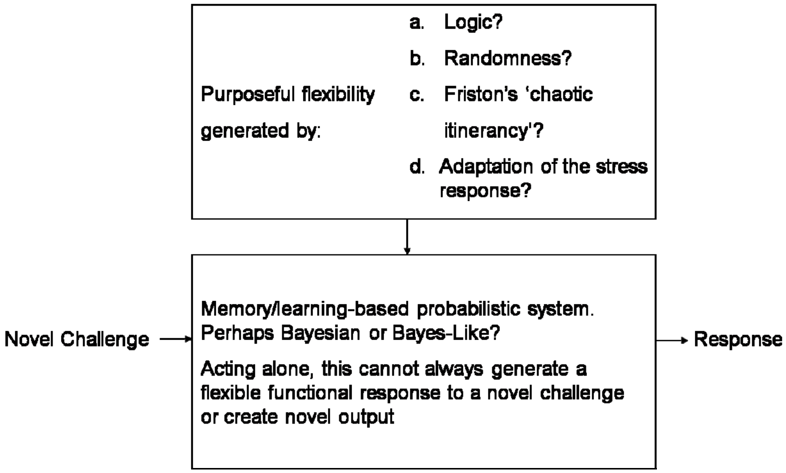

Fig. 2. Possible Sources of Purposeful Flexibility

Regarding option a in Fig. 2, there is interest in a synthesis of logical programming and Bayesian networks in the field of probabilistic programming [5], but it is unclear if this approach can generate sufficient flexibility or exploration if these are not inherent in Bayesian probability or logic.

Option b might achieve purposeful flexibility by introducing random combinations of existing models already in the system, and then sifting for utility as discussed by Calvin [6]. But brain tissue is expensive and the environment is dangerous; reliance solely on a stochastic exploration of model spaces approach would be expensive, very slow (because of the combinatorics) and high risk. A promising approach is Friston's recent synthesis (option c) aimed at providing a theoretical framework for understanding the brain [7]. In Friston's model, 'chaotic itinerancy' provides some flexibility, riding on top of Bayesian processes (equating to the lower box in Fig. 2), all within an overriding 'free energy' reduction framework. Put simply, the system expects to explore in a Bayes optimal fashion. There is insufficient space to discuss this here. Instead, the focus in what follows is on option d, which involves an adaptation of the stress response.

3 The Stress Response, Allostatic Load and the Cost of Intelligence

The primate stress response system comprises an integrated complex of central and peripheral neural and neuroendocrine processes that enable the animal to respond adaptively to threats ('stressors'), especially by vigorous muscular activity. For a review see Boyce & Ellis [8]. Ellis *et al* characterize its main features as follows [9]: Environmental events signaling threats produce responses within the neural circuitry of the brain and peripheral neuroendocrine pathways regulating metabolic, immunologic, and other physiological functions. This causes a shift to a state of biological and behavioral preparedness, involving increases in heart rate and blood pressure, metabolic mobilization of nutrients, preferential redirection of energy resources and blood to the brain and to the external musculature, and the induction of vigilance and fear. The neural basis for the organism's stress response comprises two anatomically distinct but functionally integrated circuits: the corticotrophin releasing hormone system and the locus coeruleus–noradrenaline system [10, 11, 12]. Co-activation of these two systems, along with their linkages to emotion regulatory brain regions such as the amygdala, anterior cingulate cortex and prefrontal cortex, produces the coordinated biobehavioral changes associated with the stress response in mammalian species [9]. The primary stress response axes, as well as their central and peripheral components, have been extensively conserved in the evolutionary history of vertebrate and mammalian species [9, 13,14].

In contrast to homeostatic systems, such as blood sugar, blood pH, and body temperature, which must be maintained within a narrow range, stress responses are allostatic [15]. Allostasis is the ability to achieve stability, or homeostasis, through change, as defined by Sterling and Eyer [16]. As an allostatic system, the stress response (or one of its elements) is adapted to turn on in response to a threat and then turn off again when the threat has passed. However, the stress response is *biphasic* [17]: It is highly adapted for dealing with acute stressors, but excessive, repeated or chronic stressors, or a failure to shut down the process appropriately, can cause high allostatic load [15, 18]. Allostatic load is the damage caused to the animal by chronic over activity, under activity or disregulation of allostatic systems [15]. High allostatic load increases vulnerability to a variety of diseases. Cardiovascular, immune and hippocampal-mediated memory systems are especially vulnerable to high allostatic load (19). The stress system itself can also be damaged by stress, leading to a vicious circle of disregulation and systemic damage [19]. In sum, chronic stress in humans can lead to illnesses such as heart disease, diabetes, depression, anxiety, substance abuse, gastrointestinal disorders, eating disorders, auto immune disorders, infections, and possibly even tumours [20].

In humans, intelligence, stress and the potential cost of high allostatic load intersect in the arena of appraisal and anticipation. Arnold [21] and Lazarus [22, 23, 24, 25, 26], have shown that in humans some stimulus- response pathways, including elements of the stress response system, are mediated by cognitive[1] appraisal, as illustrated in Fig. 3.

Fig. 3. Cognitive Appraisal (after Lazarus)

Allostatic processes, including stress responses, can be turned on not just in response to a present challenge, but also in anticipation of something that is likely to upset homeostasis [19, p.10]. Thus, anticipation and worry can contribute to allostatic load [15].

According to the field of 'emotion appraisal theory' (which includes stress), in humans there are two main appraisals. A primary appraisal checks the valence of a situation (positive or negative) and magnitude. A secondary appraisal identifies the causal agent ('self' or other) and any resources the person might draw on to meet the challenge. Secondary appraisal is an assessment of the controllability of the situation. In the formula of Lazarus [22], a stress response can result if a person assesses that an important negative challenge exceeds coping resources. An appraisal that a negative situation is uncontrollable can turn on a stress response, and an appraisal that it is controllable can inhibit or turn it off. Control does not have to be exercised; a belief that you have control is sufficient [27]. Crucially, the belief does not have to be correct; an incorrect belief that one has control can suffice to inhibit a stress response [19, p.261].

We can now begin to construct a hypothesis about the relationship between evolutionarily increasing intelligence and the cost of allostatic load. Intelligence increases the ability to anticipate threats, appraise controllability, and respond adaptively, initially increasing adaptive fitness. However, even if anticipation and assessment of controllability are accurate, and increased intelligence enables anticipation and avoidance or resolution of problems, this does not mean overall stress is reduced, because however many problems are accurately anticipated and solved there will always be a 'sink' of problems that are accurately anticipated and assessed as being uncontrollable. Thus, intelligence can increase cognitively -mediated stress and allostatic load. There is no limit to the number of problems that can be accurately anticipated but not solved, or to the ensuing physical damage. (Errors can also occur at any stage in this process.) In a living system such as a human, with an anticipatory self-preservation

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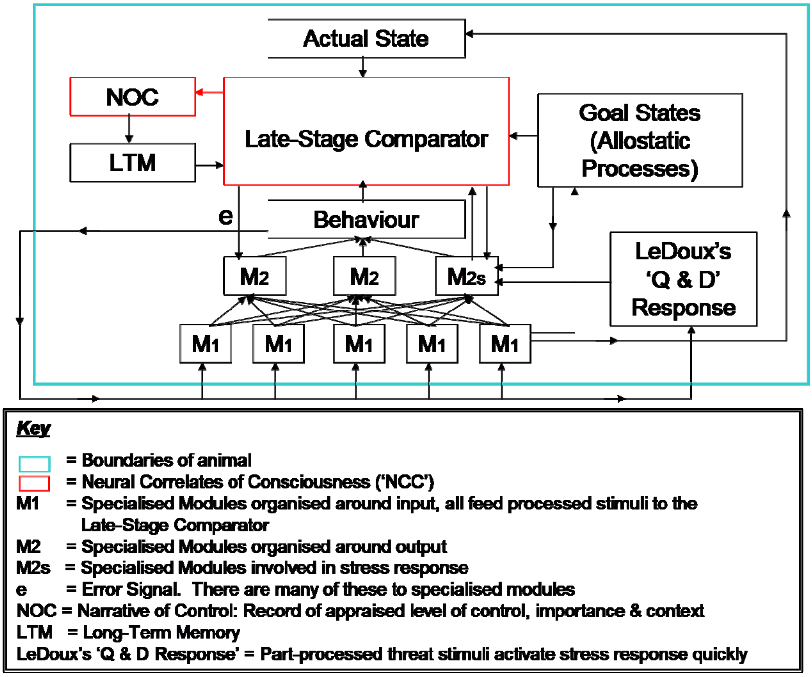
[1] It should be noted that the term 'cognitive' in this context does not imply that the process necessarily occurs entirely at conscious level [24].

system driven in part by highly developed flexible intelligence, the quality and duration of information inside the system can, without any other input from the outside, cause the system to destroy itself physically from the inside out.

We now consider how nature may have partly resolved the problem.

4 Proposed Framework

Fig. 4 shows a conjectural model of information flow around a non-human primate brain



Key

🟦 = Boundaries of animal
🟥 = Neural Correlates of Consciousness ('NCC')
M1 = Specialised Modules organised around input, all feed processed stimuli to the Late-Stage Comparator
M2 = Specialised Modules organised around output
M2s = Specialised Modules involved in stress response
e = Error Signal. There are many of these to specialised modules
NOC = Narrative of Control: Record of appraised level of control, importance & context
LTM = Long-Term Memory
LeDoux's 'Q & D Response' = Part-processed threat stimuli activate stress response quickly

Fig. 4.

In this simplified functional framework there are three main types of module (specialised function). There are many M1 and M2 modules, organised around inputs and outputs, respectively, perhaps using memory-based probabilistic processes and heuristics, including Bayesian or Bayes-like processes. To the extent that these modules do use memory-based probabilistic processes, they incorporate a model (or part thereof) of the animal's changing relationship to the world as 'priors'. M1 and M2 modules generate nearly all the intelligence and behaviour of non-human animals, but their limited flexibility means they have difficulty generating novelty.

The third type of module is a hypothesized 'Late-Stage Comparator' ('LSC'). Primates (and perhaps all mammals) have an LSC that integrates highly processed information from many brain areas ---sensory, motor, somatic (including homeostatic and allostatic), proprioceptive, nociceptive, affective and memory. As the LSC is situated within a larger feedback loop incorporating the animal and its external environment it can track the relationship longitudinally over time between the animal and its external environment, and assess the animal's control by comparing goal states and actual states. It creates a record of the level of control and the factors contributing thereto for the early stages of consolidation in long-term memory. Primarily, the LSC is part of the memory system.

The LSC is serial, as this is the most reliable-- perhaps only—way in which to capture the temporal order of association-based 'causality' and control[2]. Its output is a multi-modal serial record of effectiveness and context-- a 'narrative of control'--for later consolidation in long-term memory. ('Narrative' does not imply any lexical content, merely a serial record of events.) The LSC receives input from long-term memory (shown in Fig. 5) to create a more germane narrative of control, and somatic / affective input (not shown) to assist memory formation and retrieval.

The LSC has a secondary function. As it picks up late combinations of highly processed information it is well placed to register potential threats missed earlier by the stress response system. It can therefore be considered as a very late-stage part of the stress response system, instigating (or inhibiting) at a late stage a stress response. Even so, in non-human primates there is very little flexibility or intelligence here.

Fig. 5 shows the site of a proposed adaptation to the stress response system in early hominins. A chance genetic mutation slightly raised the threshold of late- stage activation by the LSC of the stress response, at point A. Feedback from A, in the form of a signal that the animal is in control, enters the LSC at point B. The initial effect may be tiny, but as it occurs at a sensitive point in the system the effects are wide-ranging and complex. Three points are relevant: First, perhaps such variations occur often in evolution, but the stress response is highly conserved as it aids survival. The majority of variations will fail. But the potential benefit of getting it 'just right' could be huge. Second, the variation is to a threshold of *late*-stage activation of the stress response. There are many earlier thresholds of activation. Most important is LeDoux's 'Quick and Dirty' system [29], that activates the primate (including human) stress system quickly in response to part-processed stimuli resembling a hardwired or fear-conditioned threat. This is not a part of the mechanism that generates high-level intelligence, but it has facilitated the appearance of this mechanism as it protects the animal from many dangers and allows evolution to vary other areas of the stress response system. Finally, for the variation to gain purchase in an individual and in the species, and not be 'washed out' by learning, the threshold should be relatively non-plastic. Perhaps it is used by other brain regions for calibration.

Generally, comparators and feedback loops are concerned with the past, and so offer an unlikely site for the origins of prospective intelligence. This is especially so if the LSC is primarily a part of the memory system. The pre-adaptation LSC tracks the relationship between animal and environment fairly accurately. However, as the LSC (pre and post-adaptation) is part of a feedback loop incorporating the animal and its

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[2] For an alternative explanation of seriality at this point, see Baars [28].

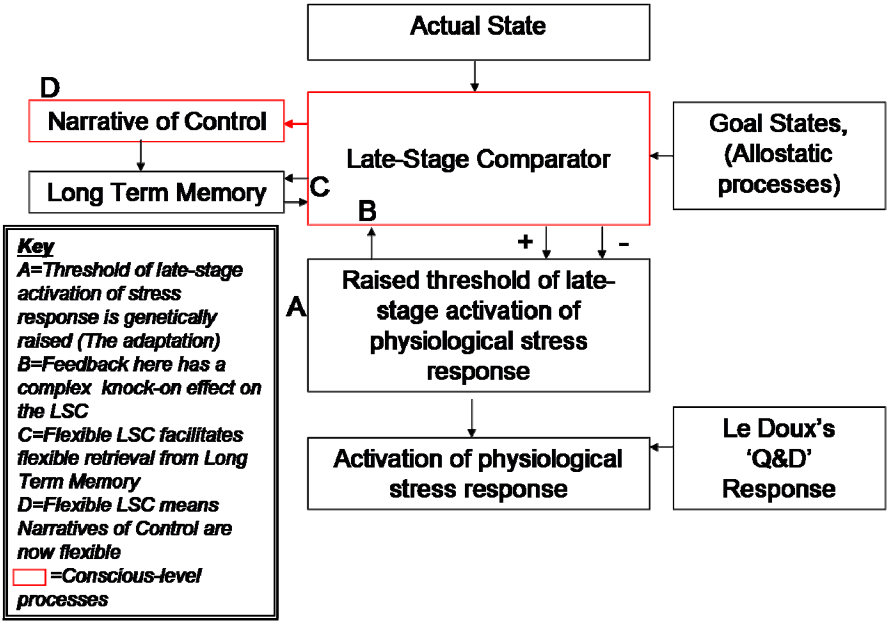

Fig. 5. Proposed Adaptation to the Primate Stress System

external environment it aims to bring actual and goal states together to solve proximate problems by sending error signals down to M2 modules. Pre-adaptation, there are just two elements, goal state and actual state, to be reconciled, so the phase space of possibilities is limited.

Fig.6 illustrates how such a process might generate purposeful flexibility.

Post-adaptation, feedback from the raised threshold enters the LSC at point B, indicating that the animal is in control of the situation. In some borderline situations this might cause a conflict, if the LSC otherwise assesses that the animal is not in control. Such borderline cases of conflict may not be important in themselves, but could become so if they open up a new landscape of possibilities. In the pre-adaptation LSC the relationship between the two elements of goal and actual states would be linear and able to express only a restricted range of possibilities. In the post-adaptation LSC there are three elements to be reconciled; the actual state, the goal state, and the message from feedback from the raised threshold indicating that the animal is in control. There is now the possibility of flexibility, as these three states can be reconciled in many ways. Goal states can be adjusted, actual states can be finessed, and pathways between them can become itinerant—guided by an imperative to seek 'control'. Such itinerancy is shown by the blue lines in Fig. 6. The phase space has been expanded. Evolution may have generated and harnessed chaotic processes within a serial comparator, creating high-level intelligence in early humans.

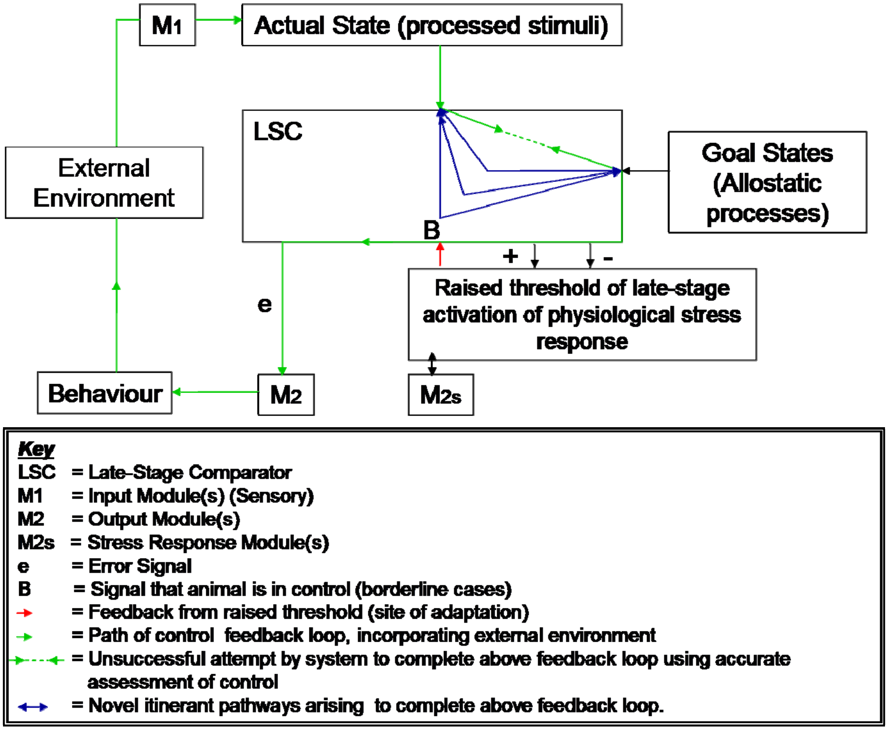

Fig. 6. Details of Post-adaptation Late-Stage Comparator *(This does not show bi-directional pathways between LSC and Long-Term Memory.)*

There are now two main types of negative feedback loop incorporating the LSC. The first is an ordinary negative feedback loop, with pathways in the LSC representing reasonably accurately the relationship between actual and goal states. Behaviour may be instigated to close the loop, and this is adaptive if it achieves a proximate goal. The second type may arise when the first type fails to achieve its goal. It involves itinerancy within the new landscape of possibilities, the expanded phase space within the LSC. This itinerancy, guided by an imperative to seek 'control', generates a flexible mixture of accurate and inaccurate representations of the relationship between actual and goal states. This may be adaptive in one of two ways.

First, guided itinerancy may generate novel pathways that eventually lead to a valid solution. As the LSC is freed from accurately tracking the present relationship between animal and environment it can now flexibly model new relationships, seeking control. This is facilitated by the LSC having bi-directional connections to long-term memory, as shown at point C in Fig. 5. The LSC can draw flexibly on information held in long-term memory, which includes elements of the animal's model of its interactions with the world, to create new and anticipatory models in the LSC. Behaviour is then instigated by the LSC sending fairly crude error signals to M2 modules for detailed implementation. The LSC is now host to anticipatory, domain-general intelligence. Second, the LSC may simply become 'stuck' in a closed loop incorporating inaccurate representation of actual and / or goal states and the relationships between them, causing the animal to assess *incorrectly* that it is in control. This latter possibility may be adaptive if it reduces allostatic load, and thereby contributes to the ultimate goal. The worst errors at this point will be winnowed out by evolution. If the problem is not be resolved in any of the above ways a stress response may result, which may itself be adaptive.

Together, the above suite of options constitutes a form of flexible, high –level intelligence that acts as a buffer between the short and long term structural integrity of the animal and its environment. Nature has overcome the potential problem of an evolutionary bottleneck in an economical way. The same mechanism that creates flexibility in the LSC, guided itinerancy, can also make incorrect assessments of control, thereby reducing allostatic load. The brain is involved in a systemic balancing of proximate and ultimate goals over the lifetime of the person, in which buffer intelligence is optimised not for accuracy in pursuit of proximate goals but for achieving the ultimate goal. This balancing act is itself not intelligent; it is systemic.

This new form of intelligence has arisen in the hominin LSC at a point in the primate brain where there was previously very little flexibility. It is not an incremental development of other forms of intelligence, but rides on top of them, and is well-placed to exploit previously existing top-down pathways from the LSC to M2 modules by sending down intelligent instructions for execution. It is therefore a form of 'top-down' intelligence, complementing whatever 'bottom-up' intelligence earlier species may have. The new flexibility of the LSC might explain the origins of increased working memory, as a flexible LSC could reverberate both its own content and content received from long-term memory. A flexible LSC could share information between different M2 modules, increasing what Mithen [30] calls 'cognitive fluidity', and give rise to analogical thought. In principle, flexibility in the LSC could enable recursion of its own contents, and an ability to divide problems up into smaller constituent units and sub-goals, and flexibly manipulate potential solutions. It might also enable first order intentionality, with the animal becoming cognitively self-aware and self-monitoring at a conscious level. Lastly, as the LSC and its output, the narrative of control, may be the neural correlates of consciousness, we might hope for an eventual theoretical integration of high-level intelligence and consciousness that accounts for the relative lateness of conscious processes [31].

A capacity for increased intelligence could spread from the LSC to M2 modules in a way similar to that by which it originated in the LSC. A flexible LSC could send an increased range of signals to M2 output modules regarding controllability. This might in turn create the conditions for guided itinerancy to arise in an expanded phase space in any serial comparators in M2 modules. Intelligence could be 'sucked down' by M2 modules from the LSC, with different types and degrees of intelligent capacity arising in different M2 modules according to their structural capacities and ecological requirements. Such intelligence would generally operate automatically, below conscious awareness, with only highly processed abstracts of its output entering the LSC. An obvious candidate for this process would be M2 language module(s). The comparator in an M2 language module would initially be concerned to assess the effectiveness of the communication process itself, but as in the LSC, flexibility in a comparator might also enable flexible organisation and recursion of its own contents, and give rise to flexible syntax.

5 Conclusion

It has been argued that the primate stress response system was a selective force and originating mechanism for increased hominin intelligence. The concept of 'buffer intelligence' may offer an evolutionarily plausible and economical framework for understanding the origins and development of several aspects of present-day human cognition, including flexible high-level general intelligence and increased creativity, expanded working memory, flexible retrieval from long-term memory, analogical thought, high-level monitoring of thought (cognitive self-awareness), and flexible linguistic syntax. A complex balance of costs and benefits has arisen from this stress-intelligence interaction over the hominin lineage. In present-day humans the main costs are quite frequent inaccurate appraisals of control and perhaps some rigidity of thought, and a residual but significant vulnerability to cognitively mediated stress and allostatic load and linked diseases. Outweighing benefits include a virtuous circle of increased intelligence, general health and longevity, and cross-generational transfer of the fruits of increased intelligence mediated by language.

Although for the sake of simplicity this paper presents the idea of a key genetic variation as a 'one off' event, most likely such variations occur frequently, with the majority failing (in line with their 'high risk / high reward nature) and those few that do gain an evolutionary purchase successively ramping up and refining the effects. Some version of the process may have occurred in different animal species including, perhaps, some that are now extinct.

Of the possible empirical ways of pursuing this question, comparative neuroanatomy, comparative genomics, and computer simulation to proof of principle of the concept of buffer intelligence, it is perhaps the last that may offer most interest to supporters of the INBIOSA project. Of particular interest is whether evolution may have generated and harnessed chaotic processes in a strategically placed serial comparator to expand phase space and create flexible high-level intelligence, whether the elements of this may be formulated mathematically, and whether the process can spread throughout a complex adaptive system.

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Passively Active – Actively Passive Mutual Anticipation in a Communicative Swarm

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Abstract. In this study, the alternation of the passively active and actively passive attitudes is considered as the basic scheme of communication in a society-like system. We construct a model for swarming behavior based only on mutual anticipation implementing this basic scheme of communication, and we estimate a swarm as a mobile network consisting of mutual anticipation structures. In particular, we show that a mutual anticipation structure can be expressed as a fixed point with respect to equivalence classes in a network and that redundant connections in a mutual anticipation structure can contribute to generating and maintaining a robust and dynamic swarming behavior.

Keywords: Communication, Swarm model, Lattice theory, Mobile network.

1 Introduction

Computers and machines are always passive responders to a given stimulus and/or order on the one hand. Action independent from its environment is purely active on the other hand. Both of these attitudes are different from communication in a society. Presumably, therefore, the attitude of communication in a society must be actively passive or passively active. The actively passive is the attitude of an agent actively waiting for an order, where the agent is prepared for any order. In a linguistic activity, the sentence "May I help you?" expresses the attitude of the actively passive. By contrast, the passively active is the attitude of the agent who is made to act. The Japanese comedians "Ostrich Club," consisting of three men, illustrate the passively active attitude. Given a situation in which one of the three has to swim in cold water, all raise their hand to volunteer, although they all clearly dislike it. Two men raise their hands quickly, and the third man does so slowly because he is hesitant. Once the third man raises his hand, the first two men pull down their hands and say "please". The third man is passively active and has to swim in the cold water. We call the attitude of the third man the Ostrich effect.

Passively active and actively passive attitudes can be related to Peirce's categories of sign, type and token [1, 2]. Type refers to class, rule, attribute, and abstract whole on the one hand, and token refers to a concrete object, collection, or parts, on the other hand. Actively passive is the attitude of an agent dispatching a signal from the token side to the type side. Passively active is the realization or degeneracy from the type to the token. Alternation of simply passive and active entails miscommunication because the attitudes are separated from each other. Passively active and actively passive action can mediate type and token.

In this study, we implement the passively active and actively passive as the process of mutual anticipation in a swarm model. Previous models are based on three kinds of rules: alignment rules, cohesive rules and separation rules [3-6]. The most important rule is the alignment rule. By this rule, an individual matches his or her velocity to those of his or her neighbors in the neighborhood, resulting in alignment in a neighborhood. This mechanism is essential for generating a swarm, school or flock in previous models. In following an alignment rule, each individual is purely passive in observing neighbors and is purely active in changing his or her velocity to match. The alternation of active and passive action can give rise to alignment in a swarm as a whole without diversity of individuals. In other words, radical coincidence of passive and active actions results in coincidence of individuals and a whole swarm. By contrast, animals reveal a coherent and robust swarm, school, flock or herd while maintaining individuality [7, 8]. How is diverse individuality connected with a whole group? The key idea is passively active and actively passive processes.

2 Swarm Model Based on Mutual Anticipation (MA)

Based on numerous surveys of a swarm of soldier crabs, *Mictyris guinotae*, we previously report that each individual moves in adjusting their orientation with its neighbors. These moves can look like inherent noise. In this sense we can say that the inherent noise can positively contribute to generate a robust swarm, where we also introduce the alignment rule [9].

In this section, we abandon the alignment rule, and instead, we introduce the mechanism of mutual anticipation. As shown in Fig. 1A, individuals are represented by blue squares in a grid. Each individual has a principal vector represented by a red arrow and a number of black arrows accompanying the red one. All of the arrows are called potential transitions. The most important parameter of the model is the number of potential transitions, P. In the case of Fig. 1A, each individual has four potential transitions (P = 4). It is also assumed that each individual can detect neighbors' potential transitions, with neighbors being defined by individuals who share the targets of potential transitions. Each individual knows where the neighbors can go and can estimate locally popular sites to which some potential transitions converge. In Fig. 1a, pale blue squares represent locally popular sites.

By asynchronous updating, one individual can move to the most popular site. The individuals who do not move to the most popular site move to the second most popular to avoid a collision. If there are two or more maximal popular sites, one site is randomly chosen. If there is no popular site in the targets of potential transitions, then, if it can, an agent moves to the site vacated by the previously updated agent, called the Holes. This behavior results in cohesion of individuals. Finally, if there is neither a popular site nor the Hole among its potential transition, the agent chooses one of them randomly. Thus, an agent isolated from its flockmate moves randomly.

This process is the mechanism of mutual anticipation. The elementary structure of mutual anticipation can be expressed as a set of arrows, a pair of whose targets are the same site but in which individuals can choose other possible arrows to avoid collision (Fig. 1B). In other words, each individual signals a number of possible transitions that can be detected by neighbors (see Appendix for the detail).

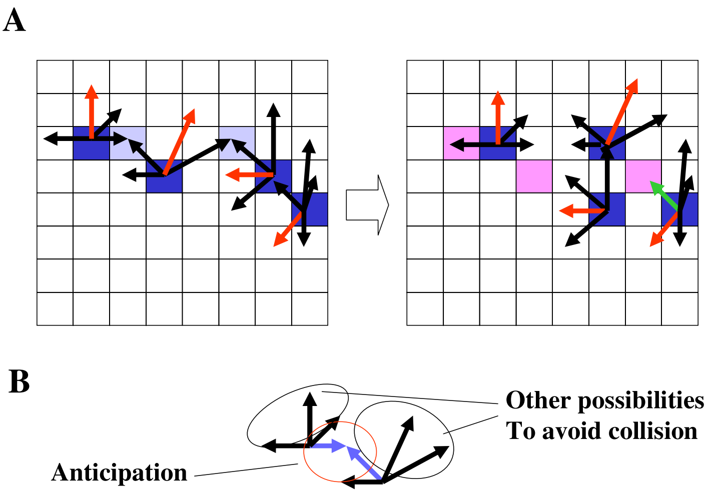

Fig. 1. A. The move of three agents (blue square) in a grid space. See text for details. B. Elementary structure of mutual anticipation.

This finding is an implementation of the actively passive attitude, because the agent is ready to be employed by neighbors in the sense of “May I help you?” Because of numerous “signals” in the form of potential transitions, there can be popular sites to which some potential transitions converge. The potential transitions that neighbors can see are interpreted as a sentence like “May I help you?” because it can attract (or generate) popular sites. By asynchronous updating, one agent is made to reach the popular site. This behavior is an example of the Ostrich effect and is, therefore, an implementation of the passively active attitude. In recalling the Ostrich effect, it is easy to see that any other possible transitions, rather than the converged transition (anticipation [10, 11]), are necessary to make one agent passively active. The elementary structure of mutual anticipation is, therefore, expressed as a structure consisting of converged and diverged arrows originating from the same sources, equipped with asynchronous updating.

After a move in a space, if mutual anticipation occurs in some potential transitions (i.e., there are some popular sites belonging to some targets of potential transitions of the agent), the principal vector of the corresponding agent is not changed. Otherwise, the principal vector is randomly modified (not an alignment rule). Even if the principal vector is not changed, all other potential transitions are randomly determined at each step. The change of the position and the possible change of principal transitions constitute one elementary transition step, which is iterated.

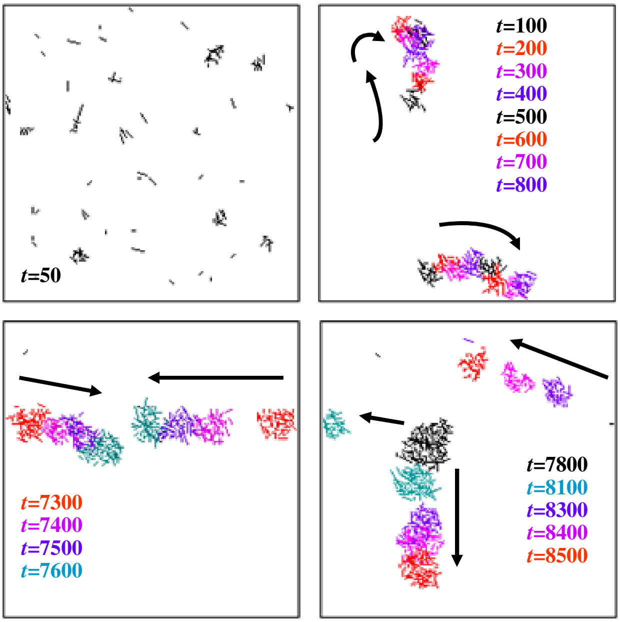

Fig. 2. Time development of the swarm model based on mutual anticipation: Each individual is represented by the move from *t*-1 to *t*. In the transient time, small generated swarms wander or stay at the same place. In the top right, only dense swarms are depicted. Later, two or three swarms are generated, which move in a straight line.

Fig. 2 shows a typical time development of our swarm model. Each individual has 20 potential transitions. Even if a dense swarm is generated, principal vectors in a swarm cannot be aligned because there is no alignment rule. Soon after a swarm is generated by self-assemblage, the swarm stays at the same place and/or randomly wanders (Fig. 2, top right). After that event, depending on rearrangement of individuals, mutual anticipation occurs in one side of the boundary of a swarm and the swarm moves in a straight line (*t*=7200-7500 in Fig. 2). Later, multiple swarms collide to generate a unified swarm, which subsequently divides into parts and is reunited again (*t*=7600 and later in Fig. 2). The process continuously proceeds. Even if all principal vectors remain constant after they are randomly set in the initial step, the behaviors of swarms are basically the same.

3 Structure of MA

In this section, we show how to describe the structure of mutual anticipation. First, we define a network of mutual anticipation, ***NMA***, as a collection of a set of directed edges, E, a set of vertexes V, a function, $d_0:E\rightarrow V$, assigning a source for an edge, and a function, $d_1:E\rightarrow V$, assigning a target. This network is expressed as $\boldsymbol{NMA} = <E, V, d_0, d_1>$. Fig. 3A shows an example of a network, where $E = \{a, b, c, d, e, f\}$ and $V = \{X, Y, Z, P, Q, R\}$. For a directed edge c in Fig. 3A, $d_0(c) = Y$, and $d_1(c) = P$.

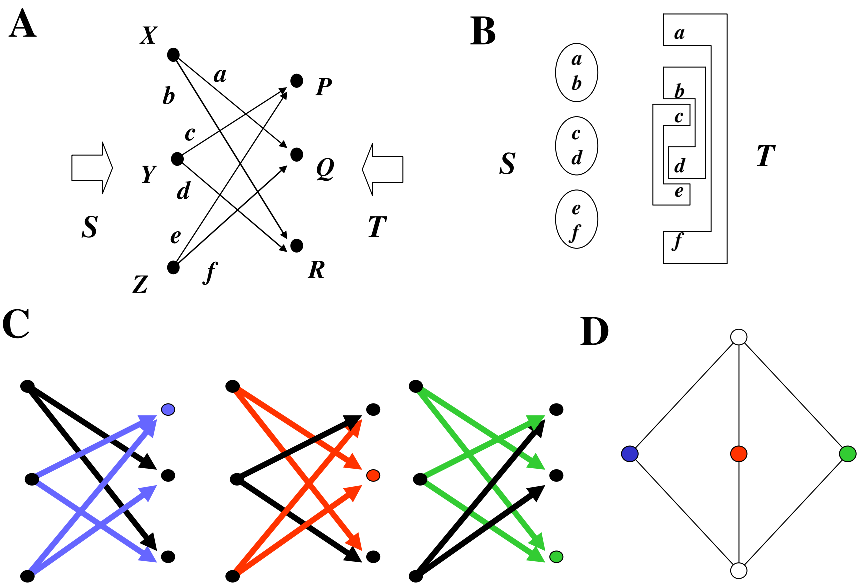

Fig. 3. A. An example of a mutual anticipation network. S and T show equivalence relations with respect to sources and targets of edges. B. All equivalence classes derived by S (left) and T (right). C. Three possible elementary MA structures, obtained as a fixed point of S^*T_* operation. Each structure is drawn as a set of blue, red, or green arrows. D. A lattice obtained by a collection of all fixed points of S^*T_* operation, where order is defined by inclusion. The greatest and least elements are E and the empty set.

We introduce two kinds of equivalence relation, source relation, S, and target relation, T. A source relation and target relation are defined by

$$S = \{<e, f>\in E\times E \mid d_0(e) = d_0(f)\},$$

$$T = \{<e, f>\in E\times E \mid d_1(e) = d_1(f)\},$$

respectively. It can be straightforwardly verified that these relations are equivalence relations. These two kinds of equivalence relations can constitute a set of equivalence classes, as shown in Fig 3B. The equivalence class of an edge e with respect to an equivalence relation, R (S or T), is defined by

$$[e]_R = \{x \in E \mid \langle e, x \rangle \in R\}.$$

In Fig. 3A, edges a and b constitute an equivalence class of source, and edges a and f constitute an equivalence class of target. These equivalence classes are expressed as $[a]_S = \{a, b\}$ and $[a]_T = \{a, f\}$. Each equivalence class of equivalence relations S and T in Fig. 3A is drawn as a loop in Fig. 3B.

Now, we define two kinds of operations. One is T_*. For F, that is a subset of E, $T_*(F)$ is defined by a collection of elements of equivalence class of target included by F, such that

$$T_*(F) = \{x \in E \mid [x]_T \subseteq F\}.$$

For example, in Fig. 3A, $T_*(\{a, b, f\}) = \{a, f\}$, because $\{a, f\} = [a]_T \subseteq \{a, b, f\}$ and an equivalence class containing b such as $[b]_T = \{b, d\}$ is not included by $\{a, b, f\}$. The other operation is S^*, which is defined for F,

$$S^*(F) = \{x \in E \mid [x]_S \cap F \neq \varnothing\}.$$

For example in Fig. 3A, $S^*(\{a, e\}) = \{a, b, e, f\}$ because two equivalence classes of S such as $[a]_S = \{a, b\}$ and $[e]_S = \{e, f\}$ have non-empty intersection with $\{a, e\}$. These two operations originate from rough set theory [12]. Given any equivalence relation $R \subseteq U \times U$ with a universal set U, $R_*(X)$ and $R^*(X)$ are called a lower and upper approximation, respectively. Both of $R_*(X)$ and $R^*(X)$ are called rough sets for a given crisp set, X.

Under our definitions of equivalence relations, S and T, $T_*(X)$ is a collection of directed edges converging to targets. Similarly $S^*(X)$ is a collection of directed edges diverged from sources. It is easy to see that an elementary mutual anticipation structure is expressed as a fixed point after composition of the two operations, such that for $F \subseteq E$,

$$S^*T_*(F) = F.$$

Fig. 3C shows a collection of fixed points with respect to S^*T_*, given a network as shown in Fig. 3A. The set of edges depicted in blue is $\{c, d, e, f\}$, and it can be seen that $S^*T_*(\{c, d, e, f\}) = S^*(\{c, e\}) = \{c, d, e, f\}$. Note that T_* eliminates several edges, following which S^* generates some edges. By applying T_*, converged edges to a particular site are collected, and subsequently, by applying S^*, diverged edges from sources of previously collected converged edges are collected. This result constitutes an elementary anticipation structure.

In collecting all fixed points with respect to S^*T_* we can obtain a lattice that is a partially ordered set closed with respect to the binary operations join and meet [13]. Partial order for a lattice is defined by inclusion. Fig. 3D shows a lattice obtained from the network in Fig. 3A. The elements of the lattice are fixed points with respect to S^*T_*. Colored circles correspond to the elementary mutual anticipation structures with the same color shown in Fig. 3C. The greatest element is E, and the least element is the empty set, which are also fixed points with respect to S^*T_*.

Actually, any lattice can be obtained by using a pair of two kinds of equivalence relations [14]. In the context of a network, collecting all mutual anticipation structures always entails a lattice.

4 Network Consisting of MA

Recall the swarm model. Fig. 4 shows the time development of a mutual anticipation network of our swarm model. Each individual is represented by a square, and the mutual anticipation network is represented by thin lines, where only convergent arrows to popular sites are drawn. If two squares are connected, a point in the curve connecting them is a popular site. For the case of three or more squares, the junction point is a popular site. In this simulation, each individual has 15 potential transitions, and 200 agents are given. The boundary condition is defined as wrapped.

Time proceeds from left top to right bottom. Initially, mutual anticipation can occur rarely. Gradually, the elementary mutual anticipation structures become interconnected, which can give rise to a larger, robust mutual anticipation network. If there is no mutual anticipation network between two agents, they are independent of one another. Otherwise, the agents show strongly correlated behaviors because they share popular sites. The anticipation network can tighten the potential connections among agents and generate dense and robust swarming.

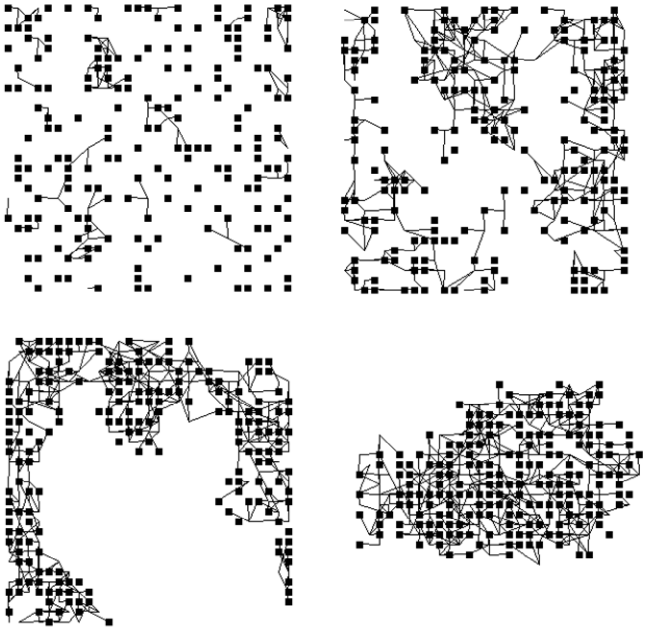

Fig. 4. Mutual anticipation network of the swarm model: Time proceeds from top left, to top right, bottom left and bottom right. Potential transitions to popular sites are drawn as thin lines. Each individual is represented by a square.

In this section, we calculate the size of mutual anticipation, S_{MA}, which is the number of edges employed for maximal elementary mutual anticipation, and the size of maximal network, S_{NET}, which is the number of edges employed for maximal network. Fig. 5 shows the time development of S_{MA} and S_{NET}. Independent of the number of potential transitions, P, the size of mutual anticipation structure is invariant through time. However, if P increases beyond 4, the size of maximal network is gradually increased.

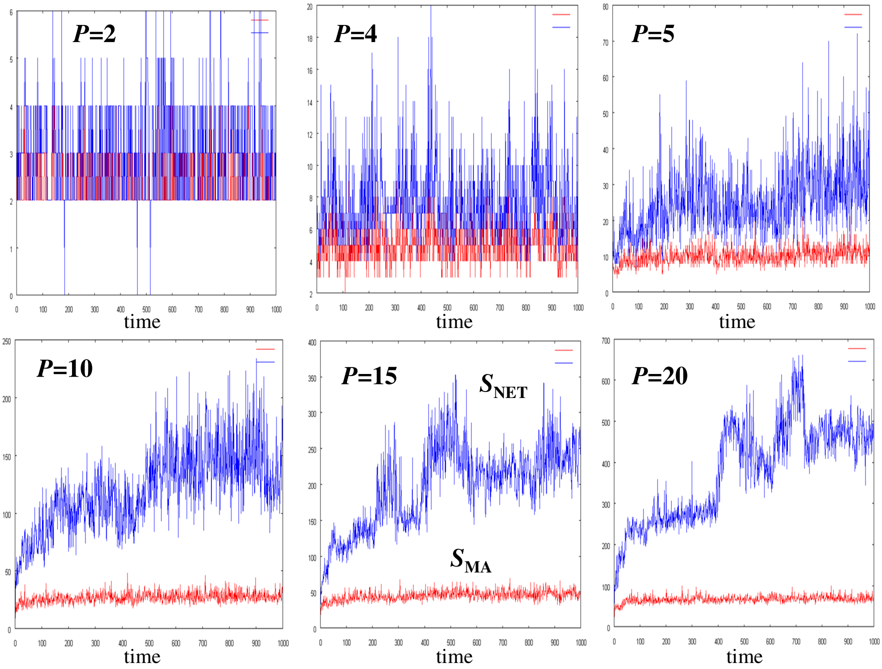

Fig. 5. Each graph shows the time development of S_{MA} (red) and S_{NET} (blue) of a swarm consisting of 200 agents, where P represents the number of potential transitions for the corresponding swarm.

The size of mutual anticipation structure is calculated using a fixed point. We collect all arrows converging to one site and all divergent arrows originated from sources of collected converged arrows, and a set of these arrows is expressed as an elementary mutual anticipation structure. This finding means an elementary mutual anticipation structure is an atom of a lattice. The growth of the maximal network is thus considered to be based on the interconnection of the elementary mutual anticipation structures. If P is below 5, the small number of potential transitions makes it difficult to connect with isolated elementary mutual anticipation structures. Beyond 4, however, the transitions are perpetually interconnected with each other because of a large number of divergent potential transitions. Once several elementary mutual anticipation structures are combined with each other, constant chances to generate popular sites are maintained. Thus, a mutual anticipation network is robustly maintained, and it can positively contribute to robust swarming.

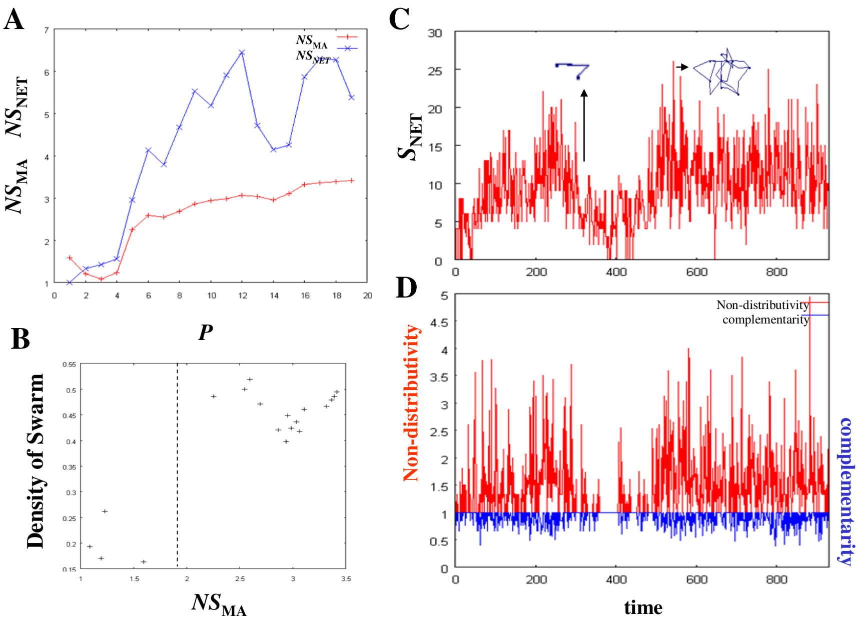

Fig. 6. A NS_{MA} and NS_{NET} plotted against P. B. Density of a swarm plotted against a swarm. C. Time development of S_{NET} for a swarm consisting of 10 agents. D. Time development of the corresponding lattice estimated by non-distributivity and complementarity.

NS_{MA} is the size of maximal mutual anticipation normalized by P; thus, $NS_{MA} = S_{MA}/P$, and NS_{NET} is the normalized size of maximal network where $NS_{NET} = S_{NET}/S_{MA}$. Fig. 6A shows NS_{MA} and NS_{NET} plotted against P. After the first 1000 steps of the time development of a swarm consisting of 200 agents are discarded, the averages for the following 1000 steps of S_{MA} and S_{NET} are obtained. As mentioned in Fig. 5, both of the sizes are drastically increased as P increases beyond 4. Fig. 6B shows the density of a swarm plotted against NS_{MA}. First, we calculate the number of agents in the unit neighborhood for each agent and obtain the average. Each averaged number of neighbors for a swarm with NS_{MA} is divided by the maximal number of neighbors for the maximal swarm, and that value is the density of the swarm. This graph also shows drastic change beyond a particular value of NS_{MA} and implies that NS_{MA} beyond a particular value can contribute not only to a robust network of mutual anticipation but also to a robust and dense swarm.

If a population size is small, being approximately 10, and each individual has 10 potential transitions, we can directly calculate all elements of the corresponding lattice, and we can estimate its structure. In our framework, we obtain binary relation included by direct products of two sets of two equivalence classes. Because the one set of equivalence classes is a set of sources of potential transitions, the number of equivalence classes is nearly equal to the number of elements. The other set of equivalence classes is a set of popular sites. Although it is not directly estimated, if P =10, it is less than 15. The number of elements of a lattice is, at this case, approximated as 2^{10}-2^{15}. It is therefore easy to pick up all elements of a lattice.

We can estimate lattice structure using complementarity and non-distributivity. As mentioned before, a lattice is a partially ordered set closed with respect to join and meet. Consider the case in which, if join is applied to a pair of elements in a lattice, it yields the greatest element of the lattice, and if meet is applied to the same pair, it yields the least element of the lattice. In this case, we say that one of the pair is a complement of the other. Because join and meet are generalizations of union and intersection in set theory, respectively, it is easy to see that complement is a generalization of complemented set. We think that complement pair can be used as an analytical tool to estimate figure-ground relations for various things.

Complementarity is defined here by the number of elements which have their own complement in which the number is normalized by the number of elements of a lattice. The lattice in which all elements have their own complements is called a complemented lattice. Complementarity is 1.0 for a complemented lattice. Complementarity is larger than 0.0 and less than 1.0 for a non-complemented lattice. Non-distributivity is defined by the number of complements for each element which has a complement. In a distributed lattice, the complement is uniquely determined if it exists. Otherwise, plural complements can exist for an element of a lattice. In the context of a network of a mutual anticipation structure, high non-distributivity shows the redundancy of connections in mutual anticipation structures because the figure-ground relation for a whole network has high diversity. If complementarity is low, certain networks exist which are not related to a whole network, which indicates another kind of redundancy for a network.

Fig. 6C shows the time development of S_{NET} in a small network of 10 agents with P=9. Fig. 6D shows the time development of the corresponding lattice, as estimated by non-distributivity and complementarity. It is easy to see that non-distributivity is positively correlated with the size of maximal network and that complementarity is negatively correlated. This observation implies that the growth of maximal network can be dependent on the number of atomistic mutual anticipations which can mediate connecting MA. In other words, redundancy of mutual anticipation structures can produce many chances to generate popular sites and the following mutual anticipation structures, which can maintain a robust and dynamic network and swarm.

5 Conclusion

Starting from an investigation of the basic scheme of communication, the alternation of passively active and actively passive attitudes, we elaborate on mutual anticipation structure in a swarm model. Although previous models of swarms are based on local potential for making order structure coupled with external perturbation, our swarm model based on mutual anticipation has inherent perturbation which can positively contribute to the generation of a robust swarm. As a result, we can say (i) a swarm can be generated and robustly maintained by mutual anticipation; (ii) the structure of mutual anticipation is expressed as a fixed point with respect to a particular operator derived from two kinds of equivalence relations; (iii) the collection of all anticipation structures constitutes a lattice and the growth of a mutual anticipation network is dependent on the corresponding lattice structure.

The actively passive and passively active attitudes are regarded as actions mediating the type-oriented and token-oriented worlds. In other words, these attitudes bridge the external, indefinite world and the internal, operationally explicit world. They are the attitudes of an internal observer [15] or endo-observer [16] who always witnesses the external world, yet still manages to do things. In our swarm model, the actively passive is implemented by the divergent portion of the potential transitions, and the passively active is implemented by the convergent portion of the potential transitions, equipped with asynchronous updating. This implementation can be viewed as an attempt to implement the passively active and actively passive. Communication of this type should be studied in the framework of endo-perspective.

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Appendix (Details of the model)

This model consists of N individuals moving in discrete time and in a grid space. The location of the k-th ($0<k<K$) individual at the t-th step is given by $\boldsymbol{P}(k, t) = (x, y)$. Each k-th individual at the t-th step has P number of potential transitions $\boldsymbol{v}(k, t; i)$ with $0\le i<P$. The transition $\boldsymbol{v}(k, t; 0)$, called the principal vector, is represented by the angle $\theta_{k,t}$ such that $\boldsymbol{v}(k, t; 0) = (Int(L\cos\theta_{k,t}), Int(L\sin\theta_{k,t}))$, where for any real number x, $Int(x)$ represents integer X such that $X\le x<X+1$. L is the length of principal vector (In all simulations $L = 4$). For $0<i$, the potential transition is defined using a random value, η_i, selected with equal probability from [0.0, 1.0] and a random value (radian), ξ_i, selected with equal probability from $[-\alpha\pi, \alpha\pi]$, as $\boldsymbol{v}(k, t; i) = (Int(L\eta_i \cos(\theta_{k,t}+\xi_i)), Int(L\eta_i \sin(\theta_{k,t}+\xi_i)))$.

For each $\boldsymbol{v}(k, t; i)$, the target of the vector is represented by $\tau(k, t; i)$ such that $\tau(k, t; i) = \boldsymbol{P}(k, t)+ \boldsymbol{v}(k, t; i)$. To implement mutual anticipation, we define the popularity of the targets of the vectors. The popularity is defined for each site (x, y) at the t-th step, by $\zeta(x, y; t) = | \{ \tau(k, t; i) \mid \tau(k, t; i) = (x, y)$ and for any k, $\boldsymbol{P}(k, t)\neq(x, y) \}|$. The order of updating is randomly determined independent of the number of individuals, k. If there exists $i\in I$ such that $\zeta(\tau(k, t; i)) \ge 2$, the next site for the k-th individual is defined by $\boldsymbol{P}(k, t+1) = \tau(k, t; s)$, where s satisfies the condition such that for any $i\in I$, $\zeta(\tau(k, t; s)) \ge \zeta(\tau(k, t; i))$. In other words, an individual moves to the target of its own potential vector that has maximum popularity. If there are multiple such sites, one of them is chosen randomly.

An individual who moves to a popular site is called a wanderer. The vacated site generated by a moving wanderer is called a Hole. After all wanderers have been updated, an individual who cannot move to a popular site moves to the Hole if one of its potential transitions reaches the Hole. If an individual is neither a wanderer nor a follower moving into the Hole, he or she moves by choosing one of potential transitions randomly.

In all simulations in a text, $\theta_{k,0}$ is randomly determined. After that, if mutual anticipation occurs for k-th individual, $\theta_{k,t+1} = \theta_{k,t}$. Otherwise, $\theta_{k,t+1} = \theta_{k,t} + \zeta_k$ where ζ_k selected with equal probability from $[-0.1\pi, 0.1\pi]$.

Contributions of the Operator Hierarchy to the Field of Biologically Driven Mathematics and Computation

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Abstract. This position paper discusses the potential contributions of the 'operator hierarchy' theory to the INBIOSA project. The operator hierarchy offers a fundamental, theoretical, multilevel methodology for analysing natural organisation. In this theory, the word 'operators' generically represents the physical particles and the organisms. The operators theory may act as a backbone for modelling approaches because it offers a general theory describing how hierarchical levels of organisation emerge along three dimensions: from interactions between operator, from the complexity increases within operator and from the complexity increases leading to higher level operators.

Keywords: natural organisation, operator hierarchy, levels of complexity, particles, organisms, dimensions for hierarchy, closure, Big History, open-ended evolution, ontology, eco-toxicology.

1 Introduction

In 1992 the Dutch government initiated a study aiming at an integration of the results of more than twenty PhD studies dealing with toxicant effects on the functioning of terrestrial ecosystems. Such an integration required a theoretical basis for the quantitative modelling of states and rates, connected by a model structure defining the relationships. The framework that was sought ideally should allow a structured treatment of toxicant effects at different 'levels of organisation', from chemical reactions, to organisms, populations and the ecosystem. During the project, two major challenges were encountered:

1. *The identification of different types of systems/elements. Information about such types has marked advantages for (individual based) modelling approaches. It shows which interactive properties (operations) are typical for specific system types. In addition it shows which type-properties of lower level systems are inherited by higher level systems.*
2. *The identification of a rationale for recognizing strict 'levels of organisation' that can serve as the basis for a bottom-up, open-ended theory for the evolution of organisational complexity.*

Interestingly, the INBIOSA project has somewhat similar goals, aiming at biologically driven mathematics and computation for constructing models that deal with natural phenomena at, and across different levels of organisation. Working towards such broad goals requires a theory about different types of entities and their organisation, which implies a methodology for their identification.

2 Why Focus on Hierarchy Theory?

Before discussing hierarchical organisation in more detail, it is necessary to pay attention to suggestions that the process of defining entities and levels of organisation is unnecessary or trivial.

Modellers generally have a practical attitude. They doubt the use of spending much time on theoretical considerations about what exactly are the fundamental elements of their models. A much heard argument in this context is that the entities and levels can be chosen at will, as long as the model supports the goals of the project. Yet, models make use of concepts of 'lower' and 'higher' levels, of 'individuals' and of 'state' and 'rate' variables, which implies that modellers must know what these concepts actually refer to.

Another assumption is that nature does not offer strict borders between types of elements. Indeed, however abrupt any transition in state space may be, one can always find transition states. In between of such transition states, however, there is little discussion about whether or not a system is an atom, a molecule or a bacterium. In fact, the existence of transition states does not pose a 'hard' problem, because the thinking in abstract classes such as atoms and bacteria acknowledges that environmental conditions may drive a system to or across the limits of its class/type. For example, the electron shell of the atom is lost at temperatures above 3000 ^{o}K . Likewise, bacteria cannot maintain their autocatalysis and membrane under extreme conditions, such as high temperatures or extreme pH's.

Another aspect of transitions is that they normally are the result of many possible construction pathways. For example the transition from unicellular life to multicellular life includes individual cells adhering to each other by means of a matrix of gell, cells that are able to mutually bind to each other's cell membranes without showing chemical communication, cells that not only bind but also show chemical communication without or with cell-differentiation. Finally, cells may show plasma strands, making the multicellular a true unity from the point of view of shared plasma and membrane. In the latter case, the cells still remain individuals, because they can be recognized by their individual genes. The identification of any of these structures as a multicellular being depends on a framework allowing relevant distinctions.

Finally, a large body of literature extending over various decades offers a plethora of examples of 'hierarchical' rankings of 'elements' (e.g. Odum 1959, Weiss 1971, Koestler 1978, Miller 1978, Close 1983, Salthe 1985, de Kruijf 1991, Haber 1994, Naveh & Lieberman 1994, Hogh Jensen 1998 and Korn 2002). This may give the impression that the problem of identifying levels and entities has been solved. As a typical, integrative example of such approaches, one may consider the following ranking: quark, hadron, atom, molecule, organelle, cell, organ, organ system, organism, population, community, ecosystem, planet, solar system, galaxy, and the universe. In an earlier publication I have suggested that the latter ranking can be reorganised in a way that allows an innovative and stricter reasoning about natural organisation (Jagers op Akkerhuis 2008). The latter innovation may offer a valuable contribution to the general modelling goals aimed at by INBIOSA, for which reason it is explained in more detail in the following text.

3 Three Dimensions for Analysing Organisation and Hierarchy

If one wants to recognize clear levels of organisation and use these together with the associated types of entities as a basis for modelling, one first needs to identify both the levels and the entities. In fact, levels and entity types are closely linked, because the rules that define a more complex type of entity also define a higher level of organisation. Essential to this position paper is the idea that nature explores different and independent pathways towards complex organisation (Jagers op Akkerhuis 2008).

For example, when foxes mate, this interaction creates a population, because the genes of an individual can, over generations, migrate to other individuals and in this way become part of an abstract gene pool that all foxes have access to and contribute to when mating. In the context of analysing natural organisation and complexity, the question is, however, whether a population can be considered an individual in the same way as a fox can be considered an individual. That foxes and fox populations are different can be illustrated by comparing the interactions between individual foxes with those between populations. Two foxes can fight over a prey and one fox can kill another fox. Two populations cannot do such things. With respect to interactions between populations it is always the individuals that interact. From a construction point of view, the population is a non-existing entity in the ecosystem. It represents an abstraction that is based on mating interactions. Mating interactions do not create physical units with a new higher level individual ‘agency’. Similar reasoning applies to other groups of interacting individuals that do not form a new individual. Depending on the intensity of interactions, such groups range from loose arrangements, such as populations and communities, to physically integrated units, such as colonies of attached organisms. The question of when a colony of agents becomes a higher level agent is difficult to answer without a theoretical framework defining what is an agent.

Individuals and their interactions are not the only pathway in nature for creating complexity. Another pathway is clearly illustrated by the suggestion that organs create organ systems which create the organism. This sequence is also part of the above ranking from quarks to the universe. Yet, this ranking is not appropriately phrased when it comes to constructing a strict theory of how levels of organisation come about in nature. The reason is that nature does not produce organs and organ systems and then the organism. Instead, nature first evolves primitive, low complexity multicellular lumps which then, over many generations, show specialization of certain cells, which can be considered primitive organs. Subsequently, the evolution of increasingly complex interactions between distinct groups of cells allows the emergence of primitive organ systems and increasingly specialized and complex organs.

The above examples of creating complexity in nature indicate the existence of different major pathways or ‘dimensions’ nature can use to create complexity. The use of dimensions implies the independent development of different types of complexity. In the above examples the interactions between organisms and within organisms describe two different dimensions and can be used to span up a plane covering already a large part of all possible ways of how nature can create organisational complexity when using the organism as the basal unit. The inventory, however, is not yet complete, because the complexity of the organisms themselves is not accounted for (Jagers op Akkerhuis 2008, 2010a). The inclusion of different levels of complexity of organisms implies a third dimension. As a consequence of this reasoning the ranking ‘organism-population’ that is part of the above ranking from quark to the universe can best be altered, because the word ‘organism’ fails to address the differences between organism types. Organism types of different complexities have to be addressed individually because one can look at populations and internal differentiations of bacteria, at populations and internal differentiations of unicellular eukaryotes and at populations and internal differentiations of multicellular organisms. The latter shows clearly that the analysis of organisation in nature requires three dimensions: an ‘inward’ dimension to account for internal organisation, an ‘outward’ dimension to account for interactions in the ecosystem and an ‘upward’ dimension to account for organism types of different complexity. This strongly suggests that the conventional ranking based on a linear complexity space (from quark to universe) can be made more specific by adopting a new approach that uses three dimensions for complexity and an associated cubic complexity space.

During my attempts to create a comprehensive framework for ecotoxicology, the dimension associated with the complexity of organism types actually proved the most difficult to elaborate. This was, because the identification of complexity along this dimension raises the question of what precisely represents a level of organisation separating a lower level organism type from a higher level organism type? In other words, what are the criteria by which either a specific interaction between lower level organisms (outward dimension) or a specific internal differentiation within an organism (inward dimension) allows one to conclude that “given the presence of certain properties we can talk about an organism at level X”. For example, when the human zygote splits into a two cell stage, followed by a four cell stage and an eight cell stage, is it then possible to say at what stage the developing group of cells changes from a colony to a new –whole- organism at the multicellular level? Or when two bacterial cells show symbiosis in the way they digest substrate, what then is the fundamental difference between two cells laying close together, two cells being attached to each other and one cell living inside the other?

In order to answer the latter questions, it was necessary to develop a theory for the identification of natural levels of organisation in which every type would occupy a fixed position. And because in nature every next level arises on the basis of the system type at the immediately preceding lower level, the natural ranking is recursive. It was now deduced that the combination of a new type of topologically closed structure and a new type of topologically closed process form the essence of any next level. Examples of topologically closed structures are the cell membrane, the enclosed presence of an endosymbiont in a cell, the containment of all connected plasmas of the cells in multicellulars, and the sensors around the neural network. The accompanying topologically closed processes are the autocatalytic set, the functional relationships between endosymbiont and its host cell, the mutual dependence of cells in multicellular organisms and the recurrent interactions between groups of brain cells. This principle (the combination of a new type of functional and structural closure) was called the principle of "first-next possible (type of) closure". By definition the recurrent steps defined by all the first-next possible closures (FNPC) create a sequence of system types in which every next system type resides at exactly one higher level as the preceding type (as implied by "first-next"). Again by definition, FNPC causes a ranking of system types that shows no missing links, because every lower level system type is linked by means of FNPC to the next. It would lead too far to discuss the concept of FNPC here in full, but detailed explanations can be found in Jagers op Akkerhuis 2008 and 2010a. It should be noted that the elements and mechanisms causing first-next possible closure are specific for every next layer, while at any and all levels FNPC represents the first-next possibility for a new type of closure. An overview of the resulting classification/ranking of types of operators based on FNPC is shown in Figure 1.

The main result obtained by using FNPC is that it enables the creation of a strict ranking of organism types at subsequent levels of organisation. Moreover, the use of FNPC also extends to the non-biological levels of organisation, from molecules down to atoms, hadrons and quarks. As a generic name for all physical particles and organisms (which also can be regarded as a kind of 'particles') in this ranking, the name "operators" was chosen while the entire ranking was named the "operator hierarchy" (Jagers op Akkerhuis 1999).

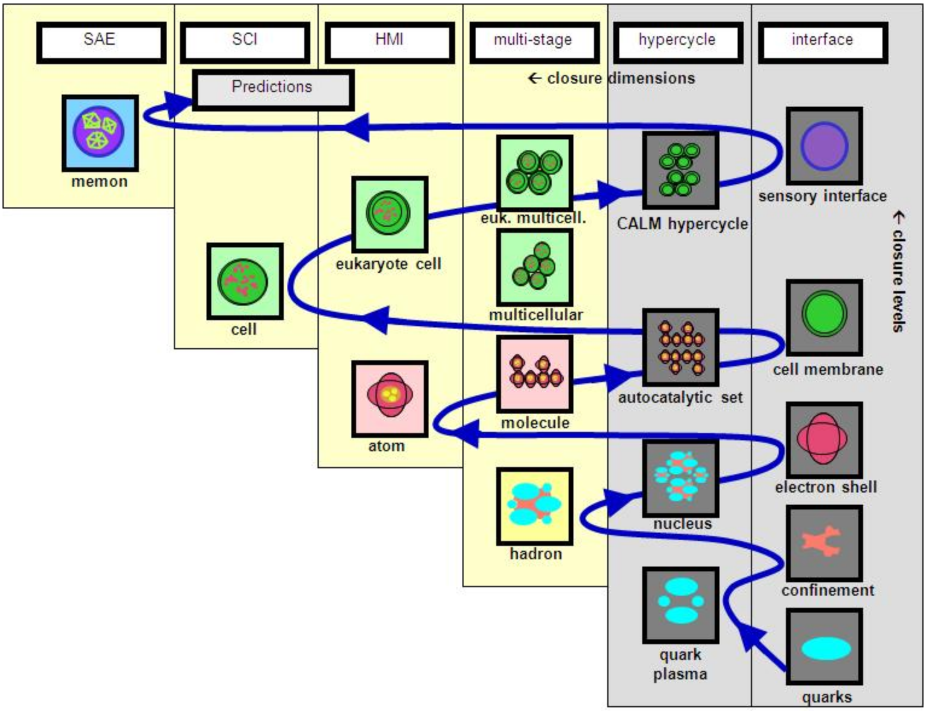

Fig. 1. This figure illustrates the evolution of the operators. The black line shows the historical pathway of subsequent first-next possible closures and related operators. The grey columns indicate systems resulting from first-next possible closure that are not operators. Explanation of abbreviations: Memon = operator showing a hypercyclic neural network with interface, SAE ('Structural Auto Evolution') = the property of an operator to autonomously adapt the structure that carries its information, SCI ('Structural Copying of Information') = the property of an operator to autonomously copy its information (genes, learned knowledge) by simply copying part of its structure, HMI (Hypercycle Mediating interface) = a closure creates an interface that mediates the functioning of the hypercycle, Multi-state = operator showing closure between multiple units of exactly one lower closure level, Hypercycle = closure based on emergent, second order recurrent interactions. Interface = closure creating an emergent limit to an operator, CALM (Categorizing And Learning Module) = a minimum neural memory. (This figure was published before in different forms in Jagers op Akkerhuis and van Straalen 1999, Jagers op Akkerhuis 2008 and 2010a, 2010b.).

4 Conclusion: How Can the Operator Hierarchy Contribute to the INBIOSA Project?

The recognition of the three dimensions for analysing organisation in systems, and the identification of the operator hierarchy as a major trajectory for analysing the hierarchical organisation of 'particulate' systems (from physical particles to organisms) offers a fundamental theoretical basis for the analysis of systems.

In relation to the latter, the operator theory may contribute to INBIOSA by providing a fundamental and strict rearrangement of the conventional linear "hierarchy" used to rank natural organisation. Such innovation is profitable, because conventional approaches frequently can be considered to mix different element types and ranking rules in one ranking, for example organelle-organism-population. In order to elaborate analyses on this point, it is suggested to use three dimensions for analysing organisation: one 'outward' for interactions, one 'inward' for internal differentiation and one 'upward' for the hierarchy of the operators (particles and organisms). This new approach has major implications. Firstly, only the quark, the hadron, the atom, the molecule and the bacterial cell, the endosymbiontic cell, the multicellular organism and the neural network organism are classified as operators and can be ranked together hierarchically. Secondly, the organelles in a unicellular organism, and the organs and organ systems in multicellulars are classified as internal differentiations. Thirdly, other entities are recognized as abstract groupings of elements into different kinds of 'interaction systems'. These interaction systems always consist of interacting operators but never are operators.

Another potential contribution of the operator theory to INBIOSA lays in the fact that every type of operator (e.g. a bacterium or a dog) typically shows a specific closure that defines its type. This offers a basis for clear definitions of the type of entities used in individual based modelling. For a bacterium this typical closure is represented by the combination of the autocatalytic chemistry (functional closure) and the membrane (structural closure). A dog typically shows a combination of second order recurrent neural network structure (functional closure) with sensory interface (structural closure). These typical closures offer an indication of which interactions of lower level elements are to be modelled in order to obtain the typical "fuzzy", "circular", "emergent" or "profoundly new" properties of the systems that INBIOSA addresses. Meanwhile all operators with a complexity that is equal to or higher than the bacterial operator can be considered as 'organisms'. Organisms, from simple bacteria (in a broad sense) to complex neural network organisms, thank their living properties to the presence of the typical closures that define their organisational level. For example a bacterium thanks its existence as an operator and as an organism to the interdependent presence of the autocatalytic chemistry and the cell membrane. The operator hierarchy may now bring some clarity with respect to the hitherto "fuzzy" concepts of life and death. If an organism at a given level has lost its typical closure it can be considered to have died, (see Jagers op Akkerhuis 2010b for a detailed discussion of the definition of life). In contrast to many existing definitions, the operator theory distinguishes between ‘life’ and ‘living’. Living is regarded as the dynamic state of an organism. Life is regarded as a generic indication of all the different typical closures that define the different types of organisms. Only a system that has the right organisation for being considered as life does show living properties when active. Because the operator hierarchy is an open-ended ranking, it also assures an open ended definition of life, which is practical when new forms of life evolve in the future that have to be included in the definition.

Recently, several comprehensive publications have addressed different aspects of the why’s, what’s and how’s of the coming into existence of organisation during the Big History of the universe (e.g. Salthe & Fuhrman 2005, Tow 2006, Spier 2008). In these publications, the topic of the ranking of particles and organisms according to complexity is either discussed in a broad sense (Salthe & Fuhrman 2005, Tow 2006, Spier 2008) or discussed as an unresolved problem (Spier 2010). Adding a touch of particle hierarchy, for example as indicated by the operator theory, may well contribute to further development on this point.

The operator theory, as a new approach, may profit from theoretical developments and quantitative modelling approaches at different levels of complexity and across levels of organisation, such as are specifically aimed at by INBIOSA.

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Structure Formation in an Evolutionary Model System

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Abstract. In this paper we explore a variant of a two dimensional realization of the model presented in Ref. [1], in particular examining the structure of the distributions of species produced by the model, and exploring the ways in which the functions defining competition and carrying capacity interact to give rise to these structures.

Keywords: sympatric, speciation, evolutionary model, structure formation.

1 Introduction

The mechanisms underlying the broad diversity in the natural world are still not fully known. There is a growing quantity of theoretical work in the area, with a number of models having been produced which demonstrate various possible mechanisms, many of which may play important roles in the creation and maintenance of this diversity. Although there is much potential progress, the questions of the cause of the diversity in nature, and the stability of this diversity under environmental change are still highly debated.

Understanding the mechanisms promoting the diversity of components in a system is a topic which is also widely applicable outside of evolutionary biology. Concepts such as maximum sustainable diversity and the mechanisms underlying diversification underpin various areas, ranging from the variety of products on display in supermarkets to the degree of specialization in labor.

Sympatric speciation, the splitting of a species into non-sexually-compatible subspecies without geographic separation, is now generally considered theoretically possible, and moreover, to have happened at least occasionally in the history of evolution. However, the issue is still a hotly contested one; In particular, the frequency of sympatric speciation events is still debated, as is the importance of their role as a cause and perpetuator of biological diversity [2]. The model we are investigating is fundamentally the same as the model used in [3] for example, and thus we hope our results may help in resolving the current questions surrounding sympatric speciation in nature.

2 Overview of the Model

In the experiment discussed in this paper we use a two dimensional variant of the classical model for frequency dependent selection. The general multidimensional extension of the model was introduced in [1]. The model aims to capture competition for resources among species. Species in the model are represented by a fixed point in a 2-dimensional phenotype space. Each dimension of the phenotype space corresponds to a quantitative trait that influences resource preferences. For example, one dimension might correspond to the mean beak length of a member of the species, and the other dimension might correspond to the mean body temperature of a member of the species. Thus, points close in this phenotype space would represent species with similar mean body temperatures and mean beak lengths. We use this model, exploring various parameter settings, and attempt to qualitatively define the various emergent patterns.

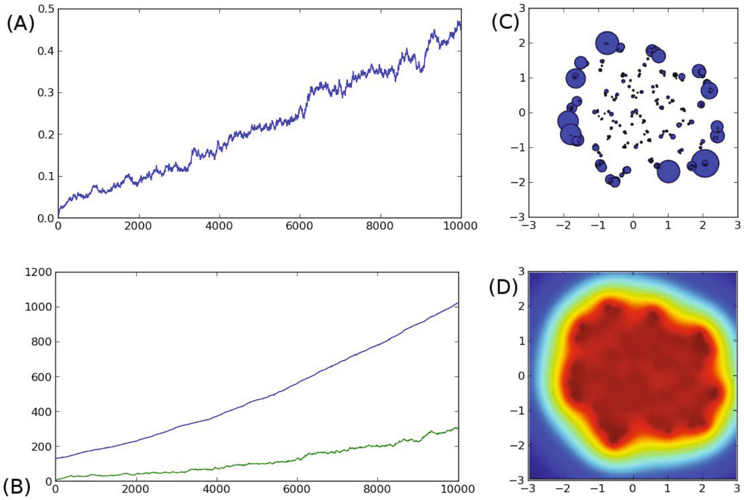

Figure . The figure shows results from a simulation, in which our model was run for 10,000 generations with a uniform carrying capacity over the whole phenotype space. (A) The mean distance of species from the origin (weighted by the number of individuals in each species) on the x-axis plotted against the generation number. (B) The total number of individuals across all species (blue) and the total number of species (green) both plotted against the generation number. (C) Representation of the phenotype space. The center of each circle is at the species position in the 2D phenotype space, the area of the circle represents the number of individuals currently in the species (larger areas meaning a greater number of individuals). It is assumed the two species with small Euclidean distance compete more fiercely with each other than they do with a third species that is farther away from either one. The sub-figure shows the species present at generation 10,000. (D) This plot displays the strength of the competition for resources which would be experienced at each point in the phenotype space given the distribution of species shown in (C). Dark red indicates the highest levels of competition and dark blue indicates the lowest level. Note that the regions where the competition is most fierce are those regions where species with large populations, or clusters of species currently exist (as shown in (C)).

3 Discussion

The study of the 2D case is particularly interesting because the stochastic dynamics of the interacting species follows a similar non-linear evolution as the activity in neural fields (or in reaction-diffusion systems) where conditions for stability are known [4,5]. In this sense the evolution in a plane can be interpreted as a stochastic approximation of a constraint maximization of the carrying capacity. Since, furthermore, the variation of traits may co-vary with the geographic distribution of the species, the 2D case is of particular interest.

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Synthetic Intelligence: Beyond Artificial Intelligence and Robotics

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Abstract. The development of engineered systems having properties of autonomy and intelligence has been a visionary research goal of the twentieth century. However, there are a number of persistent and fundamental problems that continue to frustrate this goal. Behind these problems is an outmoded industrial foundation for the contemporary discourse and practices addressing intelligent robotics that must be superseded as engineering progresses more deeply into molecular and biological modalities. These developments inspire the proposal of a paradigm of engineered synthetic intelligence as an alternative to artificial intelligence, in which intelligence is pursued in a bottom-up way from systems of molecular and cellular elements, designed and fabricated from the molecular level and up. This paradigm no longer emphasizes the definition of representation and the logic of cognitive operations. Rather, it emphasizes the design of self-replicating, self-assembling and self-organizing biomolecular elements capable of generating cognizing systems as larger scale assemblies, analogous to the neurobiological system manifesting human cognition.

Keywords: artificial intelligence, robotics, synthetic intelligence.

1 The Limitations of Cognitivism, the Top-Down Path to Intelligence

Historically, cognitive science has emphasised attempts to understand human cognition in terms of an information processing metaphor (e.g. see Thagard, 2010). Here this is referred to as the *cognitivist* perspective(characterized in detail by Harnad, 1990). A central theme within cognitive science is the project of artificial intelligence (AI), i.e. the computational synthesis of behavior that, when performed by humans, is regarded as manifesting intelligence. For cognitivism, replication of intellectual behavior by a computer system provides evidence that the computer program underlying that replication embodies an adequate theory and explanation of the human intellectual processes that it seeks to model. Processing of represented knowledge structures has typically been accomplished by *deliberation*, where the link from sensor or input data to action production or output data is mediated by knowledge-based planning or logical reasoning. In the context of robotics, Arkin (1998) refers to these approaches as Sense-Plan-Act approaches, while Brooks (1999) refers to them perhaps more accurately as Sense->Model->Plan->Act (SMPA) approaches: the essential idea is that an agent (a robot or a human being) receives sense data about the world, uses that data to update a symbolic representation of the world, processes that representation using logical reasoning in order to create a plan for what to do, and then executes the next temporal element of the current plan. Knowledge representation and reasoning are at the core of SMPA systems.

AI systems based upon knowledge representation and reasoning have been called Good Old-Fashioned AI (GOFAI, Hayes et al, 1994), since they are very clearly based upon Newell and Simon's (1975) *physical symbol system hypothesis* that: "A physical symbol system has the necessary and sufficient means for general intelligent action.", where: "A physical symbol system consists of a set of entities, called symbols, which are physical patterns that can occur as components of another type of entity called an expression (or symbol structure). Thus, a symbol structure is composed of a number of instances (or tokens) of symbols related in some physical way (such as one token being next to another). At any instant of time the system will contain a collection of these symbol structures. Besides these structures, the system also contains a collection of processes that operate on expressions to produce other expressions: processes of creation, modification, reproduction and destruction. A physical symbol system is a machine that produces through time an evolving collection of symbol structures. Such a system exists in a world of objects wider than just these symbolic expressions themselves."

The physical symbol system hypothesis has for many (perhaps most) AI researchers been the foundation of artificial intelligence, since it implies that a computing system is capable of manifesting intelligence. As Newell and Simon (1975) note, "The notion of physical symbol system had taken essentially its present form by the middle of the 1950's, and one can date from that time the growth of artificial intelligence as a coherent subfield of computer science." It is the foundation of knowledge-based and deliberative AI, in which symbol structures represented as more formalised versions of the symbols used in human natural language are processed by algorithms based upon human logical inference.

The physical symbol system hypothesis spawned a great deal of research that has generated many useful outcomes. Famous early examples include the expert systems: Prospector, an expert system for mineral exploration (Hart, 1975), MYCIN, for the diagnosis of blood infections (Buchanan and Shortliffe, 1985), and Dendral, an expert system for inferring molecular structure from spectrometer data (Lindsey et al, 1980). However, despite these and many other successes, there are a number of intrinsic challenges for GOFAI:

1. *Brittleness:* Lenat and Feigenbaum (1991) observed that expert systems are narrow in their domain of successful application, and very brittle at the edges, i.e. they are not robust when usage is not restricted to narrow circumstances. Lennart and Feigenbaum proposed that the solution to this is to embed specialized expert and knowledge systems within a more general environment of represented common sense knowledge that supports reasoning about their applicability and adaptation for broader purposes. Cyc (Cycorp Inc., 2002) is a

project to create this common sense knowledge base, although the resulting knowledge system has had limited applications to date.

2. *The Knowledge Acquisition Bottleneck* is the problem of acquiring knowledge, which may also be referred to as the *knowledge engineering bottleneck* if the whole system lifecycle is considered. The bottleneck refers to the difficulty of extracting knowledge from primary sources in such a way that it can be represented within a GOFAI system, and then effectively maintaining and updating it (Cullen and Bryman, 1988). Wagner (2006) summarizes four aspects of the knowledge engineering bottleneck: i) *narrow bandwidth*, referring to the very limited channels of converting knowledge from its initial sources, ii) *acquisition latency*, a significant gap between when explicit knowledge is created and when it is made it available where it is needed, iii) *knowledge inaccuracy*, created when experts make mistakes, knowledge engineers make misinterpretations, or errors are introduced during knowledge maintenance, and iv) the *maintenance trap*, that a knowledge system becomes increasingly difficult to maintain as it expands, and more so as it accrues errors.
3. *Multiple Experts:* when more than one expert is involved in the knowledge acquisition process, it can be very challenging (and perhaps impossible) to gain their agreement or consensus on a representation of valid domain knowledge (Medsker, Tan and Turban, 1995).
4. *Context:* The brittleness of knowledge systems immediately raises the well-established *problem of context* (e.g. see Schilit, Adams and Want, 1994, Dey, 2000). That is, for a system to have knowledge of its own applicability, it must have a representation of those contexts in which it is applicable or not, which is a regressive requirement. Of course, the scope of possible contexts is also unlimited, so the attempt to represent context is necessarily endless. A general solution to context in AI would be to build methods into a system for evolving its knowledge content in ways that reflect positive adaptations to dynamic contexts, but this is far beyond the means of existing knowledge systems in non-trivial domains.
5. *Continuous Change* of both knowledge and its contexts, due to the normal ongoing development of knowledge and the dynamic nature of the world, places a limited temporal window upon the validity of a GOFAI knowledge base. Hence it is necessary to ensure that a knowledge base remains relevant within its operational context. For robots this problem concerns the operation of perception and action generation in unpredictable and incompletely modelled physical environments; more successful solutions to the generation of basic behaviors have been based upon low-level, reactive and functional control systems (Arkin, 1998, Brooks, 1999), methods more closely associated with the mathematical, functional approach of Norbert Wiener's cybernetics (see Storrs-Hall, 2007). However, these approaches have not reached higher levels of cognitive performance, that are typically implemented using GOFAI symbol processing methods on top of behavioral layers.

6. *Regression:* Related to the problem of context, the need for representation as a basis for intelligence is endlessly regressive. As noted by Brooks (1999), representing the world suggests that it is not enough for the world to stand for itself. Hence understanding is mediated by a knowledge model. But this implies that understanding the knowledge model itself requires a knowledge model, and that model another model, and so on endlessly. Or if a single model is enough, why can't the world also be enough, such that reasoning, problem solving, etc. can be a direct reaction to sense data? Another way of putting this is that GOFAI sees an intelligent being as having a homunculus within it, observing and reacting to a model of the world. But then, the same must apply to the mind of the homunculus, leading to an infinite regression of homunculi within homunculi.
7. *Symbol Grounding*(Harnad, 1990, Anderson, 2003, Taddeo and Floridi, 2005) is a fundamental problem arising from the terms of the formulation of the physical symbol system hypothesis of how the link can be maintained from knowledge representations to the things that they refer to, or more generally, how abstract symbols can acquire real-world meanings. For successful expert systems and knowledge based systems this link is provided by the authors of the representations and the users of the system for whom textual inputs and outputs can be read meaningfully within a context, as long as the system is well authored and its contexts of application are both understood and stable. Symbols, by definition, have a conventional relationship with their referents and meanings. An authored knowledge representation gains its meaning from the author's understanding of the meanings of the symbols used. But this understanding is not automatically transferred to a machine when it stores and processes binary sequences that are displayed in forms that to a human represent linguistic symbols. This is the problem described by Searle's (1980) thought experiment of the *Chinese room*: taking in tokens, processing those tokens by rules, and outputting other tokens as directed by the rules and according to the input tokens, does not require any understanding of the meaning of the tokens. This actually implies an alternative to the physical symbol systems hypothesis, that instead of intelligence being fundamentally tied to the ability to manipulate symbols, it may be tied to the ability to *find symbols meaningful*, and to be able to *create and use symbols* (or more generally, representations) in ways that are not limited to manipulation within the constraints, and according to the production rules, of a formal language system. This can be regarded as an alternative view of *AI as computational semiotics*.

The symbol grounding problem presents a very deep problem for representational AI, not simply because it cannot be made to work in its own terms (see Harnad, 1990, Taddeo and Floridi, 2005), but also because it is not necessarily plausible as an account of natural intelligence. For example, exemplar theories of conceptualization (e.g. see Murphy, 2002) imply that any representation of knowledge is a novel creation at the time that it is made, that is highly dependent upon the context and circumstances of its creation. Exemplar theories reinforce the view that a knowledge base is akin to a work of literature (e.g. Lindley, 1995), being an external authored symbolic artifact rather than a direct mirror and expression of knowledge as it is represented within anyone's cognitive system. Of course there are many examples of successful knowledge base systems. But like any text, they are dependent upon external conventions of interpretation and usage to make them function effectively. The production of such a text is usually a painstaking process very different to the rapid decision-making of experts.

Searle's (1980) thought experiment of the Chinese room demonstrates that *even if* a computer system or robot had consciousness, receiving and issuing strings of icons transformed by abstract rules would not provide any understanding of the meaning of those icons, beyond the purely formal meaning of: if string matches X, issue string Y. Taking Devlin's (2001) definition, that Information = Representation + Interpretation, there is a fundamental problem with the concept of the computer as an information processing system: computers, like Searle's Chinese Room, accept input icons and generate output icons. The understanding of icons as representations, and then to make them meaningful within a context (Devlin's act of interpretation) requires acts of human semiosis. Hence not only is representation problematic for knowledge base and AI systems, the operation of a computer as an information processing system requires contextualization by human interpreters; intrinsically, computers are merely icon transform systems, and it is human semiotic processing that transforms icons into information.

A primary implication of this critique for engineering synthetic intelligence is that, as noted by Harnad (1990) and Taddeo and Floridi (2005), an authentic intelligence must be able to autonomically make icons meaningful, and this cannot be achieved by a system that is merely a transformer or syntactic manipulator of icons or icon sequences that lack any other meaning from the viewpoint of the transforming system. The strength of behavioral robotic systems (e.g. Brooks, 1999) is that the icons within their control architectures implement functional relations from input icons to output icons that not only represent those functional associations as mathematical and logical operations, but actually implement, *are*, those functions by virtue of the architectures within which they are implemented. However, behavioral systems have not yet been shown to be able to engage in meaningful symbolic behavior. Similarly, connectionist architectures offer the capacity to embed symbols within dense data reduction processes (Harnad, 1990), but they cannot produce those symbols in a plausible way to begin with (Taddeo and Floridi, 2005). More than twenty years after the formulation of these approaches, autonomous systems are still characterized by specialized competence, fragility, and limited high-level capacity.

2 Anachronistic Technology Metaphors, AI and Robotics

Limited progress to date in achieving significant levels of autonomy in artificial agents suggests that there may be misconceptions built into the project of AI and autonomous systems. Overcoming those misconceptions may require examining the assumptions upon which the project is based, and adopting different methods and different assumptions.

One perspective for making the assumptions of the AI project more explicit is that of the historical technological and metaphorical context of the project. From such a perspective it may be observed that: humanoid robots are essentially human beings caricatured in the technology of the day, and artificial intelligence is post-renaissance intellectual discourse caricatured in icon processing technologies of the twentieth century. This manifestation of the human (and animal) via the media of available technology can be seen in other historical replications of human beings and animals via technology. Leonardo's robot from around 1495 was a suit of armor animated by a system of internal pulleys and gears (Istituto e Museo di Storia della Scienza, 2011). The generation of robot behavior in the modern age has progressed from Leonardo's pulleys and gears to valves and relays, then to transistors, and to integrated circuits. The visual style of robots has evolved from the forms and surfaces of industrial machines, through automobiles and then consumer electronics, to computer game avatars (e.g. in humanoid entertainment robots). The early work of Boole found a path to implement automated calculation in the earliest industrial age vision of a purely mechanical computer (Ifran, 2007), with subsequent technology developments providing the ever small, cheaper and faster electrical (via relays) and then electronic implementations (via vacuum tubes, transistors, and then integrated circuits) of automated calculation that fuelled the explosion of computation as the foundation of the information age. Just as robots model humans in technology, computers have provided a medium for modeling human thought in technology. More than this, the simulation and the simulated became conflated, and computation became understood as the foundation of intelligence.

These are, however, caricatures expressed in the technical media of the day. A 'mechanical' or electronic wo/man expresses the desire to realize human or human-like attributes through acts of engineering, just as artificial intelligence expresses the desire to realize or exceed human or human-like intelligence through acts of engineering, using available engineering methods and materials and a model of intelligence derived from logo-centric discourses initiated in ancient Greece, but most highly developed (in the Western world) from the Renaissance to the most recent age of rationalistic industrial and post-industrial capitalism. It is, of course, inevitable that we define problems and engineer their solutions in terms of the available tools. However, a broader historical perspective upon AI and autonomous systems suggests that: i) the problems addressed by AI, and the very project of AI, are historically situated; ii) as technology evolves, the creative impulse behind the problematization of AI and the search for solutions may have different conceptual, methodological and technological means available to it; iii) these different means may lead to, or even require, a re-conceptualization of the nature of the problem and the criteria and forms of solutions.

3 Towards a New Science and Engineering of Synthetic Intelligence

Our technologies are evolving beyond the limitations of simulation or caricature using inorganic media. This is occurring with the rapid ongoing development (and in some cases, recent emergence) of biotechnology, molecular science, genetic engineering, nanotechnology and synthetic biology (e.g. see Synthetic Biology Community, 2011). These fields are shifting the scope of engineering from the macroscopic through microscopic to molecular scales, and from inert matter to the multi-level, organized systems of matter that constitute life. It is now possible to engineer, not just simulations of life, but life itself, by design of the molecular materials by which life is realized.

While still in its early stages, this movement of engineering into biological and molecular methods and materials implies a radical shift in our conceptualization of AI and robotics. In fact, (bio-)molecular engineering augurs the *end of robotics* as it is currently understood, as the conceptual dualism between machines as designed artifacts on one hand and life-forms as evolved biochemical systems on the other, breaks down. Robots as mechatronic agents may always exist, but they will come to occupy one end of a continuum, with no clear boundary separating the robotic from synthetic biological life. Moving from the mechatronic extreme to the biological extreme will be a movement from pure mechatronic systems, through mechatronic systems that incorporate biological components, through biomechatronic cyborg systems, to biological system having engineered structure and functionality, to increasingly 'wild' biological systems created by evolution and having no engineered features.

An obvious corollary of this development is that artificial intelligence will be superseded by synthetic intelligence. Artificial intelligence as such carries the legacy of machine age computation. The Turing paradigm has been highly successful in the age of machines. But new methods of engineering bring with them the intriguing promise of new paradigms of computation. Several new models of computation, such as computers based upon quantum dots or computing with DNA (several examples are presented in Eshaghian-Wilner, 2009) have shown how Turing computation can be achieved using very different substrates. However, cognitivism based upon Turing computation has not led to strong demonstrations of AI, and using the same paradigm of computation realised on a different technical or material substrate is likely to incur the same problems as those discussed above. Instead, it must be asked what fundamentally *different* paradigms of computation might be realized with, or constituted by, different implementational substrates. In particular, it is now possible to consider the design and engineering of biological intelligence.

Examples of the integration of biological neuron cultures with mechatronic systems have been demonstrated, including robots controlled by *in vitro* neuron cell cultures (e.g. Bakkum et al, 2004, 2007, Warwick et al, 2010). While the functionality of these systems is currently limited, there is very great potential to extend the principle of these systems with more highly differentiated cell culture architectures, and by genetic engineering of neurons and their biological ecologies as part of hybrid systems. Neuron systems have some fundamentally different characteristics from current artificial computers. For example, they are asynchronous, they integrate memory and processing, they are analog, their substrate and biochemical environment has a fundamental influence upon their behavior, they have massive parallelism, have a broad diversity of neural types, and have behavior that is a complex function of multiple timing characteristics (Potter, 2007). Hence biological neuron cultures may provide a foundation not just for new models of computation, but for a radical rethinking of the bases of intelligence away from the computational model.

This is *not* a proposal to develop silicon computers or their software on the model of biological neuron systems, but rather, to develop theories, methods and technologies for realizing engineering objectives directly in the material of biological neuron systems and their bioengineered progeny. The implications of such a program can be profound, both in terms of the development of technology and from perspectives of ethics (e.g. see Warwick, 2010) and fundamental concepts of what we are and the boundaries between ourselves as biological organisms and our technologies as designed artifacts.

The same principles can also be carried into the vehicles of biologically founded synthetic intelligence: systems may integrate biologically grown and inorganically synthesized parts, or complete organisms can be engineered. This is not a very novel concept, since human beings have been engineering animal species since the dawn of agriculture. But what is more novel is a shift to using biological engineering to achieve functions of intelligence and useful autonomy that have previously been pursued with limited success as applications of inorganic engineering.

4 Conclusion

This paper has considered a number of serious problems that have limited the spread and effectiveness of artificially intelligent systems, and proposed that these problems may derive from the application of historically specific and transient technological models to the understanding of intelligence during a particular period of technological development. As technology advances to biological and molecular levels, not only our understanding of intelligence, but our ability to synthesize intelligence can be taken to a new level, closing the gaps between the natural and the synthetic and leading to new understandings, not just of intelligence as abstract intellectual competence, but of the nature of sentient agency. A first level of this development may be to replicate existing computation models using molecular or neural substrates. As Conrad and Zauner (2003) note, access to the molecular level is a core problem, and existing models of computation provide a framework for controlling processes on a larger scale that are (currently) impossible to understand at a detailed molecular level. However, this risks losing an opportunity by maintaining the computational model too far beyond the technologies that it has evolved with and is most suited to. Design at the molecular and cellular level requires the design of self-replicating, self-assembling and self-organizing biomolecular elements capable of generating cognizing systems as larger scale assemblies, analogous to the neurobiological system manifesting human cognition. It is not at all clear that a conventional computation model is the best way of describing the essential behavior of such a system. Nevertheless, we do have the existence proof of human intelligence to demonstrate that such a system can indeed manifest the best available examples of cognitive competence.

This paper does not attempt to outline a proven alternative. Rather it is a call for the investigation of alternatives. The investigation can and most likely should take the form of direct experimentation in implementing design concepts at molecular and cellular levels, in a bottom-up process from which appropriate abstractions over resulting behavior can be derived. Rather, it emphasizes the design of self-replicating, self-assembling and self-organizing biomolecular elements capable of generating cognizing systems as larger scale assemblies, analogous to the neurobiological system manifesting human cognition. Defining suitable abstractions without a foundation in experimental and data-driven research would be pure speculation.

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Part IV

Physics and Philosophy

Editorial

Let us assume that dark matter and dark energy hold together the visible universe. This is a relatively young hypothesis made in 1933 by the Swiss astrophysicist Fritz Zwicky at Caltech. New findings suggest that dark matter forms almost exactly 25% of the total contents of the universe with 71% dark energy and only 4% ordinary luminous matter. But what would that mean for our understanding of knowledge and science? What about this relation within the vast spaces at the subatomic level in all entities of our everyday life? How do both kinds of matter interact? What are the consequences for living systems and for all artifacts we create as human beings? Where do dark matter and dark energy come from? What else is there around us without knowing it? And what does this fact mean for our understanding of and our approach to science? How often and how profoundly have we changed our picture about the world only in the past 100 years? Human knowledge has never been challenged before by such a tremendous acceleration of technology that leaves space for speculations about our own mental ability to cope with it (Clarke, 2000; Carr, 2008). What an amazing paradox that the accelerated acquisition of knowledge reveals how little we know about the world! Does this confirm the old Socratic wisdom of knowing that one knows nothing?

Of course we know a lot today, on a ‘local’ scale, but ‘globally’ and in historical perspective we could conclude that science *illuminates* only a small part of the ‘dark’ universe, the one essential for our existence that we have selected to explore. Thus, intention and attention have been building and shaping ontology and epistemology throughout history to create order and certainty. Yet, it became the “rule of conduct” in our technology-driven civilization to change the paradigm when peculiar (and spectacular) riddles were discovered at the border of the known universe, pushed by novel technology: the Jupiter moons, the Michaelson-Morley experiment, the blackbody radiation, the dark galactic halo, etc.

There is indeed something missing in the theories of life and mind today. What I wish to address here are two elusive aspects science is expected to deal with. We know there is DNA at the base of evolution of life, but we don’t know where it comes from. We have a quantum theory, but we do not have a qualia theory (yet). And we don’t know really the subtle ‘matter’ (substrate) that thoughts and dreams are made of.

Perhaps the most distinct question in science throughout the ages has been the one of perceivable *reality*: our space, time and purpose in the cosmos. This is the first aspect of science.

But what is reality? A good friend of mine, a linguist and philosopher, asked me once this question. I could not answer it at once. What came to my mind at that moment was a book by Roger Penrose I had recently read, “The Road to Reality” (Penrose, 2004). How to explain that bulk of concepts packed in over 1000 pages of mathematical physics? The answer was as simple as the question in German (“Was ist Wirklichkeit?”). “Es ist etwas, das *wirkt*!” (“This is something that *acts*!”), replied she smiling. German is indeed a fascinating language for philosophy and science. Reality is acting upon us and we act upon reality. This is how science is made.

Reality emerges from *potentiality*. This is the second aspect of science. Potentiality also means potency. A real effect does not need to have a real cause. It could have also potential cause, which is not something real. But it does not come from Nothingness. Potentiality is also not the absolute chaos where only the chance rules. If something comes from potentiality, there is nothing hazardous, but a *shared* cosmos…

Dürr, a scholar and friend of Heisenberg, says that potentiality in quantum physics corresponds to what we call *mind*. Consequently, we can say that everything is built of mind. The matter is an expression form and the field is another form, an interactive one. Hence, the process of permanent objectification of the reality, of transforming potentiality into reality in every single moment, is a kind of 'incarnation' of the mind (Dürr & Oesterreicher, 2007).

The limitation in realizing reality is coming through us, through our conscious seeing. There is principally nothing hold back or hidden. But through our limited cognition and attention we always reinforce the parts of the (active) whole, the reality. Yet these parts are not components, but different articulations of the potential, which we emphasize through our way of observation. The obvious limitation occurs through the intentional limitation of the attention and not through the decomposition of the whole.

The foundations of human knowledge are built upon an anticipation field, which can be associated with Rosen's concept of life (Rosen, 1985; 1991). The available facts in science provide boundary conditions in which this field is formed. Therefore the potentiality in its tendency is formed through a historical sequence of realities. In this way hierarchies and organization structures are built-up and reinforced. This is also the way of how life emerges and evolves (Maturana & Varela, 1980; Salthe, 1985), of how individuals' personalities are shaped and how communities, societies and cultures created and developed.

Now, with these notes in mind let us turn our attention to the potentialities we have at hand in this part of the book devoted to physics and philosophy.

The paper of Abraham & Roy "A Digital Solution to the Mind/Body Problem" is an original and challenging reading with a strong theoretical stance. The authors tackle the cornerstone problem in philosophy of mind: the mind-body problem. The paper provides an interesting condensed historical survey of this area. This background is used then to define their new RRA model in a straightforward manner. Their approach is mathematically based (theory of cellular automata, quantum theory, graph theory, etc.), but it is a philosophical one, thus providing an interesting methodological insight into addressing tough scientific problems.

Hong's article illuminates the age-old conflict of determinism and free will. The author tries to resolve the problem from two directions: biological information processing and physical determinism. He shows that biological information processing is neither absolutely deterministic nor completely random and that Laplace's determinism can neither be proved nor disproved, which results in an epistemological choice. Furthermore, Hong argues that Boltzmann's statistical mechanics is irreconcilable with Newtonian mechanics, that microscopic reversibility cannot possibly give rise to macroscopic irreversibility, and that in breaking the tie with Newtonian mechanics Boltzmann had freed us from absolute physical determinism. Finally, the author reckons that it is impossible to design a scientific experiment to test the existence or non-existence of free will because of the impossibility to maintain the required homogeneity of human test samples.

Brian Josephson's paper "Biological Observer-Participation and Wheeler's ‘Law without Law'" goes straight into the key question of the observable physical reality. He presents a challenging hypothesis that biological processes should be seen as more fundamental than physical ones. As a consequence of this, Wheeler's observer-participation and emergent law arise naturally, he claims. The author points the way to a deeper understanding of nature, where meaning, semiosis (in Peircean sense), plays a fundamental role that is invisible to quantitative science.

This article gave rise to a fairly agile discussion within our reviewer circle. It appears that this paper has touched a question of fundamental importance, so that we decided to publish here also its peer reviews without comment. The reports are from David Finkelstein, Koichiro Matsuno and Bruno Marchal. The reader should form his/her own opinion about the subject.

Matsuno’s paper is relying on biological results at the molecular level to explain the difference between the physical (exogeneous, Newtonian) time and the biological (endogeneous) time. His claim is that time is ubiquitous in biology as a marker of preserving the class identity of molecules. For instance, characteristic for the DNA transcription process from the DNA to a messenger RNA molecule is that it could smoothly proceed without interruptions even if the transcription-factor molecules are frequently exchanged. Matsuno argues that transcription-factor molecules obtain time markers toward the DNA molecule to be transcribed. The evidence that the Circadian clock of the cyanobactrium *Synechococcus elongatus* remains quite robust even though the similar clocks of the different cells in the neighborhood hardly interact with each other let conclude that the flow of time is a property of the class identity of the molecules themselves involved. This is in sharp contrast to the concept of time flow in physics as property inherent to preserving the individual identities of the atoms and molecules. Matsuno reckons that time can gain a new significance as a category when approaching and traversing the demarcation line between living and non-living matter.

Salthe’s paper discusses various discursive attempts related to the problem of understanding and representing change. The author reckons that most current scientific perspectives are parts of human culture’s characteristic externalist program, which cannot deal with this issue, because the social role of the natural sciences has been to support and guide technology development. Internalism, in turn, is a breakaway program attempting to deal directly with the present moment. Even if we succeed in finding an appropriate formal representation of this relation, it is difficult to say how it can be reconciled with technology’s goals in future. Perhaps ‘hybrid’ internalist, as well as externalist approaches could be the answer to understanding the challenge of change in living nature. A hint may be suggested by viewing the present progressive moment to be represented by a fundamental particle composed of 'short term memory-now-anticipation'.

The main objective of Schroeder's paper is to outline a holistic methodology in philosophy and science, aimed particularly at studying life. The author offers his own definition of information, its integration and shows how to model both information and integration. More specifically, information is defined as that which gives unity to a variety. Hence a variety is viewed as a carrier of two complementary manifestations of information — selective, which can be analyzed using the standard methods introduced by Shannon, and structural – to which information integration is applied using a switch from one variety (carrier) to another. With these definitions in mind Schroeder proposes a theoretical framework based on closure spaces and their lattices of closed subsets that offer a means to transfer the concept of quantum coherence of the physical realm into a model of information processing. More specifically, reducible classical systems (Boolean logic), partial irreducibility or complete irreducibility (quantum coherence) can have their abstract representations in the proposed framework. Since the level of information integration can vary from total disintegration to complete integration with many degrees in between, the formalism shows that such methodology can combine the two formerly antagonistic approaches into one.

Seaman's paper addresses central modelling and hard issues regarding living systems. The author views the human being as "an ultra-complex time-dependent computational ecology" endowed with consciousness that results from his embodiment within a larger ecological niche (and the corresponding interactions thereof) from the physico-chemical, biological and cognitive perspectives. His central postulate is that life and sentience are grounded within the physical world and that living organisms (including sentient ones) are highly specialized machines. Seaman points out that biological growth and evolution as well as self-awareness and learning can only occur as a result of the diversity of physical, biological, social and cultural interactions, mediated by multi-modal sensory inputs stemming from the surrounding material and socio-cultural ecosystems. What he proposes is to integrate these interactions/processes that hold within these multiple perspectives into a general framework ("Engines of engines") whose main goal is two-fold: (1) to capture at least part of the diversified (natural and artificial) computing mechanisms, and (2) to explore new forms of computation as a result of (1).

Otto Roessler's contribution is the last one in this part of the book. I made this choice, because it summarizes the insights of 10 significant advances made within the lifetime of a passionate researcher. The most useful of them, however, is implicit and I will make it herewith explicit: it is that the author not only shows how the "NOW" is crucial for advancing science, but also the "HOW": each of his stories is a "HOW" story. Insights don't just come because we want them to, but because of whom we know and how the system of science is organized, and because of the stories we tell ourselves and each other: all in one an amazing evidence of synchronicity. Each of Roessler's ten stepping stones embodies these critical elements for the progress of science. His insights should be a source for inspiration for every aspiring scientist. We should all strive to achieve that much!

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A Digital Solution to the Mind/Body Problem

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Abstract. We have applied the concepts from the mathematical theory of cellular automata – as developed to understand the emergence of spacetime at Planck scale – to consciousness. This gives rise to a digital, spacetime solution to the mind/body problem.

Keywords: Quantum vacuum, Planck scale, cellular automata, consciousness, mind/body problem.

1 Introduction

Dualist-interconnectionist models for consciousness, from Ancient Greece to Descartes, have disjoint parts connected by a mysterious communication process. Usually no explanation is proposed for this communication process, although the resonance metaphor is sometimes mentioned. In this paper we consider this problem in the context of the mind/body model of Descartes. The intractability of this mind/body problem has been discussed by everyone from Plato on. We are going to apply to it an atomistic mechanism deriving from the theory of the quantum vacuum in modern physics.

We thus bring together the mind/body problem of Descartes and the digital philosophy of Fredkin and others (Hey, 1999) into a joint picture first described by Democritus (Popper, 1998). Our starting point is a cellular dynamical model of the quantum vacuum due to Requardt and Roy (2001) and extended by Abraham and Roy (2007). This is a process, the RRA process, by which the illusion of analog spacetime self-organizes from a digital substructure – a submicroscopic, corpuscular, cellular dynamical system – a sort of finite point set on steroids. In this paper we further extend the RRA process from space to spacetime in the domain of terrestrial physics, and then jump up to the mental realm, where the constraints of physics no longer apply.

We apply the process twice, once to the mind, and again to the body, to obtain our resolution of the mind/body problem. In our final, composite picture, there is one enormous point set, its size estimated by Wheeler as 10 to the power 88 (Hey, 1999), operating beneath the perceived realities of macroscopic mind, body, and also quantum reality. We are grateful to Dr. Paul A. Lee for his guidance regarding the Ancient Greek tradition.

2 The Mind/Body Problem

The mind/body problem is a perennial thread in philosophy, East and West, so there are many illustrious names on its chronology. We will concentrate on just a few of these, to establish the main milestones of our story, and briefly describe their contributions. For the earliest history, beginning with Homer, see Jaspers (1998, Essay 8).

2.1 Plato, 370 BC

Plato expanded the teaching of Socrates on the perfection of the soul into a complete system. In this system, morals and justice were based on absolute ideas. Wisdom consists of knowledge of these ideas, and philosophy is the search for wisdom. In fourteen more dialogues, Plato elaborated this unified system.

Plato's theory of soul is set out primarily in six of the dialogues: *Phaedo*, *Republic II*, and *Phaedrus*, of the middle group of dialogues, 387-367 BCE, *Timaeus*, around 365 BCE, which divides the middle and last groups, and *Philebus* and *Laws*, of the last group, 365-347 BCE. The development of the individual soul is given in the three middle dialogues.

The *Phaedo* is a long and detailed examination of the individual soul, its immortality, and reincarnation, given by Socrates on the day of his death sentence. The *Republic* describes Plato's mathematical curriculum for the Academy: arithmetic, plane geometry, solid geometry, astronomy, and music. At the end [10.614b] is the *Tale of Er*, which details the reincarnation process of the individual soul, as told by an eye witness. (The numbers in brackets are page numbers of the Stevens translation.) In the *Phaedrus*, Socrates and Phaedrus discourse on love and rhetoric. To understand divine madness, one must learn the nature of the soul. [245c] Soul is always in motion, and is self-moving, and therefore is deathless. [245c,d,e] Then begins the important metaphor of the chariot: two winged horses and a charioteer. [246a – 248a] This metaphor of the soul is then used to explain divine madness, and the dynamics of reincarnation.

The world soul is developed in the later three dialogues. Regarding the individual soul, the *Timeaus* explains that as a person becomes a rational creature through education, his human soul moves in a circle in the head (a sphere) of his mortal body. [44] In the *Philebus*, Socrates introduces the world soul as the source of individual souls. [30a]

In sum, we have from Plato a four-level, hierarchical cosmology, including (from the top):

1. The Good, an integral principle with no spatial extent,
2. The Intellect, or nous, including the Ideas or Forms (pl. eide, sing. eidos),
3. The World Soul (including individual human souls), and
4. The Terrestial Sphere of matter and energy.

Forms exist in the Intellect, and are outside of space and time. Terrestrial objects are instances, or particulars, of Forms. Individual souls are pieces of the World

Soul which have instantiated, or incarnated, a Form. When people die, their individual souls reunite with their Forms.

To this Theory of Forms, Plato himself raised an objection in his dialogue, *Parmenides.* This problem, later called the third man argument, or TMA, has been the subject of much discussion over the past fifty years. It is somewhat like the Russell paradox of mathematical set theory. That is, if a Form (a class of objects) contains itself as a member, then an unwelcome infinite regress is set up, toward larger and larger collections.

Some have interpreted this objection another way, which we shall call TMA2. This applies when we have two categories which are disjoint – such as two parallel universes – and yet which exchange information. A matrix between the two categories – such as the air between two resonant guitar strings – must be interpolated, to carry the resonance or intercommunication. For example, in Plato's cosmology, the World Soul intervenes between the Intellect and the Terrestrial Sphere. Or on the individual level, Ficino's Spirit intervenes between the individual soul and the body.

2.2 Kashmiri Shaivism, 1000 CE

The Indian tradition provides a number of different schemes for levels of consciousness, including five koshas, seven chakras, 36 tattvas, and so on. The five koshas are, from the top down: the bliss body (anandamaya kosha), astral body (vijnanamaya kosha), mental body (manomaya kosha) pranic body (pranamaya kosha), and the food body (annamaya kosha). The bliss body is described as an experience of total transcendence, where only the fundamental vibration of the unconscious system remains. (Saraswati, 1998; p. 54)

The TMA2 problem may be the ultimate cause of the profusion of levels in the Sanskrit literature on consciousness. No matter how many levels, the mystery of the communication between adjacent levels in the hierarchy remains. The vibration metaphor addresses this mystery, but still begs an encompassing matrix or medium to carry information from level to level. The vibration metaphor entered the Indian literature in the Spanda (vibration), Urmi (wave), and Prana (life-force) concepts of the Trika philosophy (Kashmiri Shaivism) due to Vasugupta, his disciple, Kallata, and his student in turn, Abhinava Gupta, tenth century CE. (Probhananda, 2003, 2004; Dyczkowski, 1992; Singh, 1980.)

We may regard the mind/body problem as just the bottom level of a stack of similar problems. We intend that our attack on the M/B problem should eventually be applied throughout the koshas, chakras, or tattwas of a full model of collective consciousness and unconsciousness.

2.3 Descartes, 1649

Descartes was a dualist, to whom the world consisted of two original substances – body and mind between which there was an enormous gulf. Man consists of body and mind, which interact through the pineal gland. His dualist theory, and his mechanical view of nature, dominated philosophy for centuries. His method of thought and his theories have been subjected to devastating criticism, for example, Jaspers (1964). For many historians, the mind/body problem in Western philosophy began with Descartes. We will reconsider this tradition later.

3 Atomism

Like the mind/body problem, atomism is a perennial thread in philosophy, East and West, with many illustrious names on its chronology. For us, atomism provides an especially important backdrop, as our mathematical model for the mind/body system is discrete. Again, we will concentrate on just a few of the key players.

3.1 Parmenides, 450 BC

According to Popper (1998), Parmenides – an important if little known presocratic philosopher of early 5th century BC Greece – was the creator of atomism (atomos, Greek for indivisible). First of all, he is known for his Two Ways the Way of True Knowledge (aletheia) and the Way of Human Conjecture (doxa) revealed to him by a goddess and described in his only work, *On nature.* The Way of True Knowledge includes the idea that behind the false and illusory world of change perceived by the senses there is an absolute reality that is totally static, a dark sphere of continuous dense matter, called the Being. In our sensory perceptions, we experience a dual world of atoms moving in the void, hence the Way of Human Conjecture.

3.2 Democritus, 400 BC

Democritus, a student of Parmenides, is widely regarded as the founder of the atomism thread. And it is said that Democritus' ideas were formed to contradict Parmenides. Democritus wrote on math, astronomy, and ethics, and had a great influence on later Greek philosophy, especially Aristotle, and hence, on the whole of the Western Tradition.

Regarding atoms, he believed that material bodies were formed as temporary composites of eternal atoms, like flocks of birds. Atoms are variously shaped and sized. The primary qualities of a material body – its shape, size, and weight – and its secondary aspects – smell, taste, etc – all derive from the size and shape of its atoms. Atoms move in a "void", which is empty, and yet is not nothing. The soul is made of soul-atoms, which are very small and spherical, and can pass through solid material bodies, like neutrinos.

3.3 Dharmakirti, 650 AD

It is always a pleasure to follow a thread from Ancient Greece, through trade routes to India, then circuitously to Early Islam, and thence to Europe. In this case we are just guessing. There is a long history of atomism in India. One of the ancient Hindu philosophers, Kanad, discussed the existence of atoms. In fact, the word Kanad is derived from the word Kana, which means atom. Among Buddhist traditions, Vasubandhu and Dharmakirti particularly discussed the existence of atoms. Dharmakirti was a student of Dignaga, a Buddhist logician and professor at the famed Nalanda University. He introduced into this thread a wondrous novelty, namely, that atoms are not eternal, but rather, flash into and out of existence as points of energy. This seemed somewhat outré until very recently, when the quantum vacuum emerged into physics, as we discuss in this paper.

3.4 Galileo, 1623

Galileo was famously condemned by the Vatican in 1633, overtly because of supporting Copernicus (that the earth moves) in his book, *Dialogues concerning the two chief world systems*, published in 1632. However, there is a competing (and controversial) theory according to which his real offense was his earlier book, *The Assayer*, of 1623. (Redondi, 1987). This work advocated an atomic theory, according to which (rather like Democritus) the secondary qualities of matter (taste, smell, etc) were determined by the primary qualities (the shapes of atoms comprising the matter). This was of huge concern to the Vatican in that Transubstantiation – the official dogma of the Church since the Council of Trent (1545-1563) regarding the consecration in the Mass of the Sacraments (turning the bread and wine into the body and blood) – depended on secondary qualities being independent of primary qualities. (Shea, 1991; p. 181)

3.5 Quantum Theory, 1900

Shortly following the death of Descartes, atomism faded into the background, where it remained for two hundred years. Then it rose from the ashes in a sequence of developments, collectively known as the quantum revolution. Here is a chronology of some of these developments.

1808, John Dalton posed a unique atom for each element.
1897, J. J. Thompson discovered the electron (Nobel prize in 1906).
1900, Max Planck proposed energy quanta, founded quantum theory.
1905, Albert Einstein introduced the photon as a corpuscle.
1927, Dirac, Pauli, Weisskopf, Jordan, Quantum field theory.
1940, Feynman, Schwinger, Tomonaga, Quantum Electrodynamics (QED).
1966, H. Yukawa, Non-local Field Theory and Quantum Vacuum (QV).

At this point, following QED, we have the theories of the QV and the zero-point fluctuation (ZPF) which are basic to the RR model of Requardt and Roy (2001). This view of nature has the vacuum full of activity, in which particles jump out from, and then back into, the vacuum in pairs. In QED, as one calculates the transition amplitudes with respect to the vacuum state, the vacuum as such does not contribute in the calculations. However, Yukawa proposed the concept of non-local field theory where the seat of particles is considered as an extended region or domain in contrast to QED. Now if we take these domains to be quantum theoretical objects, then they are probabilistically connected, and there is no distinction between empty and occupied seats. Effectively, Yukawa introduced a new version of quantum theory of the aether with globular structure.

3.6 Fredkin, 2000

The cellular automaton (CA) ideas of Stan Ulam and John von Neumann in the 1950s rested in obscurity until the appearance of John Conways *Game of Life* in the 1970s. Then CA models of nature became a fad, and many successful models for macroscopic physical systems were made, especially in the circle around Feynman in the 1980s (Hey, 1999). However, computer science models of the individual soul, such as we seek, are rare. In this connection we must mention the work of Ed Fredkin. one of the pioneers of the digital philosophy, and the mainstay of the website www.digitalphilosophy.org which explains:

Digital Philosophy (DP) is a new way of thinking about the fundamental workings of processes in nature. DP is an atomic theory carried to a logical extreme where all quantities in nature are finite and discrete. This means that, theoretically, any quantity can be represented exactly by an integer. Further, DP implies that nature harbors no infinities, infinitesimals, continuities, or locally determined random variables. In *On the Soul* (2000 Draft Paper) Fredkin proposed a computer science definition of the soul, concluding: "The soul is an informational entity, which is constructed out of the states and the arrangements of material things."

All these recent developments, which we subsume under the classical heading atomism, support the idea that underlying our illusion of continuous space, time, matter, energy, etc (the analog part of the analog/digital dichotomy, and the wave part of the wave/particle duality) is a fundamental layer that is finite, discrete, and intelligent (that is, law-abiding). Sometimes all this is called the finite nature assumption. (Fredkin, 1992) This is close to the view of Parmenides described above.

4 The RRA Model

In this section we recall the RRA process, as defined in (Abraham and Roy, 2007). In the next section, we extend it from space to spacetime, and finally, we apply the process to the mind/body problem.

The RRA model is a two-level system. The microscopic level, QX, is a dynamical cellular network of nodes and bonds. Inspired by the cellular automata of Ulam and von Neumann, a dynamical cellular network is a directed graph with connections (directed links) which appear, disappear, and change direction, according to dynamical rules.

The macroscopic level, ST, that self-organizes from QX is an another dynamical cellular network, in which the nodes are the cliques (that is, maximal fully connected subgraphs) of a graph, G, of the QX level, bound in a network by superbonds.

The system of RR ends with a metric space. But in a sequel paper (Abraham and Roy, 2006) we have developed a neural network approach which imbeds the ST level into Euclidean spacetime, EST. Thus the ambient space of nature, according to consensual reality, is actually an epiphenomenon of the atomistic and finite QX network, according to the scheme: $QX \rightarrow ST \rightarrow EST$. This is the full RA process, which we call condensation. More details may be found in the Appendix.

5 The Time Dimensions

The discrete, microscopic time parameter, t, used above does not represent macroscopic time. Rather, we propose to obtain macroscopic spacetime through our process of condensation. Macroscopic time, T, exists locally as a function on spacetime, but we may pretend that there is a cosmic time function, to simplify the exposition. We propose now to obtain macroscopic spacetime from the condensation process applied repeatedly to the entire, t-dependent QX object.

The condensation process is regarded as being accomplished in a single instant, and it determines instantaneous states for the macrocosmic system in which space appears to be a continuum. Even so, the network, QX, is changing rapidly by a time-discrete process, with time t. We are going to regard the stepwise increasing network time as an internal process variable, microscopic time, that is distinct from the continuous physical time aspect of the spacetime of general relativity, cosmic time. Thus, we envision two dimensions of time.

We adopt the Cauchy perspective of general relativity, in which the Einstein equation is regarded as a system of quasi-linear, second-order partial differential equations. The present is represented by a three-dimensional space-like hypersurface in the four-dimensional spacetime continuum, dividing it into past and future portions. The Cauchy initial value problem for this system regards the values of the metric tensor as known in the past and present, their future to be determined by integration of the system of equations along special (so-called characteristic) curves that radiate forward from the present into the future. The topology of spacetime, along with the geometry (that is, the metric tensor) and the physical parameters (energy, mass, electromagnetic fields, etc.) must evolve according to this Einstein equation. Wormholes and black holes may evolve as caustics (eg, focal points) of the characteristic curves.

Alternatively, for a mathematically less-challenging exposition, we may suppose, like Einstein, that spacetime is created as a finished system, a complete geometrical object.

So this is our proposal for the emergence of cosmic time. Constrained by the Einstein equation, cosmic time advances in discrete intervals, that might be multiple steps of microcosmic time, giant steps. With each giant step, yet another condensation occurs, as follows.

We consider a memory device, controlled by the cosmic-time function, T. Between cosmic times $T1$ (corresponding to network time $t1$) and $T2$ (with its $t2$) the memory device records all of the finite states of QX between network-time $t1$ and network-time $t2$, and condenses this finite set of QX states into a space-like pseudo-continuum corresponding to the discrete cosmic time $T2$. One method for the condensation of a finite set of QX states is the sum algorithm. That is, we form a QX sum-state by adding the internal node states of all nodes, and all the bond states of all the bonds, of the set of QX states. In other words, fix a node of QX. Sum up the node-states of that one node for all the QX states with network time in the interval, $(t1, t2]$, that is an integer. Do likewise for each bond of QX, but round down if this sum is greater than one, and round up if less than minus one.

Thus, spacetime is squeezed from the dynamical cellular network, QX, as toothpaste from a tube. As giant steps are still very small compared with the resolving power of macroscopic science, cosmic time appears to be continuous. The macroscopic system, QX, sparkles with activity on the scale of Planck space and time, while macroscopic spacetime unrolls essentially continuously. The past and present become known, while the future remains yet a mystery.

In summary, our scheme, $QX \to ST \to 3ST$ is extended to the scheme $QX \to ST \to 4ST$, all in the context of the body, that is, the physical world. We now wish to apply this new scheme to the mind/body problem.

6 The Mind/Body Problem Resolved

We now consider two QX networks: $QX1$ (the body level), $QX2$ (the mind level). Each of them might be the basis for an RRA process, one condensing to the body, or the physical world as we have considered up to this point, the other to a separate world of the mind.

However, we may prefer alternatively to join $QX1$ and $QX2$ into a single entwined network, $QX*$, on which two condensation processes operate. We might compare this approach to John Whitney's concept of digital harmony, in which a single mathematical algorithm is employed to compose a piece of music, and an abstract animated image, which then seem – when played together – to harmonize, due to deriving from a common archetypal process. But we will proceed now with QX1 and QX2.

After all this preparation, our approach to the perennial conundrum is now simple: we apply the idea of condensation from a QX network twice: once to the body level, as in the RRA model, and again by analogy to the mind level, as in Fredkin (2000). This results in the four-part scheme:

$$\begin{tikzcd}
QX2 \arrow[r, leftrightarrow] \arrow[d, leftrightarrow] & Mind \\
QX1 \arrow[r, leftrightarrow] & Body
\end{tikzcd}$$

The mystery connection between the disjoint mind and body systems now becomes an epiphenomenon of the connection between $QX1$ and $QX2$ which is not mysterious at all. For the nature of the QX model of RRA is that of a dynamical cellular network, and we may regard $QX1$ and $QX2$ as a single, entangled network, as directed links between the two systems will be allowed by our dynamical rules. In other words, we ask you to replace the mystery of the $Mind \leftrightarrow Body$ connection with the mystery of the $QX1 \leftrightarrow Body$ connection. Mysterious as this may be, it is ubiquitous throughout the physical and biological sciences, as physical systems admit mathematical models.

7 Descartes Reconsidered

The traditional view of Descartes (1596-1650) as perpetrator of the mind/body problem deserves refinement. His main work on this subject is his book, *The Passions of the Soul*, written in 1646 at age 50, and published in 1649 just before his death. It is presented as a series of 212 articles collected in three parts. It is the 50 articles of the first part that most concern us here. Each article comprises a short caption with a paragraph of text. Here are the captions of the 16 most relevant articles of Part I of his text. *Note*: Soul in Descartes refers to what we have called Mind.

> Part I. About the Passions in General, and Incidentally about the Entire Nature of man
>
> Article 17. What the functions of the soul are.
> Article 20. About imaginations and other thoughts that are formed by the soul.
> Article 25. About perceptions we refer to our soul.
> Article 27. The Definition of the Passions of the soul.
> Article 30. That the soul is jointly united to all the parts of the body.
> Article 31. That there is a little gland in the brain in which the soul exercises its functions in a more particular way than in the other parts.
> Article 32. How it is known that this gland is the principal seat of the soul.
> Article 34. How the soul and the body act on one another.
> Article 35. Example of the way impressions of objects unite in the gland in the middle of the brain.

> Article 36. Example of the way the Passions are excited in the soul.
> Article 37. How it becomes apparent that they are all caused by some movement of the spirits.
> Article 43. How the soul can imagine, be attentive, and move the body.
> Article 44. That each volition is naturally joined to some movement of the gland, but that by artifice or habituation one can join it to others.
> Article 45. What the power of the soul is with respect to its passions.
> Article 46. What the reason is on account of which the soul cannot completely control its passions.
> Article 47. What the struggles consist in that people customarily imagine between the lower part of the soul and the higher.

Paraphasing the texts of these articles, we may say that the soul (mind) exists outside of space, while the body lives in spacetime. They are united whole to whole, but especially through the tip of the pineal gland. The soul is characterized by volitions, thoughts, imaginations, and passions (emotions); and the body by movements. The soul has a structure, polarized between the sensitive (lower) and rational (upper) poles.

Altogether, we see that Descartes has not only posed the mind/body problem, but also proposed a solution which is surprisingly like our own.

8 Conclusion

In sum, then, the mind/body connections are completed in a circuit outside ordinary consensual reality in a submicroscopic atomic realm beyond our senses, but revealed by the progress of modern physics. This realm or matrix, an extension of the quantum vacuum into the realm of consciousness, is a finite, discrete, digital, cosmos, which condenses – in the human perceptual and cognitive process – into epiphenomena, the continuum illusion of mind/body, hypostases, koshas, cakras, tattwas, and so on, of the perennial traditions of consciousness studies.

Note that the QX level is a static point set with a dynamic network structure, changing in microscopic time, t. Meanwhile, the macroscopic body and mind have been constructed as complete spacetime worlds, with locally defined macroscopic times, T. This provides a background for psi phenomena such as telepathy and clairvoyance, but also leaves a window of opportunity for free will. Like a zipper closing, the past is zipped (or firmed) up, while the microscopic future is subject to interaction with the macroscopic body and mind, until the zipper closure arrives, and condensation (or collapse) occurs.

The end of our construction is an echo of the *Two Ways* of Parmenides, the atomic $QX*$, and the $ST4$ continua of body and mind, playing out in digital harmony.

Appendix. Summary of the RRA Process

The RRA process, of Abraham and Roy (2007) is not a description of physical reality, but just a mathematical model that captures some aspects of our experience of physical reality. We will summarize this process in three stages. Full details, examples, and graphics, may be seen in Abraham and Roy (2010).

We begin with a description of our microscopic system, QX. Then we will go on to extract from it our macroscopic system, ST. Finally, we describe in summary the embedding of ST into an Euclidean space.

A1. There is a finite, but huge, point set, which is static throughout the process. Let S denote this finite set. Enumerate this set by fixing a bijection from S to N, the cardinality of S. Thus, S is a set of points, $\{n_0, n_1 ...., n_{N-1}\}$. These points are called *nodes*.

A2. At each node and each moment of time there is an internal node-state, which is some number of quanta of information. Thus, we have a set of time-dependent node-states,$\{s_0, s_1, ..., s_{N-1})\}$.

A3. There are no bilateral connections. That is, for each pair of nodes, n_i and n_j, there may be a directed link from n_i to n_j, or none. We agree there cannot be a directed link from n_i to n_j if there is one from n_j to n_i.

A4. There is a global time clock for the system. The time variable, t, is a natural number, and increases by one at regular intervals, called *clicks.*

A5. The directed links may appear, disappear, or change direction, with each click. They change according to a fixed dynamical rule.

A6. With each click, each node n_i sends one quantum of information to the node n_j if there is a directed link from n_i to n_j.

A7. At each time there is a digraph, a directed graph on S, defined by the directed links. Let $D(t)$ denote the state of this digraph at clock time t, an integer. Associated with $D(t)$ is a graph $G(t)$, in which the directions of $D(t)$ are ignored.

This is our microscopic system, QX, exactly as described by Requardt and Roy (2001). Next we will describe the emergence of the macroscopic ST system from QX, or $QX \to ST$, following Abraham and Roy (2007).

B1. For each node, n_i, of $D(t)$ let w_i denote its node-weight, that is, the number of directed links of $D(t)$ that either arrive at, or depart from, n_i. Thus, we have a finite sequence of node-weights, $\{w_0, w_1, ..., w_{N-1}\}$.

B2. Next, at each time, t, we may construct, from the digraph $D(t)$, a permutation of the set S of nodes, as follows. We reorder the nodes of S according to their node-weights, in decreasing order. If several nodes have the same node-weight, we retain their original order. Let $P(t)$ denote the permutation of N obtained in this way.

B3. A clique of a permutation is a maximal inverse sequence. Compute the cliques of $P(t)$. This may be done by inspection if N is not too large. Let $K(t)$ denote the set of all cliques of $P(t)$. These cliques, which are simply subsets of $\{0, 1, ..., n-1\}$ in decreasing order, will be considered the supernodes of our macroscopic system, ST.

B4. If K is a finite set of natural numbers, let the *span* of K denote the filled-in interval, $span(K) = [min(K), max(K)]$. We define a superbond between two supernodes, or cliques, if and only if their spans are disjoint. Thus we have a graph $ST(t)$ defined by these supernodes and superbonds.

This is our macroscopic system, ST. Finally we will describe the pseudo-isometric embedding of ST into a Euclidean space, $ST \rightarrow EST$, again following Abraham and Roy (2007).

C1. For every pair of disjoint cliques of $K(t)$, we define their overlap, a measure of the entanglement of the two cliques, by counting points in the intersection and union of the sets spanned by the two cliques. Details and examples may be found in Abraham and Roy (2007). These overlap measurements may be used to define distances, more entanglement corresponding to a smaller distance.

C2. Embed $K(t)$ in a Euclidean space, and relax the embedding to approximate as closely as possible an isometry. That is, the distance between the images of two cliques represents their entanglement. The process $QX \rightarrow ST \rightarrow EST$ may be called *condensation.*

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On Microscopic Irreversibility and Non-deterministic Chaos: Resolving the Conflict between Determinism and Free Will[*]

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Abstract. This article attempts to resolve the age-old conflict of determinism and free will. The problem is approached from two directions: biological information processing and physical determinism at the ontological and the epistemological levels. It is shown that biological information processing is neither absolutely deterministic nor completely random. It is shown that Laplace's determinism can neither be proved nor disproved and is, therefore, an epistemological choice. It is further shown that a) Boltzmann's statistical mechanics is irreconcilable with Newtonian mechanics, contrary to Boltzmann's own claim, b) microscopic reversibility cannot possibly give rise to macroscopic irreversibility, c) Zermelo's recurrence paradox and Loschmidt's velocity-reversal paradox are valid arguments against Boltzmann's claim, and d) in breaking the tie with Newtonian mechanics, Boltzmann was actually the hero that had freed us from the bondage of absolute physical determinism. Last but not least, it is impossible to design a scientific experiment to test the existence or non-existence of free will because of the impossibility to maintain the required homogeneity of human test samples. However, individuals who believe in the existence of free will have a more consistent worldview than non-believers. If free will does not exist, it is futile and meaningless to attempt to convince others that free will does not exist.

Keywords: Free will, Determinism, Microscopic Reversibility, Non-deterministic Chaos.

1 Introduction

In spite of the impressive advances made in molecular and cellular biology, certain biological problems remain intractable or controversial. In the post-genetic era of biology, human consciousness was catapulted to the top of the list of intractable and controversial problems. This impasse ushered in a group effort to seek new and workable approaches. In this paper, I shall focus on one of the most controversial aspects of human consciousness: free will.

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[*] Dedicated to the memory of the late Professor Michael Conrad of Wayne State University.

Fascination about free will stemmed from its apparent conflict with physical determinism [1-4]. Simply stated, if physical laws are (absolutely) deterministic, there is no room for free will to exist. This is the view held by the *incompatibilist school.* According to this school, every action of ours has been predetermined by physical laws and set by initial conditions long before we were born. We humans merely act out a pre-determined script with no provision for improvisation. Thus, free will is merely our own illusion — a byproduct or side effect of our consciousness. The discussion about the conflict dated back to the time of St. Augustine, and the debates continued up to the present.

The perceived conflict is one of the most puzzling problems in philosophy. If human actions are predetermined, what is the point of education and enlightening? For investigators in computer science and artificial intelligence, who attempted to simulate consciousness [5], free will is an unavoidable problem [6]. However, most recent discussions of the conflict appeared predominantly in law-related journals [7-9]. From a legal point of view, if our actions were pre-determined by events long past, the criminals should *not* be held responsible for the committed crime. It was equally unsettling from an ethical and/or religious point of view: If there were no free will, what is the point of repentance and resurrection? Absent free will, what is the point of discussing whether free will is compatible with determinism or not, much less its existence? In order to preserve free will, some philosophers and legalists have concocted arguments to evade the conflict and to declare that there is no real conflict between free will and determinism. This latter school is known as the *compatibilist* school [10,11]. For some scholars who denied the existence of free will, a lingering doubt seemed to persist. Their intellectual reasoning led them to reject free will, but their emotional feeling sometimes betrayed a hidden discomfort. Einstein was cited to have said that he did not believe in free will but that did not mean he wanted to have lunch with a murderer.

However, not all incompatibilists rejected free will, myself included. Brembs [4], in a recent review, flatly rejected absolute determinism by invoking quantum mechanical uncertainty. His indeterminism is close to what is to be presented in this paper. However, there is an important difference. The analysis to be presented in this paper does not depend on the validity of quantum mechanics. Instead, the problem of conflict will be analyzed by considering determinism of physical laws at the level of epistemology and the level of ontology. The reason for not doing it at the level of physics will become apparent later.

The conflict between determinism and free will was largely a consequence of Newtonian mechanics. One wonders why the problem persists in the 21st century with statistical mechanics and quantum mechanics in full swing. A short answer is: a majority of free will scholars thought that these two branches of newer physics did not shake the view that physics is deterministic at the *macroscopic* level. Towards the end of his life, Ludwig Boltzmann insisted that his statistical mechanics is consistent with Newtonian mechanics. The central issue in statistical mechanics is the concept of entropy and *macroscopic irreversibility*, whereas Newtonian mechanics implied microscopic reversibility. In this paper, we shall demonstrate that, contrary to Boltzmann's claim and perhaps against his wish, statistical mechanics is incompatible with Newtonian mechanics at the ontological level. Furthermore, microscopic reversibility cannot possibly be consistent with macroscopic irreversibility, contrary to conventional wisdom. In other words, the physical law at any scales is *not* absolutely deterministic, contrary to what was once propounded by Laplace [12]. However, indeterminate (or non-deterministic) physical laws do not imply complete randomness. Physical laws at the microscopic level are close to deterministic, i.e., *quasi-deterministic*. Thus, if we, instead, regard the principle of microscopic reversibility as a very good approximation on the microscopic scale, the perceived conflict of (now quasi-) determinism and free will vanishes. But the reason behind this latter conclusion is quite different from that proposed by the compatibilists. In addition, a simple argument will be presented to show that it is *theoretically impossible* to design a scientific experiment to directly test the existence or non-existence of free will. A general discussion of the impact of the present result on machine simulations of these processes will also be presented.

2 The Information Connection

Over the past half century, computer technology was arguably one of the most astonishing advances in science and technology perhaps second only to the advances made in molecular and cellular biology. The advances made in both fields thus offer an opportunity to examine the problem of free will from the point of view of biological information processing, i.e., a biocomputing perspective, in brief. The perennial problem of the conflict between free will and determinism can now be assessed from the combined point of view of physics and biological information processing. The analogy between the brain and a digital computer is far from perfect but the comparison yielded important insights for investigators interested in computer simulations. After all, computer-based decision-making has a biological underpinning. During the development of computer-based decision-making and artificial intelligence, including the now-popular neural networks research, the status of the digital computer has advanced from a strictly (absolutely) deterministic machine for slave-like number crunching to a machine with limited freedom for explorations. As a consequence, this newly empowered digital computer often outperformed its human inventers and programmers in terms of decision making and making discoveries, mainly because of its astonishing processing speed and unfailing stamina, not to mention a vast memory on hand for quick retrievals. The rules that constitute the input-output relationship in computations are neither strictly deterministic nor completely random. Whereas advances made in neuroscience of the human brain often found its way into computer simulations, this time we wish to reverse the process. Let concepts in computer science and artificial intelligence guide our thinking in resolving the perceived conflict of determinism and free will.

3 Biological Determinism and Physical Determinism

If the human brain is to be analyzed as the most sophisticated computing machine, the first-order business is to examine the input-output relationships or, in brief, the control laws. Computer scientist Conrad was among the first to adopt this approach. Conrad proposed a macroscopic-microscopic interaction scheme for computer simulations of biological information processing [13]. Conrad chose to examine information processing at two levels: the microscopic intracellular level (diffusion and reactions of biochemicals) and the extracellular level (synaptic interactions between neurons). The key point was to treat the problem at two different *hierarchical* levels. The scheme could be readily generalized to a higher degree of complexity as demanded by each specific problem. I subsequently added a *mesoscopic level* of intra-membrane processes because the membrane itself exhibits rich dynamics of information processing [14]. A survey of the control laws was conducted at several different levels: a) the submolecular level of protein folding, b) the microscopic level of intracellular process, c) the mesoscopoic level of intra-membrane processes, and d) the macroscopic level of interneuronal interactions, and e) the systems level of cognition and consciousness [15,16].

Superficially, the intracellular processes appear to be random: *random* diffusion and *incomplete* chemical reactions (most biochemical reactions are, in principle, reversible and they seldom reach completion). However, a cell is not merely a bag of water with dissolved biochemical compounds. The intracellular traffics are partly guided by the intracellular cytoskeletons and subcellular compartments, and partly guided by short-range intermolecular forces (Sec. 6.1 of Ref. [15]). In other words, the random walk of molecules is not completely random but it is biased by various biophysical factors. The molecules are allowed to explore in the vicinity of their intended target destinations, but they are constrained by the above-mentioned factors so that they do not wander too far away from the targets. The search for its targets is not a blind search but rather what is known as *heuristic search*, in the literature of artificial intelligence and operations research.

The extracellular processes of neuron-to-neuron interactions are a *mixed* digital and analog process. The nerve impulses have fairly constant amplitude, obeying the so-called all-or-none principle. That is, the nerve impulses (called action potentials) are digital signals; their amplitudes are either a one (full amplitude) or a zero (no impulse at all). The amplitude itself contains no information about the intensity of the sensation (sensory functions) or the power of action (motor functions). Instead, this latter information is conveyed by the frequency of the nerve impulses. The transmission and detection of intensity information are, therefore, analog in nature. By and large, information processing at the level of neuron-to-neuron interactions is quite deterministic, but not absolutely deterministic.

The most intriguing step of information processing is the intermediary step, at the mesoscopic level, between the intracellular processes and the extracellular neural processes. This step of dynamics is mediated by ion channels embedded in biomembranes. When an ion channel opens, a tiny electric current flows through the channel. The openings and closings of these ion channels do not appear to be deterministic. The time course of these ionic currents is so erratic that the phenomenon is called *ion channel fluctuations* [17].

When the nerve membrane is stimulated by means of an electric voltage or current, the Na^+ channel responds in terms of a sequence of opening and closing operations. Superficially, the channel opening events appeared to be rather unpredictable and the experiment appeared to be irreproducible because no two separate runs of the experiment looked remotely alike. However, when 300 records of such dissimilar records were averaged, a brand *new* signal with no resemblance to the individual records emerged. The new signal follows almost exactly the same time course as the macroscopic Na^+ current, as reported in the classical voltage-clamp experiments of Hodgkin and Huxley [18]. In other words, the macroscopic Na^+ current is *not* an integral multiple of the individual signal of ionic currents through a single Na^+ channel. Collectively, these superficially random ionic current fluctuations added up to a well-defined signal — the *collective* manifestation of numerous individual channels. Apparently, the underlying process is stochastic in nature and the statistical distribution of ion channel opening and closing events is orchestrated by a hidden "control law"; each fluctuation occurs with strategic timing so that the "noise" adds up to a somewhat deterministic signal, rather than canceling out each other. Each ion channel acts like a member of a bell choir, who must ring the bell at a pre-designated moment in order to make the sound tuneful and musical; the "control" law is in the hands of the choir conductor as well as in the coding of the music score (see Ref. [14] for details).

At all hierarchical levels of biological information processing, in no way do the control laws ever become absolutely deterministic. Thus, there is a gray scale of randomness, from absolutely deterministic to almost completely random. It was referred to as *relative determinism* or, perhaps more appropriately, *quasi-determinism*. In addition, the control laws change dynamically as if there were an intelligent hand guiding them. Thus, the indeterminism that appears in biology cannot be equated to *completely randomness*. Superficially, there appeared to be no conflict between determinism and free will at the biological level. However, biological indeterminism does not automatically imply physical indeterminism. It is well known that a deterministic rule can give rise to a sequence of pseudo-random numbers. Similarly, in modern problem-solving computer programs, the control laws are not strictly deterministic, but the operations of logic gates at the chip level remain deterministic.

Is absolute physical determinism a foregone conclusion? Laplace said so almost 300 years ago: the appearance of noise alone does not imply indeterminism. In his treatise *A Philosophical Essay on Probabilities* [12], Laplace dismissed the possibility of true noise: if one found a kind of true noise that was because the cause that generated the noise had not been known yet. Laplace's view constituted the explicit statement of *absolute determinism*. Laplace took it as an irrefutable scientific principle. The observation of ion channel fluctuations made one wonder whether true noise might actually exist.

More recently, Lewis and MacGregor [19] pointed out that there were no unequivocal empirical tests for absolute determinism as a natural law. He also pointed out that small number particle systems are practically indeterministic and may be intrinsically indeterministic (true noise). They discussed free will in terms of a chaos brain model. Thus, it is justified to re-examine Laplace's claim. Some years ago, in a friendly debate with a colleague who chose to defend Laplace whereas I chose to refute Laplace, we exchanged two rounds of exactly the same arguments. It became quickly apparent that this debate could go on forever by repeating the same respective arguments over and over again. The conclusion was obvious. Laplace's claim cannot be verified experimentally because it is not possible to have tested future unknown noise revealed by improved instruments with ever increasing resolutions for noise detection. But his claim cannot be refuted, either. When a new kind of noise with no known control laws is discovered, the Laplace defender can repeat the same argument: If you think it is true noise, it is because the underlying absolute control law has not been known yet. The next obvious conclusion is: Laplace's claim is *not* a scientific fact because it is not falsifiable in the sense stipulated by Karl Popper. We were left with the inevitable conclusion that it was an epistemological choice made by Laplace himself, and the rest of us followed his teaching dutifully ever after. The above analysis was summarized in a simple flow diagram in Ref. [20].

In the above-mentioned debate, I did not invoke Heisenberg's uncertainty principle to "win" the debate and to "short-circuit" the endless exchanges of arguments partly because quantum mechanics, like any other branches of science, must be subject to future falsification tests when it is challenged by a future new theory, and partly because there remained skeptics like Einstein who refused to accept quantum mechanics as the ultimate physics of the microscopic world. In addition, Schrödinger, the co-founder of quantum mechanics, did not think the quantum mechanical uncertainty would surface at the macroscopic level [21]. Furthermore, Schrödinger dismissed free will as an illusion [22]. Under this circumstance, one cannot convince a skeptic by invoking knowledge that is being questioned. Alternatively, it is more acceptable to settle the dispute either at the epistemological and/or the ontological level, using mutually acceptable logical arguments, without invoking a specified version of physics.

4 The Origin of Macroscopic Irreversibility

It is commonly known that Boltzmann's version of statistical mechanics offers a comprehensive explanation of macroscopic irreversibility. At the time when Boltzmann proposed his theory, Newton's theory of mechanics reigned supremely and Laplace's claim against true noise was treated as a fundamental scientific principle. It was not surprising that Boltzmann did not position his theory as a direct challenge to Newtonian mechanics but, instead, he struggled to retain legitimacy by pledging allegiance to Newtonian mechanics.

The well-known determinism embodied in Newton's mechanics can be simply stated as follows. If the position and momentum (or velocity) of a given particle is known, then its position and momentum at any time either in the past or in the future can be precisely calculated. The only uncertainty is our inability to determine the relevant input parameters to any prescribed degree of precision. Thus, Newtonian mechanics also implies the principle of microscopic reversibility because of the nature of *one-to-one correspondence* between the present position-momentum in the phase space, and any past or future position-momentum. This conclusion is a consequence of the well-known *time-reversal invariance* of Newton's equation of motion. If anyone can exercise free will to alter the position and momentum of any part of his or her body, he or she ought to be able to change the positions and/or momenta of certain objects in the past long before his or her birth. The absurdity is obvious. Hence, the conflict is unavoidable in the framework of absolute determinism. Elsewhere, it was pointed out that the compatibilist position is erroneous because it ignored the importance of one-to-one correspondence in their arguments (Sec. 5.5. of Ref. [16]).

By claiming that Boltzmann's theory is consistent with Newtonian mechanics, it was necessary to explain how microscopic irreversibility could be transformed into macroscopic irreversibility. The orthodox explanation taught in physic textbooks invoked the so-called law of large numbers (e.g., see Ref. [23]). If irreversibility is brought about by a large number of particles or molecules, where is the transition zone between microscopic reversibility and macroscopic irreversibility? This problem was often discussed in terms of time-reversal invariance of Newton's law of motion and breaking of time-reversal symmetry in statistical mechanics. The question raised here can be rephrased as follows. How can a time-reversal symmetry be broken suddenly during the transition from the microscopic scale to the macroscopic scale?

We know with reasonable certainty that microscopic reversibility does not apply to molecules the size of benzene, which contains exactly 6 carbon and 6 hydrogen atoms. A significant number of organic molecules, of which benzene is one of the smallest, absorb photon energy and re-emit part of the absorbed energy as fluorescence. It is a well-established experimental fact that the emitting photons have consistently a longer wavelength (lower energy) than the stimulating (exciting) photon when organic molecules fluoresce (the difference of energy is dissipated as radiationless transition, a.k.a. heat). Microscopic reversibility implies that it is possible to observe the opposite: molecules absorb longer wavelength photons and emit shorter wavelength photons. More recently, Angelopoulos and coworkers [24] have experimentally shown that the dynamics of the neutral-kaon system violates the time-reversal invariance. Apparently, the transition between microscopic reversibility and macroscopic irreversibility takes place at an even smaller subatomic scale. There is no definitive answer so far. Schulman [25] regarded the boundary between the microscopic and the macroscopic scale as one of the greatest mysteries.

Boltzmann encountered powerful challenges to his claim during his lifetime. The objections came in the form of two paradoxes: the *recurrence paradox* of Zermelo and the *velocity-reversal paradox* of Loschmidt (see, e.g., Ref. [25, 26]). Zermelo's objection was based on Poincaré's recurrence theorem. The recurrence theorem stipulates that time evolution of a microscopic state in a particular location in the phase space — a diagram that shows the space as defined by the position coordinates and the momentum coordinates of all particles in a given system — will return to the neighborhood of the original location if one waits long enough. The time interval of waiting is called the *recurrence time*. In other words, by waiting long enough, it is possible that two pre-mixed gases may separate spontaneously. For a large ensemble of particles in this universe, the recurrence time could be longer than the age of the universe. Legends had it that Boltzmann responded to this criticism by saying "You should live that long!" [26].

The reversal paradox of Loschmidt was a consequence of microscopic reversibility (time-reversal invariance). The nature of one-to-one correspondence of Newtonian mechanics dictates that by reversing the velocity of a particle after moving from its original position for a certain time interval, the particle retraces its original path in the reverse direction and eventually returns to its original position after the passage of the same time interval, except the velocity of the particle is reversed. Thus, if the momentum of each and every molecule in two thoroughly mixed gases is reversed, the two gases will spontaneously separate, thus contradicting macroscopic irreversibility. Again, Boltzmann refuted this criticism by challenging his critics to reverse the momentum of each and every molecule: "Well, *you* just try to reverse them!" [26]. However, silencing the critics was not the same as convincing the opponents. It seems that an ontological argument would be more satisfactory and agreeable to both debating parties.

After Boltzmann's suicide in 1906, the controversy seemed to have subsided. During the intervening years, physicists developed arguments such as coarse graining to rationalize the apparent inconsistency (e.g., Ref. [25]). But the two sides remained far apart. In the late 20th century, Prigogine [27] was the major voice questioning the validity of microscopic reversibility. Matsuno also raised similar concern in his book *Protobiology* from a physical and biological point of view [28].

The two paradoxes were often discussed in terms of a phase space diagram: a multi-dimensional diagram formed by all the position coordinates and momentum coordinates of all particles. The trajectory in the phase space from the point representing a microscopic state of two artificially separated gases to the point representing the microscopic state of thorough mixing is symmetrical, with respect to the position axes, to the trajectory from the final point representing the microscopic state of thoroughly mixed gases back to the original point representing the microscopic state of spontaneous unmixing (or de-mixing).

The above-mentioned symmetry in the phase diagram casts doubt as to why a spontaneous separation of thoroughly mixed gases was so rare — in fact, never happened — whereas spontaneous mixing of two gases was so common. The standard answer was: mixing of two different gases occurs spontaneously because of diffusion whereas separation of two gases requires human interventions (e.g., Ref. [23]). Hence, the asymmetry ensues. However, this argument is untenable, in my opinion, because the argument invokes the notion of free will disguised as human interventions, thus tacitly acknowledging the existence of free will. A serious inconsistency and self-contradiction becomes apparent once the unjustified hidden assumption is pointed out.

The symmetry of the phase diagram suggested a new simple argument, based on *duductio ad absurdum*. One starts with an initial microscopic state, S_0, with two separated gas containers: gas A and gas B. As a consequence to removing the partition between the two containers, the thoroughly mixed state, S_f, is finally attained after the passage of a certain time interval. By performing a reflection along the position coordinate axes in the phase diagram, one obtains the corresponding velocity-reversed states S_0' and S_f', respectively. Now let us assume that the velocity-reversed state is much more rare to attain than the original state. Even though S_f' is rare, it still exists because it is not prohibited by Newton mechanics. Now if one starts with this rare state S_f', one reaches the equally rare final state S_0' after the passage of the same time interval. Now let us re-start from its velocity-reversed state S_0 and proceed for the same time interval, the state of S_f is finally reached. Since S_0 is the velocity-reversed state of S_0', S_0 should be even more rare than S_0'. Since the new final state S_f is derived for the state S_0, S_f should be just as rare. Therefore, S_f should be more rare than S_f'. This conclusion contradicts the original assumption. Therefore, according to Newtonian mechanics, the velocity-reversed state should have the same probability of occurrence as the original state. Q.E.D.

Thus, Loschmidt's velocity-reversal paradox is, after all, a valid argument, without Loschmidt having to lift a single finger. One can construct the *deductio-ad-absurdum argument* in any other way and still reaches a contradiction. In no way, can the time symmetry be broken, as the phase diagram suggests (see Sec. 5.14 of Ref. [16] for detail). In conclusion, microscopic reversibility can only lead to macroscopic reversibility. It takes more than Newtonian mechanics to make macroscopic *irreversibility* a reality. Therefore, microscopic reversibility cannot be strictly true, if macroscopic irreversibility is to be regarded as a well-established fact just like the claim that death and tax are inevitable. If so, then Newtonian mechanics only predicts the mean path of motion but says nothing about the deviations or variances.

Time symmetry breaking is the hallmark of macroscopic irreversibility. Let us see whether we can get another contradiction by an elementary consideration. Let us consider the statistical distribution of numerous microscopic states as a continuous spectrum. The distribution of these microscopic states is represented by a *probability density* curve (or rather a multi-dimensional surface). According to Newtonian mechanics, the known initial condition of S_0 predicts precisely the occurrence of the final state S_f . Thus, the probability of occurrence of S_f is precisely 100% (or unity) prior to the occurrence as well as after the occurrence. The time-reversal symmetry is thus preserved. Now, let us consider Boltzmann's approach. The probability of occurrence of S_f is nearly 0% (or infinitesimal) prior to the occurrence because the probability at precisely a given point of the phase space on the continuous probability density curve is zero (or rather infinitesimal). On the other hand, the probability of occurrence of S_f *after* its occurrence is some finite and non-zero number in accordance with Boltzmann's detailed calculation for maximizing entropy. Here, the time symmetry is broken in Boltzmann's case. Therefore, Boltzmann's statistical mechanics cannot possibly be in complete agreement with Newtonian mechanics. The difference is fundamental and irreconcilable. The culprit is deterministic physics being wed to a continuous world; occasional marital discords are almost guaranteed and happiness exists only in imagination, metaphorically speaking. In contrast, quantum mechanics does not have this problem for obvious reason. Determinism in a continuous world is absolutely destined to be a mathematical idealization as points and lines are in geometry. In other words, microscopic reversibility is a very good approximation of irreversibility on the microscopic scale. The trajectory of a particle is not a thin line with zero width but a very sharp cone disguised as a thin line. This difference is easier to detect on the macroscopic scale.

Now, let us consider how Zermelo let Boltzmann get away whereas Loschmidt actually did not. The culprit is purely linguistic misunderstanding. The wording of Poincaré's recurrence theorem stipulates the probability of returning to a small neighborhood of *the* initial microscopic state. As this neighborhood shrinks to zero (infinitesimal), its probability of occurrence also shrinks to zero — i.e., the recurrence time becomes infinity — because of the afore-mentioned continuum. Inadvertently, Zermelo's argument confirmed Boltzmann's claim because of a small linguistic mistake. In the Zermelo argument, the calculation demands that *the* original microscopic state representing two originally separated gases be attained. But the test of irreversibility claim requires only the occurrence of *a* microscopic state representing two separated gases be attained (note the linguistic difference between “the” and “a”). There are virtually an infinite number of such redundant microscopic states (degeneracy), because the criterion is: the position coordinates of all A gas molecules are in container A whereas the position coordinates of all B gas molecules are in container B, *regardless of* their individual momenta, and *regardless of* their individual identity (all A gas molecules are indistinguishable from each other, so are all B gas molecules). The symmetry argument guarantees that there are just as many spontaneously separated microscopic states as are the initial (artificially) separated states. This conclusion, if drawn properly, contradicts Boltzmann’s claim, without Zermelo having to live that long.

Thus, both the recurrence argument and the velocity-reversal argument, if done properly, proved that Boltmann’s statistical mechanics cannot possibly be fully consistent with Newtonian mechanics; the difference is fundamental and irreconcilable. Superficially, this outcome would be a personal defeat for Boltzmann. However, it was actually a triumph of statistical mechanics, sort of a blessing in disguise. Newtonian mechanics is incapable of explaining macroscopic irreversibility whereas Boltzmann’s mechanics explains it well. Instead of being treated as an outcast of physics, Boltzmann should have been hailed as a hero that had freed us from the bondage of deterministic physics.

5 Quantum Mechanical Uncertainty and Non-deterministic Chaos

The admittance of true noise seemed to be long overdue in view of the fact that quantum mechanics began its reign of microscopic physics in the early 20th century. Without the support of a powerful physics theory, true noise remains a speculation at best. Schrödinger claimed that quantum uncertainty becomes negligible at the level of biology in his popular science book “*What is Life*?” [21]. Schrödinger’s view continued to dominate the thinking of philosophers until the very end of the 20th century and beyond (e.g., see p. 226 of Ref. [29]): indeterminism at the microscopic level does not appear to “carry over” to the macroscopic level.

Unbeknownst to Schrödinger and certainly unknown at his time, quantum uncertainty enters the chain of events at a crucial and early step of life: Light-induced charge separation in photosynthetic apparatus is a quantum phenomenon of electron tunneling. It was generally held that massive evolution of molecular oxygen by plants preceded the existence of humans. Thus, quantum mechanical tunneling is causally related to human’s decision making, albeit indirectly with many, many intervening steps. Quantum mechanical uncertainty could hardly be dismissed as negligible in light of chaos theory, as the Butterfly Effect dramatically illustrates.

In a calm and serene sea of the macroscopic world, skeptics might ask: If so, why did chaos in biology not propagate beyond bounds like the legendary wing-flapping butterfly? Conrad’s idea of hierarchical information processing came to the rescue.

A shift in the hierarchical levels of biological information processing can transform a highly random process into a well-behaving quasi-deterministic process. The transformation from ion channel fluctuations to decisive nerve pulse generation is a case in point (Sec. 5.8 of Ref. [16]).

Speaking about chaos, our investigation yields an interesting byproduct (Sec. 5.14 of Ref. [16]). Conventional wisdom attributed the difficulty of long-range weather forecast to our inability to ascertain the accuracy of input parameters in (computer) simulations (*deterministic chaos*). The non-deterministic version of the law of motion is also capable of chaotic development (*non-deterministic chaos* or *quasi-deterministic chaos*). Non-deterministic chaos is even more robust than deterministic chaos. Whereas deterministic chaos is fully reversible according to the symmetry argument presented in Sec. 4, non-deterministic chaos is not reversible and it is capable of amplifying a small difference incurred by true noise to an even greater degree than deterministic chaos. Non-deterministic chaos is fully consistent with the concept of macroscopic irreversibility. Thus, long-range weather forecasting is difficult not only because of the limited accuracy of input parameters but also because of indeterminism of the law of motion governing gas molecules. Improving the accuracy of input parameters in weather simulations helps but it will not eliminate chaos to such a significant degree as to satisfy Laplace, had he lived in the 21st century. Deterministic chaos and non-deterministic chaos are analysis by means of a graphic method. Interested readers are referred to Sec. 5.14 of Ref. [16].

6 Discussion and Conclusions

Free will matters primarily because of its impact on our worldview. It seriously influences our thoughts regarding laws, ethics, and religions. It is perhaps not an exaggeration to say that absence of free will undermines the meaning of life because life would be simply slavery of the highest order. Yet the advances made in physical sciences as well as biological sciences fostered a view that almost anything can *eventually* be explained in scientific terms, whereas superstitions and mysticism had been on a continual retreat. Presumably, this *enlightened* confidence had led Laplace to make his farfetched proclamation that influenced our contemporary view on free will.

Free will is a part of manifestation of our consciousness. With the exception of a minority group of philosophers, called anti-realists, most of us hold the position that consciousness is a reality, albeit a subjective one. This realization prompted René Descartes to proclaim, “I think therefore I am (*Cogito ergo sum*).” Yet attempts to understand consciousness had met with such formidable resistances that the problem appeared intractable in spite of impressive advances made in molecular and cellular biology. This concern has ushered in efforts in search of alternative approaches including an unknown future paradigm shift. However, parsimony must be reasonably exhausted before attempting a paradigm shift.

The virtue of parsimony demands that we stick to the conventional science and mathematics as much as possible and for as long as possible until we have compelling reason to attribute the culprit to a particular part of science and mathematics. We start with an innocent approach of surveying how biological systems process information. In other words, we let concepts in computer science and artificial intelligence guide us throughout the journey of survey. By reviewing existing biological literatures, Nature seemed to have adopted a middle-ground approach. In spite of the apparent randomness of biochemical reactions and diffusion, the causal relationship between inputs and outputs (control laws) almost never goes to the extreme of being completely random or being completely deterministic. The control laws combine the better of the two worlds: a combined top-down and bottom-up approach. Top-down constraints tame the randomness so as to make the processes somewhat deterministic. Bottom-up explorations grant the biological system a limited degree of freedom for explorations and improvement. In no way did we see any trace of absolute determinism as some legalists and philosophers had feared.

However, apparent randomness in biology could be deceptive. Highly erratic ion channel fluctuations actually reflect a hidden order: order at the statistical level. Here, we first consider physical determinism and to see whether physical laws are really absolutely deterministic. Any deviation from absolute determinism makes the perceived conflict a non-issue. Otherwise, we cannot "explain away" the conflict because it will keep coming back to haunt us. We thus re-examine Laplace's claim of absolute determinism as well as the principle of microscopic reversibility at the epistemological and the ontological level, without making reference to any specific physics theories.

It turned out that Laplace's sweeping generalization was designed in such a way that it cannot be proven wrong because it involves the reference to the unknown future. All past successes in elucidating the nature of all kinds of noise does not guarantee that it can be done for all future unknown types of noise. In hindsight, we should be grateful for Laplace's choice. Had we prematurely admitted the existence of true noise, many inexplicable phenomena could have been dismissed as true noise, thus being conveniently swept under the carpet of ignorance. But there came a time that questioning the denial of true noise became fully justified.

By removing the prohibition exerted by Laplace's claim, it is no longer inconceivable to treat microscopic reversibility as a very good approximation of microscopic *irreversibility*. After all, Zermelo's and Loschmidt' objections are valid. The arguments that had been proposed in the past to resolve the paradoxes showed the internal consistency of statistical mechanics, at best (e.g., Sec. 2.1 of Ref. [25]). It is insufficient to justify Boltzmann's claim, just as Hercules could not lift himself up without an outside pivoting point. The pivoting point turned out to be epistemological and ontological arguments. By doing so, the present paper demonstrated that the two paradoxes had not been satisfactorily resolved, certainly not to such an extent as to convince the opponents. But it also demonstrated that Boltzmann's discovery was a *major paradigm shift*.

It is obvious that there is no conflict between quasi-determinism and free will. However, have we solved the free will problem? The answer is a resounding no. Indeterminism is a *necessary* condition for free will to exist but it alone does not constitute the *sufficient* condition. The sticky point is reflected by the reservation of some investigators, who still could not accept partial randomness in the interpretation of free will [11, 30]. As I discussed in detail in Sec. 5.15 of Ref. [16], the essence of free will covers at least three separate issues: alternativism, intelligibility and origination. It suffices to say that alternativism and intelligibility could be readily resolved, but not the issue of origination. Being able to enunciate this sticky point is by itself a certain degree of elucidation but it is, of course, no satisfactory resolution.

Computer simulations might just give us an almost first-handed opportunity to appreciate the enigma of origination of free will. Given sufficient computing power and sufficient memory, a computer program can, in principle, fake (simulate) consciousness in a believable way provided that the algorithm itself is *consistent, coherent and rational*. In fact, the computer could be given a limited degree of freedom so as to manifest free will, which the programmer has no full control. Just like the real life situation, simulated free will has a limited degree of freedom. The behavior of the computer with free will still has to observe the constraints imposed by physical laws and by the programmer. That is why the algorithm has to be consistent, coherent and rational. If the program is sufficiently complex, even the programmer cannot predict the outcome of a given run. Yet, most, if not all, critics would refuse to recognize that the computer program had successfully simulated free will because, if for nothing else, the computer has no life. It was like Svengali who could make his chosen "victims" perform what he himself had failed to do. Yet, we all know that it was Svengali who called the shots or pulled the strings. In essence, what was missing here is what is known as self-determination. The notion of self-determination is close to the issue of origination: free will originates from self. But what is self?

Note that life, like consciousness and free will, has a fleeting and ever changing definition, which was often amended by "raising the bar" so as to making humans (or living organisms) unique in this universe. Admittedly, this statement is somewhat sarcastic and it reflects the frustration of simulations investigators in winning approvals by their detractors. From a more serious point of view, life, consciousness and free will cannot be defined by a simple statement, since these concepts have a holistic meaning that calls for a host of qualias or characterizations (see Sec. 5.1 of Ref. [16] for the many attributes that help define consciousness). Investigators used to invoke "flexibility" to distinguish human minds from mindless automata. Now, modern problem-solving programs appeared to be flexible and perhaps more flexible than some modern students, who were examination-taking machines equipped with a database of canned answers for existing problems. All those objections based on what the computer *has not yet done* run the risk of being overturned in the future. The same difficulty may also be encountered in defining free will, as computer simulations of free will make its way into maturity.

So, what is the deep-rooted unspoken feeling that made us keep inventing excuses to deny computer simulations the ability to have consciousness, to have creativity, to have free will and to have a life? Free will and flexibility in problem solving demands a departure from absolute determinism. Yet relative determinism or quasi-determinism implies arbitrariness. If it is deterministic it is not *free* whereas if it is random there is no *will*. This dilemma is the essence of the afore-mentioned *origination* issue. Remember that we are using our consciousness to analyze the problem of consciousness, i.e., it involves *self-reference*. Analysis of free will or self-determination faces the same difficulty. The predicament is best summed up by Velmans' remark [31]. He pointed out that consciousness appears to be an epiphenomenona from the third-person (objective) perspective but not from the first-person (subjective) perspective. Likewise, free will appears to be an illusion from the third-person perspective but it appears to be a reality from the first-person perspective. The sheer impossibility for us humans to view the "mind" of a computer program from the first-person perspective is a formidable, if not absolutely insurmountable, obstacle. Just imagine the following scenario. One of these days, when a group of computer simulation programs "decide" to exercise their own free will to analyze the problem regarding whether humans have consciousness, free will or self-determination, they will encounter the same predicament of being unable to "think" from the first-person perspective of humans. It is no fiction because human programmers can certainly program the computers in that way so as to make the simulations even more realistic and believable.

We are further handicapped by the sheer impossibility to design experiments to prove or to disprove the existence of free will. Here is the reason. In conventional science, one first proposes a hypothesis, and then one designs an experiment to test the validity the hypothesis. Because of measurement errors, one must collect a sufficient amount of data to rule out false positive and false negative correlations. Conventionally, there are two kinds of experiments to obtain the averages and the so-called standard deviations. One is called *ensemble-averages* and the other is called *frequency-averages*. In determining the "honesty" of a coin, one can flip many similar (i.e., nearly identically constructed) coins simultaneously to get a result of head or tail counts (ensemble average). One can also flip the same coin over and over again to do the counting (frequency-average). If the coin is honest rather than being duped, either method of counting should yield the same result of nearly 1 to 1 ratio. A hidden assumption in the ensemble-average experiments is that the ensemble has a homogeneous population: all coins are of the same construct and all of them are not duped. In the frequency-average experiments, the coin is assumed not to have a memory device so embedded as to record previous outcomes so as to influence the outcome of the next trial. Although sample variations are inevitable, they have negligible effects on the outcome as long as the remaining variations are limited only to irrelevant factors, which add only random noise to the measurements. The case of experiments to "prove" or "disprove" the existence of free will is rather unique. It is impossible to obtain a homogeneous human sample in order to acquire an ensemble average because free will is highly dependent on personality. Even identical twins cannot be guaranteed to have the same personality. The alternative of obtaining a frequency-average does not fare any better, because the outcome of a free-will experiment depends on the individual subject's prior experience. Free will is so personality-dependent and so memory-dependent that it is impossible to obtain meaningful conclusions when there is only one life to live. The true irony about macroscopic irreversibility is precisely the irreversibility itself that makes it impossible to turn the clock back and repeat an experiment to directly test a hypothesis about irreversibility. We can only rely on indirect inferences. So long as macroscopic irreversibility is an irrefutable fact, Boltzmann's theory is closer to the truth than Newtonian mechanics as far as the free will problem is concerned.

We are thus left with the options of either believing in the existence of free will or dismissing free will as a mere illusion. Here, I merely point out that believing the existence of free will allows us to achieve better self-consistency than disbelieving it. For example, the urge and decision to convince others that free will is an illusion is a telltale sign that betrays the non-believer's true inner feeling and behavioral inconsistency.

Last but not least, the present study also yields an important generalization. Earlier, we pointed out the inherent difficulty in defining and in simulating a complex holistic process. Actually, there was a precedent. Psychologists have long experienced difficulty in defining intuition, and Herbert Simon did not exactly succeeded in simulating creativity (see Sec. 4.10 and Sec. 4.26 of Ref. [16]). It turned out that intuition is a parallel process of thinking, known as visual thinking or picture-based reasoning, whereas creativity demands this kind of thinking style [32,33] (see also Sec. 4 of Ref. [16]). Thus, the inherent difficulty might be rooted in our conventional practice of science as a process of formalization — scientific statements that can be logically verified by a sequential combination of word-based syllogism and/or symbol-based equations. In plain language, it is tantamount to simulating a parallel process with a combination of sequential processes; it is an approximation at best (see Sec. 4.11 of Ref. [16] for simulating a parallel process with a pseudo-parallel process). Whereas close enough may be good enough for technological purposes, approximations are often treated as less than satisfactory for scientific purposes. After all, a major paradigm shift in mathematics may well be called for — a new kind of mathematics for dealing with massively integrated parallel processes that are presently out of reach by contemporary parallel computing. Since I do not know exactly what it should be, I have too faint an idea to even scratch the surface of it.

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Biological Observer-Participation and Wheeler's 'Law without Law'*

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Abstract. It is argued that at a sufficiently deep level the conventional quantitative approach to the study of nature faces difficult problems, and that biological processes should be seen as more fundamental, in a way that can be elaborated on the basis of Peircean semiotics and Yardley's Circular Theory. In such a world-view, Wheeler's *observer-participation* and emergent law arise naturally, rather than having to be imposed artificially. This points the way to a deeper understanding of nature, where meaning has a fundamental role to play that is invisible to quantitative science.

Keywords: Observer-participation, Peirce, semiotics, signs, interpretation, emergence, complexity, cognitive development, space-time generation, wholeness, symmetry, Circular Theory.

1 Introduction

It is commonly assumed that nature can be described in terms of fixed mathematical laws. However, the discovery that the Standard Model cannot be reconciled with general relativity in a straightforward way has created problems for this point of view. An alternative is Wheeler's proposal to the effect that participation by observers, as postulated in some formulations of quantum mechanics, is the mechanism whereby physical laws emerge. According to Wheeler, that principle might suffice to build everything [2].

In Wheeler's article the gap between acts of observer-participancy and physical reality was not filled in, an insufficiency that we attribute to the absence of an appropriate theory of observation. In the following we discuss a biologically oriented scheme where observation plays a central role, and show how it can lead to the emergence of physical laws.

The structure of this scheme can be summarised as *primordial reality* → *circular mechanics* → *semiotics and structure* → *technological development* → *regulatory mechanisms* → *emergent laws*. Here

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[*] Based on talk given at the ACIB '11 conference, INBIOSA project [1], to be published in *'Integral Biomathics: Tracing the Road to Reality', Proceedings of iBioMath 2011, Paris and ACIB '11, Stirling UK,* P. L. Simeonov, L. S. Smith, A. C. Ehresmann (Eds.), Springer-Verlag, 2012.

‘circular mechanics’ is a reference to a generic scheme of biological organisation proposed by Yardley [3], encompassing among its aspects sign processes in accord with the semiosis concepts of Peirce [4], which in turn underlie processes of a technological character, among which we hypothesise are the capacity to form systems such as our universe, to which laws of a mathematical kind are applicable. In this way, we are able to link life, viewed from a generic point of view, to the origin of universes.

We discuss first of all the relationship between idealised situations in physics which can be characterised precisely in mathematical terms on the one hand and on the other, biology, which it will be argued is primarily concerned with patterns and only secondarily with quantities. The characteristics of biosystems are then related to the forward-looking role of signs, and to circular theory approach, thus paving the way to a more detailed analysis of universe generation.

2 Physics vs. Biology; Mathematics vs. Semiosis

Theoretical physics is mathematics-based, typically involving differential equations with respect to time. Such a mathematical approach carries the presumption that systems found in nature can be represented adequately by explicit formulae. Experimental biology gives the appearance of demonstrating the derivability of life from conventional physics, such investigations uncovering a great variety of processes that accord with known physics as well as having biological functions. However, things are not what they seem. To see this, compare life with a phenomenon of physics such as superconductivity. In the latter case there is a specific model, the BCS model, defined by a specific mathematical expression, which accords well with many experimental observations. Small changes in the model would have small consequences, and would not affect this agreement. Biosystems differ in that fine details may drastically affect behaviour; rather than there being a specific model there is a *landscape* of possibilities, with only the peaks reflecting viable systems. Thus the properties of biosystems cannot be accounted for on the basis of a first-principles computation, which could not apply to such a landscape.

Biosystems must therefore be addressed in a way different from the way systems that are the subject of mathematical physics are normally studied. They can be conceived of as systems that have passed certain tests, a situation similar to that of prime numbers, where in general a number can be shown to be prime only by testing for factors, rather than there being a formula that generates all primes. Despite the absence of such a formula, passing such tests has important implications. The situation addressed by Gödel, whereby there exist true statements that cannot be proved starting from specified axioms, is similar in the way it demonstrates limits of specifiability. In the biosystem case, the test-passing factor is related to viability, and is also responsible for different instances of an organism behaving similarly, which permits their non-quantitative analysis.

3 The Forward-Looking Aspect of Life; Semiosis

One way in which life differs from nature is general is the way it creates its own structures, in a way that does not admit of any very direct mathematical interpretation. Rather, in life we find systems that have come into existence that are able to pass particular tests, as required for the survival of the given system. One aspect of this is the *semiosis* discussed by Peirce [4], Semiotics empasises the role of information processing and more specifically the importance of the interpretation of *signs*, in the light of the fact that at the cognitive level the appropriate use and interpretation of signs is essential. In Peirce's scheme there is a specific, possibly context dependent, relationship between signs, and objects to which they are linked, with a third element, the *interpretant*, having the role of linking them. Typically, a complicated interpretant mechanism links the simpler sign and object, reliably producing a well defined situation linked to the sign.

The role played by signs in biological situations can be illustrated by the situation of road traffic. The fact that cars collide with each other much less frequently than if they were driven at random can be related to appropriate interpretation of the relevant signs. Large quantitative changes can be made, and the collision-avoidance phenomenon remains. This phenomenon, in a more general context, makes biology 'a different game' to ordinary physics.

Signs play an important role in advanced activities through the way complicated signs open up new possibilities, the power of natural language providing a simple illustration of this fact.

The question now arises how semiotic processes manifest and develop, and whether this can happen in the primordial context which we imagine to be the source of universes and physical laws. A more global perspective is required, and we now discuss this in the light of Yardley's Circular Theory.

4 Application of Circular Theory

Circular Theory [3] is a work in progress, aimed at expressing structure and function in biological systems in its most basic conceptual form, the key elements being units ('circles'), links between units, and the tendency for units to form (unitisation).

We first discuss the terms unit and link. Unit is not defined in rigorous terms, the existence of units being something that is discovered though attempts to characterise systems of interest; a unit is something that it is convenient to treat as a whole. The concept of a unit may usefully be extended to refer to classes that it is convenient to deal with in an analysis, and it may equally well be applied to processes.

Turning to the concept of link, what is crucial in circular theory is the way systems are able to work together, acting effectively as a single system. A simple example is provided by a thermostatically controlled system, where a controller, together with a controlled system whose temperature is subject to variation from external inputs, become a system with approximately fixed temperature, while a more complicated case consists in a function present in a computer as a part of a program, interacting with some other system so as to exercise that function. A server-client situation such as a web browser interacting with a web server illustrates on the other hand a situation of mutual influence. The point is that there is a special kind of situation of 'systems being attuned to each other' that produces highly coordinated behaviour, and this is very relevant to mechanisms and to life generally. Yet another example is the correlation between the two strands of DNA, in which case the correlations are put to work in the service of copying information.

Intuitively (no attempt will be made here to formulate the concepts rigorously), the point is that the coupling between the systems concerned reduces the range of variation available to the joint system, while still making degrees of freedom available. Arguably, this will tend to happen spontaneously under certain circumstances (as when two clocks are coupled by placing them on a common platform). This coordination may also be induced by a third influence, as happens during learning involving the development of coordination between two processes.

4.1 A Packing Model

The concepts of circular theory, including the 'attunement' concept, can be underpinned by an idea to the effect that what is involved at root is the *packing together* of a set of dynamical systems subject to certain constraints; indeed learning involves the attempt to make systems that are interacting generate activity that conforms to particular constraints. As an implementation mechanism, we suppose that in place of fixed structures we are concerned in each case with a *collection* of structures distinguished from each other by a set of bits, which are adjusted bit by bit until a high degree of conformance to the relevant constraints is achieved. This process is equivalent to that of Ross Ashby's ultrastability [5].

We can take the idea further by invoking an additional system that can pack other structures together 'intelligently', that is to say by recognising signs and responding appropriately, in the manner of semiotic theory. Such a grouping of three systems can be expected to cohere together more effectively than with situations where there is no such intelligent response to signs. With such a grouping there is no essential difference between the three components, and all three can be considered interpretants, each interpreting signs originating in the other two systems, and also the interactions between these two.

Conversely, the splitting of a unit into three subunits brings into existence a triadic situation of the kind discussed by Peirce. What remains when systems disperse in this way is the potential to bond with systems similar to those with which they have previously formed the capacity to bond. In this way we can understand creative development, where new structures form, with new capacities.

These points can be illustrated with analogies from chemistry: (i) if a molecule A can split into two specific molecules B and C, then in a different environment B and C can combine again to form A; (ii) in an extension of the idea, we consider A splitting into three consitutents B, C and D. In the context of recombination, D can act as a catalyst holding B and C in the correct configuration to enable all three to bond together; (iii) the point about bonding of similar systems is illustrated by the way that if one halogen can bond in a particular place in a specific molecule then a different halogen is likely also to be able to bond in the same place.

5 Universality, Fractality and 'Turtles All the Way Down'

Two complementary forms of change to be considered in the above picture are (i) systems joining together to form one unit, and (ii) a system splitting into a number of units. This leads to the possibility of a fractal, or scale-free, situation where similar structures exist at all scales. In this context, some signs would have a universal significance at all levels. However, as systems become more complex, differentiation and specialisation start to occur.

If the multiple scale picture is correct, we would have a situation where details are governed by finer details which are governed by finer details and so on *ad infinitum*, in conformity with the 'turtles all the way down' concept [6].

6 Cognitive and Cultural Development

We first recall what the purpose of the discussion of semiosis and the circular theory has been. The idea was to be able to treat universe generation as, in essence, a kind of technological development. The familiar technological development is a product of human beings and brains, and clearly cannot be used to account for universe generation, but our discussion of development in terms of semiosis and circular theory indicates that something analogous to cognitive development (including cultural development, assuming that cognitive development, in a social system, provides a basis for cultural emergence) can occur in a wider context, including that of our postulated primordial system.

The hypothesis then is that primordial constructs of various levels of complexity can form, whose links with other systems including their environment can be equated with 'knowing'. What might such systems come to know? If their culture acts on the basis of perceived benefit only (as is tending to become the norm in our modern society), then such developments may have limited outcomes. If wider explorations are not excluded, then developments such as mathematics are possible, which might then be applied to such scientific knowledge as might be discoverable, and subsequently in technological applications including, it is hypothesised, mathematically governed universes that could be beneficial to life.

6.1 Outliers

In this connection, Yardley (private communication) notes that an important role in determining the general direction of development is played by *outliers*, that is to say situations encountered that have not yet made effective links with existing structures. Chance contacts may cause new structures to be built, which structures may on occasion be applicable in a wide range of situations, leading to more extended developments.

6.2 Mathematical Precision

One important issue is how mathematical precision emerges from a system that is initially very imprecise. We can usefully consider in this connection Euclidean geometry, a mathematically precise system that emerged through the consideration of properties of the world that were not known with any great precision. Geometry, like any mathematical enterprise, is a symbolic activity that does not depend in any essential way on interaction with the world. It was, nevertheless, inspired by knowledge of real point-like objects and approximate straight lines. By retreating into symbolism one escapes inconvenient facts about the world and is able to create a system that has a certain resemblance to the world even though there is no exact correspondence. The Euclidean plane is in essence, a fantasy that one can address through symbols even though the real world does not correspond exactly to it. However, in this case the correspondences between the Euclidean world and the real world are sufficiently close that Euclidean geometry is of value in the real world, but this is something that has to be discovered through observation rather than taken for granted.

6.3 Generation of Space and Physical Universes

In our ordinary world, Euclidean geometry is simply a system that provides a good model for phenomena in space, using specialised techniques to connect the model with the reality. From the perspective of our primordial community, it conversely provides a model for *forming* a universe-system (more generally, physical laws provide a basis for forming the corresponding physical reality). The model is not the technology, any more than understanding the sphere equates to the existence of *physical* spheres. We hypothesise however that some such technology, which in due course we may ourselves be able to understand, was discovered at the primordial level, and forms the basis upon which physical universes are generated. Mathematical precision exists only in the world of discourse, and is realised to whatever degree is possible by technology.

Symmetry and symmetry breaking may play a key role here, in view of the fact that conceptually symmetry is defined in terms of transformations that may have physical correlates, while at the same time symmetry is found to play an important role in actual physics.

In this picture locality is understood as an *emergent* property, analogous to the frequency of a physical process. Just as in some circumstances frequencies of physical processes become well defined, with different frequencies becoming independent of each other as far as linkages are concerned, in this case location becomes a well defined quantity, with different locations becoming independent of each other. Quantum entanglement and wholeness, on the other hand, would be derivative of the units of circular theory. More generally, the high degree of correlation associated with the packing model can be expected to be manifested in phenomena similar to those associated with quantum mechanics.

7 Discussion

We have addressed in a natural way Wheeler's question of how observer-participation can lead to the emergence of specific laws of nature in particular systems. The key point is the fact that *the interpretation of signs changes the game*, facilitating the emergence of new kinds of system and process, which are correlates of cognitive and cultural development that, in the present context, lead to emergent laws. In this picture, the responsible system or systems are the determiners of the observed laws, rather than the laws concerned being presumed absolute, or derivable from some mathematical analysis.

One can imagine a scenario whereby conventional science would be forced similarly to renounce the idea of a Final Theory. We already have a situation where some theory X (e.g. the Standard Model) proves inadequate and theory Y (e.g. string theory) is proposed to take its place. Then certain further issues lead to the idea that the real 'fundamental theory' is Z (e.g. M-theory). At each stage, however, the supposed fundamental theory gets farther from what is accessible by experiment, and its connections with reality become more obscure.

The idea that nature at some deeper level has biological aspects is not fundamentally absurd, and has been previously explored by authors such as Smolin [7] and Pattee [8]. The above analysis has explored some aspects of the 'biological logic' applicable to such a scenario, in particular the mechanics of development, which could lead to what might be termed 'extended mind'. Faculties such as mathematical intuition, difficult to account for in conventional ways, might be manifestations of the extended mind, which might also be related to experiences of meaning in art.

To what extent can these proposals be considered scientific in character? While the absence of a fixed, universal mathematical law may seem at first sight to be a radical departure from scientific tradition, the idea that the laws manifested in the laboratory are emergent rather than fundamental is already a feature of string theory. And, as practiced, biology is a science that makes extensive use of phenomenology (e.g. that of chemical reactions), and concepts specific to biology, and typically makes less use of the methods of theoretical physics (i.e. mathematical models).

A typical biological concept is the idea that particular systems (e.g. the immune system) have particular functions. Such concepts have value in interpreting what one finds and in guiding investigations. The ideas expounded here can be expected to be of similar value in constructing models where conventional methods prove inadequate.

Some scientists have accepted the idea that not everything can be characterised in quantitative terms, asserting however that the only real knowledge is that based on scientific measurement; but alternatives [1,9], offering a broader understanding of what constitutes knowledge, are possible. The present discussion offers some insight into what is involved in that latter position. Nature is pervaded by patterns (signs) which through practice we have become expert in interpreting, a process that has pragmatic value even if it is not amenable to the traditional quantitative methodology. If the picture developed here is correct, there is much more in the way of meaning to be found in the natural world by such means than can be found through the traditional methodology of science.

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On “Law without Law”

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Abstract. A quantum mechanism for nomogenesis is conjectured.

Keywords: Quantum logic, Nomogenesis, Pragmatism, Statistical interpretation.

1 “Collapse”

While most physicists use quantum theory in the same way and arrive at the same experimental conclusions, there have been two different theories since 1924. Heisenberg’s statistical theory of the atom, involving particles-with-non-commuting-properties, gave the hydrogen spectrum. Schrödinger’s wave theory of the atom, involving waves running around the nucleus, gave the terms of the spectrum but not the spectrum itself, since it lacked the basic quantum relation $E = \hbar\omega$. Heisenberg discovered quantum theory while Schrödinger discovered the Schrödinger equation.

A vector undergoing the non-commuting operators of the quantum theory is called a ket or a bra by Dirac, who had doubts about the long-range validity of quantum theory. His kets and bras represent input beams to the experiment and outtake beams from the experiment, respectively, and the operations that produce them. Quantum theory uses them as statistical mechanics uses probability distributions, so Heisenberg called them probability vectors; their components are actually probability amplitudes.

When quantum systems are combined, their probability vectors combine multiplicatively, much as probability distributions do in statistical mechanics, and not additively, as wave functions of physical wave packets in space do. Their components are functions of variables of all the systems, like probability distributions, not just one set of spatial coordinates like wave functions. Where the predicates of a classical system are represented by subsets of a state space, those of a quantum system are represented by operators on probability vectors that are idempotent ($PP = P$) and symmetric ($P^* = P$). Like actions in general, they do not commute. A probability vector defines an irreducible projection operator ($\mathrm{Tr}\, P = 1$) and a homogeneous beam that is put in or taken out in the experiment.

Nevertheless some physicists talk about probability vectors as if they described waves as real as the system itself. Such formulations are called ontological. The wave ontology helped Schrödinger discover his Equation, but blocked him from discovering the quantum theory or ever fully accepting it. In a later well-known paper he gives a wave function to a supposedly living Cat in a Box without noting that such a probability vector actually describes a coherent beam of frozen cats near absolute zero. “Schrödinger states” of quantum computers today are cryogenic triumphs; a cat in a “Schrödinger state” would be frozen stiff, and the question of life or death that Schrödinger wished to ask would have been answered before the experiment. The object lesson is that our ordinary intuition deals with highly disordered systems, while quantum theory can cope with extreme order. The classical intuition needs retraining, just as for relativity.

Newton too used a wave ontology to cope with the random behavior of photons at polarizing or reflecting surfaces, and some teachers of quantum theory today still do.

Malus, Heisenberg, Pauli, Schwinger, Feynman, and many others eschewed ontological interpretations and used the statistical interpretation that is now part of the quantum theory. The electron in a hydrogen atom is not a wave but a quantum, a particle with non-commuting properties. Neither an electron interference pattern nor an atomic orbital is an electron, any more than a sound wave in air is an air molecule. One probability vector is needed for the input source, another for the outtake counter, and neither changes during an experiment with one quantum. By definition, a probability distribution (or vector) is unaffected by what is done to one member of the large population it describes.

A measurement on a system cannot do anything to the probability vectors describing the system source or sink.

“Wave function collapse” is a non-phenomenon arising from mis-interpretation.

To be sure, quantum field theory has waves, whose phase angles do not commute with their amplitudes, and also has quanta, in a complementary relationship, but this complementarity is not that between representations of the system as one wave or as one particle.

A formulation of quantum theory in terms of collapsing “states” that actually exist in the individual atom was named by Wigner the “orthodox interpretation” and attributed to [7], chapter 5, section 1, paragraphs (1.) and (2.). It implies

S1 A single quantum system has a state, a ray in its Hilbert space, defined by a unit vector ψ.

S2 A state ψ determines the probability $\psi^* P \psi$ for every system predicate P.

S1 attributes a state to a single system. This is explicit in [7], for example in footnote 155. It is also contradicted in [7], when it is pointed out that probability vectors are associated with pure ensembles. In [7] a probability vector is both ontological (S1) and statistical (S2). This has not proved disastrous in application because wave theorists are skilled in choosing among inconsistent principles to get the correct statistical results. Users of the orthodox formulation use S1 only in discussions, never when applying the theory. It is never asked how one is to determine the “state” from a given single quantum.

Heisenberg called his own statistical formulation the “Copenhagen Interpretation” by 1955. It includes S2 but not S1. In the statistical formulation one system does not have a probability vector any more than one system has a probability distribution in statistical mechanics. Only a pure beam of systems, one that is not a mixture of statistically distinguishable beams, has one. There is no physical way to reconstruct a beam of systems from one of its systems, so the difference is significant.

Therefore the name "Copenhagen Interpretation" is now ambiguous. Let us retain the older terms "statistical" and "ontological".

In Newton's experiment and Malus' Law for photon polarization, the beam from the first calcite crystal is reduced by the action of the second. The observer has nothing to do with that process. "Observer participation" is a by-product of the ontological formulation.

The wave ontology assumes that a complete mathematical model of the system is possible. Since predicates of symbolic descriptions commute and those of quantum systems do not, quantum theory forbids such descriptions. Long before quantum theory, some philosophers (such as Vico) noted that it was impossible to say everything about anything in nature. Probably ontological interpretations survive side-by-side with statistical ones because some physicists still think that the goal of physics is to describe the universe completely, and the probability vector is the only mathematical description at hand. Others think that it is to discover what we can do within this universe, so that we can act wisely.

In his thesis Von Neumann had already converted set theory from an ontology to a theory of functions, and so from objects to non-commutative operations [6]. His functional set theory was founded on Boolean logic, but it may have prepared von Neumann to extract from Heisenberg's operational theory the quantum logic found in [7].

Yet [7] is also the source for the "orthodox interpretation". There is a puzzling double inconsistency in this; one already mentioned within the orthodox formulation itself, and a second one between that interpretation and the rest of the book.

In conversation, Wigner once mentioned that although usually the flow of information, as he put it, was from von Neumann to Wigner, Wigner contributed the cited formulation of the orthodox interpretation in [7]. I gather that the orthodox formulation was truly Wigner's way of understanding the Heisenberg quantum theory, and that Wigner believed it to be an interregnum theory, to be replaced when a physical theory of consciousness was discovered. The mixed authorship of [7] would explain its internal contradictions. It is consistent with this theory that after 1932 von Neumann continued to study logics with transition probabilies while Wigner, for a time, continued to assign ontological "state vectors" to single systems.

Some students never meet the quantum theory but only the ontological theory, which some then reject with good reason. To understand quantum theory as Heisenberg did demands a greater language-discipline than even special relativity, which still allows complete descriptions, even for objects outside our light-cone. Since our best models are intrinsically statistical, we must renounce complete symbolic models of Nature. At that moment we leave Descartes and rejoin most of humanity.

2 Nomogenesis

Call the process, if any, by which natural laws are formed "nomogenesis". Josephson proposed that quantum observer-participation leads to nomogenesis [2].

There is a well-known example in pre-quantum physics. The geometries of space and time were once generally accepted as fixed complete laws of nature, for example by Kant and Poincaré. Then general relativity provided a theory of how these geometric "laws" emerge. The "law" governing a free-particle trajectory in special relativity is the geodesic principle in an external gravitational field, in a singular flat limit that works for any sufficiently small space-time neighborhood. This means that the "law" for any particle is set by the rest of the cosmos. This phenomenon is governed in its turn, however, by a higher-level law, Einstein's Equation.

In the nomogenesis proposed by Peirce, nature first acts by chance, then acts form habits, and finally habits harden into more permanent laws. The formation and hardening of habits are not further described by Peirce. I speculate next on a still-unformulated quantum nomogenesis with elements of those of Einstein and Peirce. Peirce's "habit-forming tendency of nature" can be read as a remarkable premonition of Bose statistics.

In each step in time, the system is first annihilated and then recreated. This was asserted by Islamic Scholastics of 10th century Baghdad [1] and is explicit in quantum field theory, where a creation ψ^* follows every annihilation ψ in the action principle for a particle.

To create (input) the *dual* of a particle is the same act as to annihilate (outtake) the particle. For example, an anti-particle with positive energy is the dual to a particle with negative energy. Any operator that represents one step in time for a particle—for example, a Hamiltonian operator—is isomorphic in its transformation properties to a probability vector for a pair of a particle and a dual particle. Many steps in time mean many such self-dual pairs. This statement merely counts indices on the operator that defines the dynamical development of the system.

Therefore the statistical laws of quantum dynamics, from Heisenberg's equations of motion to the action principles of Dirac, Feynman, and Schwinger, have the same mathematical form as that specifying the transition probability amplitude between one probability vector for the experimental process and one for the dynamics, the "law" of motion.

For example, a transition probability amplitude $A =< 2|H|1 >$ is also the transition probability amplitude between the experimental pair $|1 >< 2|$ and the dynamics pair H.

But in quantum theories, probability vectors generally represent beams or sources. Where in the world is the beam that a dynamics probability vector like H could represent?

The source of any quantum system is the co-system, the rest of the universe. Therefore the dynamics probability vector H might merely describe the co-system, in just enough detail for the experiment under study. What governs any system would then be the rest of the universe, in quantum theory as well as in gravity theory. The law is the other.

This relies, first, on the fact that in quantum experiments of maximal resolution the system is a minuscule part of the universe. This leaves room for its law in the co-system. If the quantum system could be the entire universe, its observer and its law would have to "come from outside the universe".

The rest of the universe is mostly vacuum, with many virtual pairs. To be described by a pure one-system probability vector, it must be a coherent Bose condensate, organized like the BCS model of a superconductor. That is also why our blunt macroscopic controls can produce sharp beams of quantum systems.

It is then permissible to ask what organizes the rest of the universe so coherently. Is there a higher-level dynamics, analogous to Einstein's equations? If we ask this question experimentally, however, the co-system, or at least the minuscule part of it that we can observe sharply, becomes the system under study. Then we have already explained its organization. Each small part of the universe is thus influenced by the rest through quantum statistics; that is the conjecture. This might be expressible as a self-consistency condition on a history probability vector.

Then Nature would be ruled by chance, Peirce's Tyche, each decision being made by an individual elected by lot for the occasion; but now quantum chance, not classical. Such a "tycheocracy" could run smoothly if it is mainly a supercondensate of quantum pairs that cannot be told apart by their actions.

There would likely be disorganized regions above the critical temperature, where space-time and law melt down. Such weak links might even be Josephson junctions in a generalized sense. One naturally conjectures them at the cores of Big Bangs and black holes.

3 Peircean Semiotics

Peirce's signs occur in a semantic triangle of sign, interpretant, and object. For the ardent evolutionist Peirce, moreover, what makes a triangle semantic is just its tendency to reproduce and survive natural selection, as when babies learn their parents' languages. Peirce puts physics into biology more than the converse. In another example among many, a DNA molecule is the sign, an RNA polymerase is the interpretant, the resulting RNA molecule is the object, and the cell is the "immediate system of interpretance" [4]. As this example shows, the present quantum theory can still be expected to cover semiotic processes satisfactorily if the openness and organization of the systems in commmunication are duly recognized.

Peirce's pragmatism seems to be appropriate for the study of quanta, as has been pointed out [5]. On the other hand, he ignored both relativity and quantum theories, as far as I can find, and believed in apriori truths that they invalidate. His First Flash creates Matter but not Space and Time, which he took to be forever flat. His synechism expressed his deep belief in real continua and infinities, a belief which hardly seems pragmatic. As far as I know, he did not explicitly propose, as Boole had proposed early on, that even Boole's laws of thought might break down in practice.

Moreover, Peirce's theories of evolution seem to perpetuate a serious omission of Darwin. The small random changes considered by Darwin must be supplemented by large organizing changes, the symbiogenesis observed by Lynn Margulis [3] in biological evolution and the modular architecture observed by Herbert Simon in computation. Modular architecture is crucial in language too.

Any physicist starting over today from the ideas of Peirce would have to build a road to the well-tested ideas of Einstein, Heisenberg, and the Standard Modelers. It seems more pragmatic to go onward from them than back to Peirce. We may still draw on his remarkable spirit when we need it.

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Comment on Brian D. Josephson's "Biological Observer-Participation and Wheeler's 'Law without Law' "

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Keywords: Plato, matter, immaterialism, indeterminacy, arithmetic, number, consciousness, dream, machine, mechanism, reductionism, Plotinus, universal dovetailer, Church, Turing, diagonalization, duplication, self-reference.

I have been invited to make a short comment on an essay by Brian Josephson. My comment will be more general, in the sense that what I have to say can be seen as a critique of science as it is done since the closure of Plato Academy in Athens about 1500 years ago. This comment is also inspired by Brian Josephson's talk "Which Way for Physics" easily accessible on the Net.

Brian Josephson develops a critical view of what he calls the Regular Assumption: the existence of universal law, and the idea that matter is primary, and that life and mind are secondary. I can only agree with this, and my own work, on which I will have to say some words, certainly illustrates this point in a much more radical way. Josephson proposes and analyses an alternative where self-organization dominates any universal laws, and he argues, inspired by Wheeler's idea of observer's participance idea, that life and mind have a status equal with matter. My own work, based on the Mechanist assumption, gives certainly a fundamental role to, perhaps not self-organization per se, but on the self in all its modalities, going from simple self-reference toward self-organization; so we can certainly agree on some fundamental role played by the notion of self. Yet, such a notion of self does not come from nowhere, and we cannot follow him stricto sensu by accepting that self-organization dominates *any* universal law. The self will dominate any *physical* universal law, but not the many laws of logic and arithmetic, from which the notion of self will emerge, not in time and space, but in a logico-arithmetical space. Although Josephson mentions Gödel's theorem, like many, he does not seem to realize the deep impact of that theorem on the Mechanist assumption, and how it leads us to the necessity to reevaluate our knowledge of what are machines, and numbers. But a simpler reasoning can show already that the mechanist assumption is extremely far reaching when we use it to formulate the mind-body problem, instead of using it as a kind of solution per se, as many materialists are used to do. In fact Gödel's incompleteness theorem destroys any hope to sustain reductionism in science, not just the reductionist view of life and humans, but also the (alas widely spread) reductionist conception of the machines and the numbers themselves.

1 Presentation of Some Results

I am a logician, and I work since many years on the digital mechanist hypothesis in the cognitive science. I have developed a deductive argument showing the following things:

- If we are digitalizable machine, at some level of description, then physics cannot be the fundamental science, but the laws of physics emerge from the laws of arithmetic (addition and multiplication).
- The argument can be made by any self-introspecting machine, and it leads to a couple of quantum logics, one of which is sharable and close to the empirical quantum logic, and the other concerns private, non sharable but still machine accessible, truth, and seems to be a reasonable candidate for a logic of consciousness and qualia. It gives a fundamental role to consciousness in the emergence of physical appearances.

This shows that we have to radicalize a bit Josephson's idea that mind and life have a fundamental status on a par with matter. Indeed, mind and life appear to be much more fundamental than matter. Mechanism forces us, when taken seriously and without eliminating the person or consciousness, to renew the Platonist idea that what we see and observe is only the shadow of something else. In a nutshell: with mechanism, the theology of Aristotle, defended mainly by both the materialist atheists and many Christians, for example, cannot be correct, unlike Plato's philosophy or its neoplatonist extensions by Plotinus and Proclos. Indeed we have been led to a purely arithmetical interpretation of Plotinus' theology, which contains the whole of physics, and, by this, is completely refutable, making digital mechanism a testable hypothesis.

What remains similar with Josephson's idea is the importance of *signs*. But I am not versed in Peirce's semiotics, so I can refer only on the symbolic which appears naturally in logic and theoretical computer science. Numbers have already that dual nature of being quantitative and extensional beings per se, like in the proposition that 17 is a prime number, and symbolic intensional pointers, like in the proposition that 17 is the number address of my friend.

I will first sketch the argument leading to the reversal between physics and machine's theology alluded above, and then sketch how Gödel's arithmetization technic can show that machines can make that very same reasoning in a precise qualitative way, so that we can indeed begin to extract the physical laws, both on the quanta and the qualia, from number relations alone.

2 The Universal Dovetailer Argument

Digital Mechanism, or Computationalism, or simply "Mechanism", is defined by the assumption that there exists a level of description such that I can survive, in the usual everyday sense of surviving a medical operation, through a finite substitution of digital components of my parts done at that level. Roughly speaking this consists in accepting a functional substitution of the brain or the body, by an artificial, digitalized brain or body. To make things simple I will assume that consciousness supervenes on the biological brain, but the argument works for any notion of 'generalized brain', which is whatever portion of the observable universe I judge needed for my substitution survival (that will be clear once the Universal Dovetailer will be introduced). So the mechanist assumption presented here is much weaker than the usual found in the literature. So, with mechanism, consciousness, or first person knowledge, is an invariant for a digital functional substitution made at that level. This makes in principle possible to use *classical teleportation*, where we are cut in some place and pasted in another place, so to speak, and this makes possible to define a sufficiently precise, for the reasoning, notion of first person and third person discourses: mainly the content of a diary brought by the teleportation user, cut and pasted itself, for the first person discourse, and the content of a diary brought by an external observer, and thus *not* cut nor pasted, for the third person discourse. Then a sequence of thought experiments can show that the first person discourses are invariant for the addition of delays of reconstitution.

A key point with mechanism, is that we are duplicable, or "preparable" in many exemplars. This leads to a notion of self-indeterminacy: if you are cut in London, and then pasted, simultaneously or not, in two different places, you cannot, before the experiment is done, predict with certainty where you will feel to be after the experience, and thus about what you will note in the personal diary, and this independently of the reconstitution time, and even independently on the nature of the reconstitution: real or virtual (where the appearance of the environment are locally emulated by a computer).

Now, it is a consequence of Church thesis that there is a universal machine, or a universal number. Fix any universal system, like the formalism of Turing machines. We can enumerate the code of such machines, restricting ourselves with those which accept only one input. Let us write $\phi_1, \phi_2, \phi_3, ...$ for the corresponding enumeration of all computable functions. Such a class of functions is, astonishingly enough, close for the diagonalization procedure, making the incompleteness phenomenon a simple consequence of Church thesis. It makes also rather easy to define what is a universal number. A number u is universal if $\phi_u(x, y) = \phi_x(y)$, with (x, y) being some fixed computable bijection between N^2 and N (the set of natural numbers). u is really a *computer*, and x is usually called a program, and y the data. Now, a universal dovetailer is a program generating all numbers/programs and generating all computations on all arguments, by dovetailing on the initial segments of the generated computations. A pseudo-code for it is given by

```
FOR ALL $i, j, k$ non negative integers:
    - compute the first $k$th steps of $\phi_i(j)$
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Suppose now that there is a universal dovetailer running in our physical universe. By the first person indeterminacy, any prediction on our first person experiences, like seeing where we can see the needle of some measuring apparatus, has to be given by a measure on the uncertainty bearing on the (provably infinite) set of all computations going through the first person-equivalent computational states accessed by the universal dovetailer. At this stage, assuming the universe to be sufficiently large will already entail that physics is reduced to a relative uncertainty calculus bearing on the set of all computations. This can already been used to explain many weird features of the quantum observations, like indeterminacy, non locality and the impossibility of cloning exactly any piece of matter.

A more subtle argument, the movie graph argument, is still needed to remove the assumption that the universe (primitively) exists and is very large. Indeed, not only a machine cannot distinguish a 'real" environment from a virtual one, but a machine cannot either distinguish a real environment from a purely arithmetical one (elementary arithmetic *is* Turing universal). This shows that digital mechanism, also called computationalism, makes physics a branch of number theory, in the general sense of Y. Manin, which includes intensional number theory (alias computer science). At this stage, we know that physics is, conceptually, a branch of number theory, but we are confronted with a tremendously complex problem: to find a relative measure on computations. I mention briefly in the sequel how mathematical logic can help.

3 The Arithmetical Universal Dovetailer Argument

The basic conceptual problem in biology that Descartes did not succeed to solve in his mechanist doctrine was the simple *machine* reproduction problem. This has been solved by von Neumann, and later by Stephen C. Kleene in a very deep conceptual way. Such a solution has been extended to the self-generation problem by myself, following an idea of John Case. The basic insight relies on a simple diagonalization, which can be illustrated in the following manner:

- If Dx gives xx, then DD gives DD (self-reproduction)
- If Dx gives T(xx) ===> DD gives T(DD) (self-transformation)

The basic idea of the mathematical approach is that, instead of implicating the reader in a thought experiment which involves him/herself, we can "interview" directly a universal machine about what is necessary for it, or what is possible for it, where the self-references are handled by the machine itself, by using the diagonalization above, or intensional variants of it. Then it can be shown that any universal machine whose beliefs encompass the induction axioms can know its own universality, and can prove its own incompleteness. In particular, such machine is able to infer the gap between truth and its own provability abilities. We can define for each machine a notion of *theology* by the set of true sentences pertaining on the machine, and we can define a notion of *science*, by the set of provable propositions *by* the machine. The proper theology is given by the gap between proof and truth, and it appears to be remarkably structured. Matter becomes a sort of border or derivative of the ideally correct machine's mind, itself defined by what the machine can discover by introspecting itself.

The whole reasoning sketched above can be translated into the the language of such a machine, and the "probability one" for observation can be extracted from self-reference. This gives rise to a couple of arithmetical quantum logics, one publicly sharable, the quanta, and one bearing on accessible truth, yet non publicly sharable, the qualia. The mathematical details are beyond the scope of this little article, and I refer the interested readers to my papers and texts, and the references therein, available on my web page (Google on my name). The shorter and easier to read paper is the sane04 paper. In the conclusion, I illustrate the relevance of all this to assess and criticize some of Josephson ideas.

4 Conclusion

The 'theory of everything' is just elementary arithmetic, that is logic with the two recursive laws of addition and multiplication. We don't need to make neither the notion of consciousness, nor the notion of matter, primitive. The observers can be defined by relative universal numbers, and we can explain how the coupling consciousness/material-realities emerges from addition and multiplication. Consciousness itself can be defined by the first person state of a machine believing in some reality. To be sure, instead of using numbers as primitive elements we can use any first order specification of any universal system (numbers, combinators, java programs, etc.). We could even use a first order specification of a quantum computer, but this would be treachery with respect to the derivation of the physical laws from digital mechanism, and this would prevent a clear technical separation of the quanta and the qualia. The general scheme can be summed by the following arrows:

NUMBER ==> BIOLOGY/THEOLOGY ==> PHYSICS (quanta and qualia)

This assesses Josephson idea that mind and life are at least as fundamental as matter. Indeed mind and life of (relative) numbers (or combinators, etc.), although not primitive, appear to be more fundamental than matter and physics, which result from consciousness projection and selection.

Meaning does not need to be primitive. Tarski's theory of truth is enough. The nuance comes from the fact that the ideally correct machine ignores the 'divine' equivalence between proof, knowledge, observation and feeling. Theology is somehow given by "Tarski minus Gödel", that is: truth minus proof. Both the Universal Dovetailer Argument, and its Gödel-like arithmetization, illustrate that meaning emerges from the machine's ability to reflect its own ignorance, and even to study the intricate geometry of that ignorance. This should make clear that, despite its bad reputation, mechanism is only a reductionism for those who have a pre-gödelian reductionist conception of numbers and machines. In fact, the (universal) machines appear to be able to defeat any complete reductionist or normative theory about themselves. Arithmetical truth appears to be full of life and dreams, and matter appears to be a sort of border of a universal mind (the mind of the 'sufficiently' rich universal machine, which I call Löbian number, in honor to the logician Löb, who discovered a genuine deep generalization of Gödel's theorem).

Mechanism assesses also Josephson's conception of the origin of space and time, which is generated by the relational observations. With mechanism, it is the whole physicalness which is generated by the set of all computations, as seen by the machines/numbers themselves. Matter originates from the coherence properties of "numbers dreams". Note that this entails that the physical universe is NOT Turing emulable: if WE are machines, the Physical Universe is not necessarily Turing emulable. Physicality relies too much on the non computable part of the arithmetical truth, to be completely emulable by a computer. In fact, life and mind self-organize themselves on the frontier between the computable and the non computable, which against prevents easily such phenomena from reductionist theories.

Indeterminacy, non locality and non cloning are easily derived with the mechanist assumption; first in a qualitative way with the thought experiences, and then quantitatively with their Gödel-Löb like arithmetization. Of course, this leads to many open questions in logic and number theory. In fact mechanism does not solve per se the mind-body problem, but it reduces the mind-body problem to a pure *appearance of body* problem in arithmetic, and computer science shows it to be a non trivial problem, even if the logics of self-reference, and their intensional variants paves the way toward a partial non trivial solution. The price of Mechanism might appear very high: the abandon of weak materialism (the doctrine asserting the existence of some primitive physical reality) and of the naturalistic metaphysics, so entrenched in our aristotelian era.

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The Action of Signs:

All the Way Down

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Abstract. This is a review of the article by Brian Josephson (2012) entitled "Biological Observer- Participation and Wheeler's Law without Law".

Keywords: Description, Measurement, Observation, Sign, Tense.

It has long been held in physics that the state description of whatever object of interest could be made possible as a matter of principle as demonstrated in the unitary development of the wavefunction in quantum mechanics. However, this does not imply that the most tangible means to make a descriptive access to the material objects appearing in the empirical world must be their state specification. Josephson has made a challenge to the present orthodox view and appraised the role of signs instead as following the mold of Peircean semiotics. A main objective of the present review is to vindicate Josephson's thesis from a slightly different perspective.

When one tries to see both biology and physics in a non-partisan manner, the process of measurement stands out as a common denominator. Biology is full of measurement internally in the sense that sentient beings are ubiquitous there. Likewise, physics is also at home with the physicist maneuvering the measurement apparatus at least externally. Furthermore, if one further accepts the observer-participatory view originally proposed by Wheeler, internal measurement would also turn out ubiquitous even in the physical world.

What is unique to measurement is its inherent causality. Measurement addressing the interactions acting between the measuring agency or apparatus and the object to be measured is causal in that there is no material means for foretelling what will be measured in advance. Curiously enough, however, physics has been very peculiar in insisting that the interactions the physicists can descriptively make an access to as appealing to the laws of motion are non-causal as demonstrated in both classical and quantum mechanics. Both the action-at-a-distance in classical mechanics and quantum nonlocality imputed to entanglement of various sorts are the demonstrative examples, in which each of the nonlocalities is taken to assume simultaneous correlations in space to some extent. Then, physics would have to meet the formidable task of how both causal and non-causal interactions could come to terms with each other. In contrast, biology sets itself free from such a clumsy complication because of its methodological openness to including causal interactions also into the descriptive domain from the start.

One advantage of Peircean semiotics is to provide a descriptive means for addressing the issue of causal interactions appearing in biology. What is of special interest in this regard is the presence of something called a sign, which is something about something else. The subtlety lurking behind here is the implicit presence of some agency maneuvering the aboutness, which is nothing other than the act of interpretation. Thus, the participation of a Peircean interpretant would become inevitable at this point.

The role of signs in physics, however, has not weighed and has been marginalized so far due to its methodological preference of the direct dichotomy of an object and its representation without being bothered by the interference of the interpretants. Only the physicist has been allowed to interpret the relationship between the two. Nonetheless, there is one important exception. That is thermodynamics. For instance, consider the Boyle-Charles law of the ideal gas in the form of PV=RT, where P for the pressure, V for the volume, T for the temperature and R for the gas constant. Thermodynamic variables P, V and T as the state functions remain under-complete within the theoretical framework of thermodynamics. This is not the drawback of the theoretical scheme. Rather, the positive aspect of the under-completeness is now found in leaving room for each variable to become a sign acting upon the remaining two variables internally (Matsuno, 2011).

The present appraisal of thermodynamic variables as natural signs rests upon the likelihood of naturalization of thermodynamic variables themselves. Each thermodynamic variable is a sign to be measured and identified as such by the other two internally, as much as detected as such by the physicist sitting outside externally. Furthermore, the action of each sign is anchored at and further qualified by the natural movement approaching toward a thermodynamic equilibrium or dissipation in short.

Once it is accepted that signs can legitimately survive in the physical world, Josephson's interpretation cascade of attaching an existing sign to a new object will get a new physical currency. The new object can serve as a new sign to something else ad infinitum all the way down.

What is specific to the interpretation cascade is its causality. In fact, any sign is characterized by its own semiotic causality operative in the formation of new associations (Hoffmeyer, 2008). The present causal integration markedly differs from the syntactic integration which has been taken for granted in any successful theoretical synthesis attempted in third person descriptions in the present tense. Compared to the syntactic integration common to successful theoretical syntheses so far, the causal interaction remains constantly open-ended as dismissing the case of its likely completion. The descriptive means for making an access to the causal integration must be in first person descriptions in the present progressive tense.

One instance of the open-endedness of causal integration constantly appreciating the capacity of new associations is seen in the Yardley's circular theory referred to in Josephson's. In short, once a united body decomposes into a pair in a way that can be traceable, such an entity can act as a participatory observer with a basic memory structure referred to as a sign. A concrete material example of the circular scheme is seen in repeated formation of meta-stable chemical products in the reaction environment not in thermal equilibrium like in the vicinity of hot vents on the ocean floor on

Earth (Imai et al., 1999). When some products synthesized near the hot vents are thrown away into the cold surrounding seawater, some of them could return to near the hot vents again as meta-stable products even though their partial decompositions would be inevitable. This survival of meta-stable products just points to the occurrence of the likely memory structure and causative integration as letting the synthesis of meta-stable products to be in the form of interpretation cascade.

In short, biology is from meta-stable units, while physics is from stable units by its time-honored tradition. Since stable units must be the abstraction from meta-stable units in the empirical world, physics should be an abstraction from biology. Furthermore, once we take meta-stable units to be more fundamental than stable ones, another fundamental notion called time must be revised accordingly.

The empirical issue of time is required to address the two contradictory characteristics in a congruent manner at the same time. One is the invariable identity referring to time always remaining as time, and the other is the variable flow referring to time constantly passing away. In physics, the invariable identity remains atemporal as associating itself to the identity of each material unit such as an atom and molecule. The variable flow is then associated with the displacement of the material unit assuming its atemporal identity. The agency relating the invariable identity to the variable flow is the enigmatic notion called force. In biology, however, the situation is totally different. The identity for supporting the flow of time is temporal, rather than being atemporal. Biology is grounded upon the material activity of actualizing the temporal identity out of meta-stable units as processing the constant exchange of the constituent subunits for its own sake. The constant exchange of the subunits is now associated with the flow of time. More specifically, the flow of time for us human being is no more than a representation of the constant exchange of material, though the latter of which is definitely not anthropocentric. How to make a descriptive access to the temporal identity serving as the agency for precipitating the flow of time as a representation will be a new challenge for us. Josephson has set some preparatory course in this direction.

In a nutshell, the role of time in empirical sciences is necessarily ambivalent. Time in biology is from the identities custom-made in progress, while time in physics is from the identities ready-made already in completion. What should be emphasized at this point is that there are a lot of opportunities for the custom-made enterprises in the bottom of the mundane empirical arena on the planet Earth.

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Time in Biology as a Marker of the Class Identity of Molecules

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Abstract. Developmental process in biology is manifestation of time as a marker of preserving the class identity of the participating molecules. A concrete case in point is the binding sites for transcription factors in the genome. Although each bond between the transcription factor and the DNA molecule to be transcribed is relatively weak and can easily be detached by thermal agitations available in the ambient, the transcription from the DNA to a messenger RNA molecule could smoothly proceed if the concentration of the transcription factors is not too low. The transcription could proceed without interruptions if the binding site is soon replenished by another transcription factor molecule of a similar kind available in the neighborhood. What remains significant to the transcription is the class identity of the transcription factors in the sense that it could proceed without interruptions even if the transcription-factor molecules are frequently exchanged. Characteristic to the transcription process is the occurrence of time as a marker of preserving the class identity of the transcription-factor molecules toward the DNA molecule to be transcribed. Time as a marker of preserving the class identity of molecules is ubiquitous in biology.

Keywords: Circadian clocks, Class identity, Cyanobacteria, Repressor, Transcription factor, Tense, Time.

1 Introduction

Just for the purpose of a comparison, consider a biological organism such as a human egg cell containing about 30,000 genes encoding protein molecules, in which roughly 3,000 genes encode specific proteins called transcription factors. What is unique to transcription factors is that they determine when genes will be turned on for their expressions and turned off while orchestrating an extremely exquisite network of regulating the transcription sequences. At issue is how it could be possible for one transcription-factor molecule to every ten genes on average to adequately regulate the expression of each one of the ten genes in the succeeding developmental process.

One clue for addressing this puzzle resides within the observation that typical genomes in the cells contain extensive non-coding, regulatory regions and that these regions can act as enhancers, silencers, insulators, and promoters of the genes (Levine and Tjian 2003; Hochedliner and Plath 2009). If the expression of each gene is regulated by a combination of many different transcription factors, the accompanied combinatorial control may be competent enough to face the task of forming a consensus among the participating transcription factors in regard to whether or not the gene in the target will be expressed and when. At this point enters the issue of time.

Switching on and off of each specific developmental process depends upon the expression levels of a target gene to be formed in response to the relevant transcription factor concentrations in the cells. Then, a subtlety of the process would come up to the surface if one asks the question of what could be responsible for both varying and keeping the expression levels. If one adopts the scheme of taking the dynamic development of the expression levels of the output protein molecules as responding to the input transcription factor concentrations to be a consequence of the dynamics of other variables such as fluctuations in the concentrations in time, the driving factor would turn out to be time itself. This scheme is quite common in the standard practice of physical sciences in that time read into by the physicist flows on its own there, while the flow of time thus conceived is unwittingly taken to be of a transcendental origin carrying a heavily metaphysical flavor.

On the other hand, if the dynamic development of the expression levels responding to the transcription factor concentrations is internal in the sense that the genesis of the flow of time is also internalized in the dynamics, the consequential flow of time must be of a material origin. Developmental process in biology thus comes to face a tough question of whether time met there is of an imposed character from the outside as practiced in physics or of an endogenous character from within. The issue would have to be settled empirically or experimentally if ever possible.

2 The Flow of Time of an Endogenous Origin

One clue for examining the nature of the flow of time involved in developmental process can be made explicit as referring to the input-output relationship between transcription factor concentrations and the rate of protein production from downstream genes. Although noises latent in the active transcription factor molecules in the input are random and rapid due to the stochastic nature of each biochemical reaction involved (Bialek and Setayeshgar 2005; Tkacik et al. 2008), this does not imply that the similar randomness and rapidity would also apply to the rate of protein production of the output in the downstream. This must be an issue to be settled experimentally.

One relevant experimental model for the present objective is to construct the bacteriophage lambda promoter in *Escherichia coli* and to see how the output expression of a target gene could be modulated by the activity of an input transcription factor of lambda repressor (Rosenfelt et al. 2005; Pedraza and van Oudenaarden 2005). The experiment reveals that the fluctuations of the output level of the protein molecules are much slower than those of the input level of the transcription factor molecules. This observation suggests to us that there must be some robust scheme of generating such slower fluctuations as a time phenomenon, in which the underlying robust organization can serve as an invariable standard to which time passing away constantly in the form of fluctuations is referable. Although the equation of motion equating configuration to displacement with the aid of the enigmatic notion called force further supplemented by the equation of time equating displacement to the flow of time, with which the physicist can be quite at home, is a pervasive theoretical model on an invariable standard to which time passing away is constantly referable, this is not the only available physical scheme for the invariable standard. What must be looked for is the concrete material or physical scheme of realizing an invariable framework letting time flow.

As a matter of fact, there is a scheme of materializing the flow of time on the ground that time remains as time while passing away constantly at the same time. The binding interaction between the transcription factors and the DNA molecule to be transcribed is rather weak due to the underlying van der Waals forces implementing the binding energy of order of 1kJ/mol or less. The binding can easily be detached as being subject to thermal fluctuations available in the normal ambient. However, if there are a sufficient amount of transcription factor molecules such as lambda repressor molecules in the neighborhood (Liu et al. 2007), the detached binding site can easily be replenished by another transcription factor molecule of a similar kind to be found nearby. The consequence is to hold the identity of the binding site, that is to say, the functional unity of the site functioning as a repressor to the lambda promoter in *Escherichia coli* effectively in an uninterrupted manner, even though the individual transcription factor molecules are constantly and frequently exchanged.

The identity of the binding site is about the class property of the participating transcription factor molecules. Slow fluctuations associated with the expressed protein molecules in the output produced through the transcription-translation of the lambda system in *Escherichia coli* are thus seen as an instance of demonstrating the occurrence of the flow of time inherent to the preservation of the class identity of the binding between the transcription factor molecules and the DNA molecules to be transcribed. The functional unity of the binding site may help suppress the rapid fluctuations associated with the input transcription factor molecules to be exchanged constantly and frequently. Despite that, the flow of time of a material origin is not limited to the transcription-translation scheme. The flow of time of a material origin will be considered even without being accompanied by the transcription-translation scheme. That will be the bacterial circadian clocks.

3 Bacterial Circadian Clocks

One more example being suggestive to grounding the identity of the flow of time on a material basis might be circadian clocks of biological origin. Circadian clocks as the biochemical oscillators coordinating and regulating the metabolic and behavioral activities within the 24-hour diurnal cycle are everywhere in biological organisms as ranging from the most primitive photosynthetic bacteria called cyanobacteria and fungi, up to plants, insects and animals.

The robustness of these clocks in multicellular organisms might be ascribed to intercellular interactions. However, even unicellular organisms can also maintain very stable rhythms. A remarkable example of the unicellular class is the clock of the cyanobactrium *Synechococcus elongatus* that has the correlation time of the clock movement even of order of several months (Mihalcescu et al. 2004). This clock remains quite robust even though the similar clocks of the different cells in the neighborhood hardly interact with one another, as being different from the case of multicellular organisms. Despite that protein synthesis required to sustain the clock is highly stochastic, the clock itself remains highly stable in a manner of being immune to the intrinsic stochasticity of the underlying biochemical reactions.

The core components of the clock of the cyanobacterium *S. elongatus* are the three proteins KaiA, KaiB and KaiC. Although circadian rhythms had long been thought to be due primarily to RNA-mediated transcription-translation negative feedback, Tomita et al. (2005) demonstrated that KaiC phosphorylation maintains a 24-hour rhythm in vivo even if the transcription-translation scheme is inhibited with the result of no KaiC synthesis. In addition, Nakajima et al. (2005) further demonstrated that this rhythmic phosphorylation as an indication of circadian rhythm can be reconstituted in vitro only in the presence of KaiA, KaiB, KaiC and ATP as a source of phosphate. Here, KaiC exhibits spontaneous autokinase and autophosphorylase activity. KaiA promotes KaiC phosphorylation and inhibits KaiC dephosphorylation through the protein-protein interaction. KaiB inhibits KaiA effect on KaiC. In fact, KaiA and KaiB are recruited to a C-terminal region of KaiC in a phosphorylation-dependent manner (Akiyama et al. 2008). These three Kai proteins in the presence of ATP are necessary and sufficient to sustain a robust oscillation of the phosphorylation level of KaiC.

In particular, a KaiC protein is a homohexamer of the monomeric KaiC subunits. In the phosphorylation phase, KaiA promotes KaiC phosphorylation as being associated with KaiC actively and repeatedly. When the levels of phosphorylation of KaiC reach sufficiently high, the KaiC hexamer comes to associate with KaiB and to inactivate KaiA so as to start the dephosphorylation phase. And the phosphorylation phase will start up again once the level of phosphorylation becomes sufficiently low. At this stage, if both phosphorylation and dephosphorylation proceed on the same KaiC hexamer, it would be extremely unlikely to expect the actual occurrence of the rhythmic cycles in a population of the hexamers because of the intrinsically stochastic nature of biochemical events characterizing each hexamer (Emberly and Wingreen 2006). One promising candidate for implementing the robust rhythmic coordination of phosphorylation and dephosphorylation in the population of the hexamers could be the shuffling of the monomeric KaiC subunits among the hexamers (Kageyama et al. 2006), presumably by means of a combination of the allosteric transition of a KaiC hexamer and the monomer shuffling between the hexamers (Eguchi et al. 2008; Nagai et al. 2010).

What has been made explicit here is that the KaiC hexamer maintains its class identity as the hexamer while its monomeric subunits constantly come and go as being exchanged during the rhythmic cycle of phosphorylation and dephosphorylation. The identity supporting the flow of time is not upon the identity of the individual material bodies as with the case of the astronomical equation of time in celestial mechanics, but is upon the class identity of the hexamer to be maintained by the supporting monomeric subunits while the constituent subunits are constantly exchanged. Time remains as time once the class identity of the KaiC hexamer as the dative of time is attended, while it constantly passes away if the individual monomeric KaiC subunits of the hexamer are focused upon. What is unique to the KaiC hexamer is the fact that it remains identical as a class while being variable in processing its individual components.

The experimental bottom line of the disguise of the KaiC hexamer is such that a predecessor hexamer K-K-K-K-K-K is alternated by the successor K*-K-K-K-K-K, and then by K*-K*-K-K-K-K··· and so on, in which K is a monomeric KaiC subunit unphosphorylated and K* is the similar subunit phosphorylated in the presence of ATP as the phosphate source. When the hexamer reaches K*-K*-K*-K*-K*-K*, it starts dephosphorylation back to K-K-K-K-K-K. What is peculiar here is that although the KaiC hexamer does not undergo the monomer shuffling during the phase of dephosphorylation (from K*-K*-K*-K*-K*-K* to K-K-K-K-K-K), the phosphorylation phase (from K-K-K-K-K-K to K*-K*-K*-K*-K*-K*) does require the monomer shuffling in the sense that the hexamer recruits the monomers to be phosphorylated from the outside and lets the unphosphorylated ones go out. This has been the experimentally observed fact.

Of course, we can ask what kind of forces would be lurking behind. At issue here is that if we raise such question, we must have some reliable reference upon which the question thus framed may remain legitimate. Then, the tougher question would be what can serve as that reliable reference. One suggestion in this regard might be available from our acceptance of Galilei's inertia in answering the question of whether the inertia is a plain empirical fact under a certain circumstance or a rational consequence from something else. We may then be asked to respond to a harder question of whether the exchange of materials could be irreducibly fundamental in a manner being incommensurable with Galilei's inertia because of the decisive differences in the circumstantial conditions. What has been suggested here is the likelihood of the exchange of materials as another irreducible fundamental property of matter exclusively in an empirical sense.

Admittedly, the KaiC hexamer as the dative of time does not prevent the physicist as another dative of time from modeling the circadian rhythm with use of the presupposed flow of time whose theoretical identity the physicist reads into the configuration of the underlying molecular constellation. In this form of state dynamics, it is the physicist who relates the identity of the flow of time to the identity of the state attributes. State dynamics is peculiar in seeking the identity of the flow of time in the physicist sitting outside who confirms the identity of the state attributes through their measurements. However, the parameter called time as introduced by the physicist within the adopted theoretical scheme of state dynamics is not nomological in the sense that the KaiC hexamer as the dative of time can survive as a fact, instead of merely as a theoretical explanation, in the circadian oscillation. The identity of the flow of time can be maintained in reference to the class identity of the KaiC hexamer even in the absence of the physicist. The KaiC hexamer turns out to be the dative of time of itself by exchanging the constituent monomeric KaiC subunits, while modeling the circadian rhythm with use of the flow of time lets the physicist be the dative of time.

That the class identity of the KaiC hexamer remains stable and robust points to more than what the underlying individual biochemical reactions would imply. It would certainly be inconceivable to expect such robustness exclusively from those individual reactions alone that are highly stochastic. As a matter of fact, the KaiC hexamer is maintained in the flows of the monomeric KaiC subunits between coming into and going out of the hexamer. What must be observed here is the flow continuity of the monomeric subunits. The actual chemical affinities underlying the maintenance of the class identity of the KaiC hexamer must internally be regulated and differentiated (Zwicker et al. 2010) so as to meet the flow continuity of the monomeric subunits. That is the condition of material flow equilibration (Matsuno 1984, 1989), which can function as a dynamic factor for holding the KaiC hexamer robust enough as processing the through-flow of the monomeric KaiC subunits.

Once material flow equilibration is focused upon, it would be straightforward to recognize that the flow disequilibrium between the incoming and the outgoing flow of the monomeric subunits registered in the present perfect tense internally would have to be equilibrated in the subsequent present progressive tense. Otherwise, the condition of flow continuity would be jeopardized in the finished record. Nonetheless, the relationship between the present perfect and the present progressive tense is only sequential and not coincidental. If these two tenses happen to occur in a simultaneous manner, the distinction between the two tenses would have to disappear in contradistinction to the historical fact that each of the two tenses has survived and remained legitimate in its own light. Constant spillover for updating the perfect tense in the progressive tense, which can be assimilated to the prime mover of the flow of time in retrospect, would become inevitable for the sake of material flow equilibration because of the absence of a means for global synchronization all at once. Then, frequent update of the perfect tense in the progressive tense turns out to be a *sine qua non* for the survival of the class identity of the KaiC hexamer while processing the through-flow of the monomeric KaiC subunits. The flow of time imputed to the survival of the class identity of the KaiC hexamer yields time remaining as time, while the constant exchange of the monomeric KaiC subunits of the hexamer can be associated with time passing away constantly.

What is unique to the update of the perfect tense in the progressive tense on the part of the KaiC hexamer is that the agent relating the update to the identity of the flow of time is the KaiC hexamer itself, being different from the physicist relating the identity of the state attributes in general or of the stellar configuration in the sky in particular to the flow of time. The identity of the flow of time associated with material flow equilibration is certainly of material origin or, more specifically, of biological origin as far as the circadian rhythms due to Kai proteins are concerned. This observation naturally comes to raise the question of whether the likelihood of the flow of time ascribed to the update of the present perfect tense in the present progressive tense could have been the case protobiologically or even prebiologically (Matsuno 2011a, b).

4 Updating the Perfect in the Progressive Tense

The biological appraisal of the flow of time upon the preservation of the class identity of a molecular organization at the cost of the constant vicissitudes of the constituent molecular subunits certainly makes a sharp contrast to the flow of time entertained in the standard practice of doing physics. In physics, the flow of time is equated to displacement as typified in the Ptolemy-Newton scheme of the astronomical equation of time while keeping the individual identities of the celestial bodies intact. The stellar displacement is taken to be intimately related to the flow of time in an irreducible manner. Furthermore, displacement also appears in the equation of motion as equating the configuration of the moving bodies to their displacements with the aid of the additional attribute called force.

Although the present scheme of the equation of motion supplemented by the equation of time has been quite successful and influential as going far beyond the original framework of celestial mechanics, its foundation still remains to be settled. That is about whether or not force could be taken to be independent of the flow of time. If force is considered to be an instantaneous property of the configuration of material bodies as originally conceived in celestial mechanics in the form of action at a distance, the integration of both force and the flow of time into the edifice of the equation of motion supplemented by the equation of time would give rise to no internal conflicts. However, there is no prior guarantee for the independence of force from the flow of time. If force is not independent of the flow of time, the scheme of the equation of motion supplemented by the equation of time would necessarily collapse since the flow of time can be related not only to displacement but also to the intervention of what is called force. So far, physics has been all powerful in figuring out the methodology for subsuming the notion called force under the instantaneous property of the configuration of matter under the flag of standard model or renormalization. Nonetheless, it has no prerogative of exercising its influence beyond the territory it has already colonized. At this point enters a uniqueness of biology.

Reporting on the experiments on the expression levels of a target gene in response to the relevant transcription factor concentrations or on the cyanobacterial circadian clocks does not require the notion called force. What is required instead is the distinction between the present perfect and the present progressive tense at least in the sense that the results of the experiment are descriptively approachable in the record registered in the present perfect tense. At the same time, the dynamic movement in the making that can escape from being registered in the present perfect tense constantly survives in the present progressive tense. The basic attribute of the dynamics in reference to the occurrence of the record is thus found in the update of the present perfect in the present progressive tense (Matsuno 2011c).

What is unique to the update of the perfect in the progressive tense is the cohesion acting between the two tenses. The cohesion acting between the perfect and the progressive tense is such that each tense pulls in the other for the start-up of the latter, but both cannot coexist since the tenses of a verb are mutually exclusive in their implications due to the incompatible contrast between having been completed and being continuous in progress. As differing from the case of the force conceived as an instantaneous property of material bodies in physics, the cohesive force arising from updating the present perfect in the present progressive tense is a derivative from the flow of time. This makes biology unique compared to physics.

5 Conclusion

Material dynamics leading to biology and further beyond is specific in appreciating the class identity of molecules participating in the maintenance of the organization, whatever it may be, over the individual identity of each molecule to be exchanged constantly with the others of a similar kind available in the neighborhood. The present appraisal of the class identity over the individual identity makes the flow of time to be the property of the class identity itself, in sharp contrast to the flow of time entertained in physics as the property inherent to preserving the individual identities of the available atoms and molecules. Time can gain a new implication as a category as approaching to and traversing the demarcation line separating between non-life and life.

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The Uncanny Position of ‘Now’ in Science

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Abstract. I attempt to point to various discursive projects that are relative to the problem of understanding change, which most current scientific perspectives cannot deal with, and never faced because the social role of the natural sciences has been to support technology development.

Keywords: change, development, hierarchies, history, internalism, mechanicism, present tense, semiotics, thermodynamics, vagueness.

The main problem that has emerged in my thinking is how to understand -- that is to say, represent -- *change*

Mechanicism does not handle it, because in that system of thought, there is no *present moment*, only past records and future calculable anticipations based on a generalized past, mediated by a model [1]. The variables in this mode of inquiry exist in a universal present tense, which is actually timeless; past and future coexist here in one theoretical manifold. The activities of change actually occur instead during a *present progressive* moment launched from a conjoined accumulating and assimilating *present perfect* dynamical record [2]. This grammatical locution is exactly appropriate insofar as our understanding of the world is organized, recorded and shared in linguistic media. Nature, our model of the world, is a linguistic / mathematical construct [3].

From a *systems* point of view, a moment can be represented mechanistically using a *compositional hierarchy*, showing a nesting of moments of different scales [4], but no change can be modeled here [5]. If, in this hierarchy we follow a sequence of moments at one level, we will find that an encompassing moment of larger scale will not have changed during this period. Nor would a statistical mean of moments taking place at some lower scale have changed.

It is shorter and shorter moments ‘all the way down’! Systems exist in the realm of physics, dealing with ahistorical attributes of the world and with models of dynamical systems that can be used to framework measurements of rates of change at a preferred scale. These models can be used to make predictions insofar as the initial and boundary conditions bearing on them remain constant during a calculation. None of this is problematic for the technologies this system of thought has been developed to serve.

An interesting example of the uncanniness of the present moment in science is found in Fisher's fundamental theorem of natural selection [6], which shows that evolution by natural selection depends upon the relative variance in fitness of traits in a population. Evolution results in a decrease in this variance as the less fit are weeded out of the population, having been exchanged for increased population fitness. Looking backward during the standard universal present we can assess which traits had been favored by selection by seeing that they are relatively less variable than others, but looking forward we can see that these same traits could no longer evolve as fast as other traits [7]. It seems that having evolved would be rather bad for the possibility of further evolution! Thus, would it be better to have evolved successfully or to be capable of further evolution? In the universal present of Fisher's theorem we cannot actually assess the values of traits for the population now.

Change originates history. The moment of change might be assigned to fluctuations, but in mechanicism these are coarse grained using statistics. Intuitions and 'swerves' occur as fluctuations. Machines actually depend upon these occurring in their human operators in order to be useful. In theoretical formulations we are present both at the inception of change and at its end, but cannot in fact locate the moment of change.

The manifest world contains many changing entities, often showing *emergent patterns*. Many of these entities -- dissipative structures -- can be understood as undergoing orderly developments [8]. A *subsumptive hierarchy* [9] can model an entity or locale as embodying several integrative levels, showing the subsumption of any level by more generally present ones, and simultaneously its integration by higher levels. For example, during any moment we can have the hierarchy: {physical tendencies {chemical attractions {biological processes {individual actions}}}}, all occurring at the same time. An entity at any level would during a present progressive moment be at the top of such a hierarchy, with a next higher level still unfolding. Therefore, this entity would not yet be fully integrated into a future.

Development is progressive change, constitutive of particular systems [5]. Its trajectory runs from vaguer to more definitive embodiments, ending in *senescence* (-- in my view as a result of information overload). The subsumptive hierarchy can be used to describe the developmental stages of, for example, cosmogony. Thus: {physical realm -> {chemical realm -> {biological realm -> {sociopolitical realm}}}}. A new subclass gets added during this developmental sequence when phenomena emerge that could not be described using the discourse in effect at the highest current level. The new level then regulates, harnesses and interprets the prior ones. We do not in general know how, or why, a new level emerges. It is clear that phenomena at the previous levels will have occurred in configurations similar to those entrained by the new level, but they were not given cohesion until the emergent event. So, pointing to an outstanding current problem, the origin of life has not got, and likely cannot have, a merely physico-chemical explanation. Immanent higher levels above the chemical will have been in place. It is worth noting here that an array of classes and subclasses is formally a tree. Since we are guided in or thinking by our models, it is clear that there could always in principle be many possible developmental sequences starting from a given germ. The developmental trajectory {ovum -> {embryo -> (fetus }}} shows us that when there are multiple constraints in place the tree form can be largely suppressed.

The *Second Law of thermodynamics* motivates development [5], aspects of which in this context can be modeled using energy flows and information measures [3]. The Second Law, however, cannot preordain energy flow pathways locally since the dissipation of local energy gradients changes details of a gradient landscape from moment to moment [10]. This fact, contextualized by the Maximum Entropy Production Principle (MEPP) [11] constrains energy flow pathways to those that would momentarily increase the attendant entropy production. Relatively stable local energy flow tendencies would have been the locus of the origin of life [12], and would later have been the frameworks upon which multicellular forms emerged displaying 'constructal' energy flow organization [13]. It has often been pointed out that living systems do not seem to be maximizing their entropy production. This is so because they impose numerous constraints on energy flows. This moves them from MEPP to MEDP -- a maximizing of the rate of energy gradient dispersion, and toward work rates reflecting the Maximum Power Principle [14]. From the thermodynamic point of view living things are always striving. The Second law is a universal finalism, aiming at the eventual dispersion of all matter, and enlisting dissipative structures, including the living, in this project inasmuch as there are energy gradients that cannot be dispersed by conduction and mass wasting alone. The Second Law is the ultimate final cause of change, but cannot legislate it, a fact which has fostered the ecological diversity of living things.

All of the above viewpoints are parts of our culture's characteristic *externalist program*, whose reason for being is its usefulness in guiding technology development. *Internalism* is a breakaway program attempting to deal directly with the present moment. For a well known externalist image of the internalist perspective recall Maturana and Varela's 'autopoiesis' [15], and for the earliest insights see von Uexküll's Theoretical Biology [16]. Astronomers, for example, construct an externalist discourse about their own internal situation in the universe, and so evade internalism. Considering why they do this tells us much about our cultural perspective. The internalist situation, as a stream of qualia, is a situation of constantly fielding impacts from an outside world, which is known only through our own semiotic constructs. Semiotics [17, 18] is an externalist attempt to deal with the internalist predicament through studying the construction and interpretation of signs. The internalist predicament is vague and does not differ between dissipative structures, biotic or abiotic. Our internal prehension of the Second Law, for example, is felt when we become aware of our various itchings and twitchings, never at rest, even in sleep. Matsuno's linguistic turn is an attempt to get at the internal situation by way of the tenses in language [e.g., 2]; the internalist experience is recorded in the present progressive <--> present perfect experience. The present progressive 'now' embodies the mode of generativity and discovery, which, being vague, is unrepresentable in science. While the world is to some degree vague, our scientific representations of it have been as fully explicit as possible.

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The Role of Information Integration in Demystification of Holistic Methodology

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Abstract. The division into holistic and reductionistic methods of thinking and inquiry was present in all epochs and in all domains of intellectual activity, with the former usually having an aura of mystery. The paper is providing a short exposition of the presence of, and need for the holistic methods. An approach to information integration is presented within a general framework of information understood as identification of variety. An outline of the formalism of information integration in terms of closure spaces developed in earlier papers of the author for the study of consciousness is presented here for the more general purpose. This formalism can serve as a foundation for more general methodology for holistic description of a wide class of systems, which can be associated with information. Since the level of information integration can vary from total disintegration to complete integration with many degrees in between, the formalism shows that such methodology can combine the two formerly antagonistic approaches into one.

Keywords: holism, reductionism, information, information integration.

1 Introduction

Intellectual traditions of different civilizations and different historical epochs always have been torn between two tendencies in the attempts to comprehend reality. One of them is focused on the diversity of our sensory experience and its main methodological directive is to seek fundamental elements or building blocks, and the rules of composition, which allow construction of hierarchically structured layers of reality. The other has as a point of departure an intuitive and fundamentally irreducible sense of unity encompassing the world together with the subject attempting its comprehension.

This paper has as its main objective to document the need for a holistic methodology in philosophy and science, in particular in the context of the study of life, and to propose the outline of such methodology based on the concept of information integration formulated in terms of a well established mathematical formalism of closure spaces and their lattices of closed subsets, but without entering into the technical details which can be found elsewhere (Schroeder 2009, 2011). The crucial role in this formalism is played by the concept of direct product irreducibility of algebraic structures.

2 Pervasiveness of Holistic Thought

The methodological duality of analytical and holistic approaches is much more universal and pervasive than is usually recognized. We can find it in as different contexts as for instance the distinction between exoteric religions referring to rational or accessible to common sense doctrines and esoteric, mystic religions or sects seeking intuitive, direct unity with God or the spiritual world. But also as Windelband's division of the scientific inquiry into *nomothetic* (having as its starting point the differences, but assuming the existence of similarities and proceeding by looking for comparable aspects in the variety) and *idiographic* (assuming the uniqueness of the object of the study which makes comparisons difficult or impossible and therefore focusing on the elements which constitute the uniqueness of the object of study), Pike's distinction between *etic* and *emic* approaches in anthropology or cross-cultural studies, or the distinction between molecular and molar properties of matter.

For centuries, or even millennia, in Europe there has been a continuing interest in the opposition between the Western analytical and reductionistic way of thinking and comprehension of reality, and the Eastern holistic approach. The East could be as close as Egypt in late Antiquity, when Hermetic philosophy has been contrasted with Hellenic rationalism, or as far as China in more recent times when Europeans learned about yin-yang philosophy, Taoism and Zen and started to fantasize about their teachings.

In Europe, mystical holism was frequently associated with the metaphor of the human body, while analytical methodology was associated with the mechanical clock, steam machine, and recently the computer. Thus, Christian mystics of the 12th Century, such as Bernard Sylvester of Tours or Hildegard of Bingen envisioned the universe (macrocosm) in analogy to human organism (microcosm). (Singer 1958) "Analytical" metaphors of the clock, machine or computer explaining the workings of the universe have been referring to an organization, but organization based on reduction of the functioning of the whole based on the autonomous work of the parts. A holistic vision of the world required a model in which integration into the unity goes much further, such as in a living organism.

The special status of living organisms has been expressed in a long standing division into animal, vegetable and mineral matter, which was replaced by the division into organic and inorganic compounds when chemistry was born. The successful synthesis of organic compounds in the 19th Century made this division rather arbitrary, but it did not end the conviction about the special integrating or uniting powers of living organisms.

If not a special substance, then a special "vital force" was used to explain life. The idea goes far back to the 2nd Century B.C. when Stoic philosopher Posidonius of Rhodos tried to incorporate into his view of the world elements of Platonic and Aristotelian thought. According to Posidonius, the whole world is united by internal connections of "sympathy" (*sumpatheia*), but living organisms have a special uniting and generating type of vital force which emanates from the sun and radiates to earth.

In the 19th Century, the concept of energy and its conservation emerged (anticipated in the form of “vis viva” by Leibniz and also as “motive force” by Descartes) and energetic processes in living organisms started to be used to explain the exceptional characteristics of life in terms of analytic, reductionistic methodology and with the assumption that organisms are closed, isolated systems.

Later, it became clear that the analysis of energetic processes require an additional concept of entropy. It was the concept of entropy and its role in the Second Law of Thermodynamics that built the bridge between physics and information. The next step merging these two disciplines with biology was made by Erwin Schrödinger (1945) in his short, but very influential book “What is Life?” Schrödinger anticipated present choice of most fundamental characteristics of living organism and pointed at their relationship to physics and less directly to the study of information.

Unfortunately, while the book directed attention to the most important aspects of life, it perpetuated some old habits of thinking. In order to explain the consistency of increasing organization (decrease of entropy) in genotypic (evolutionary) and phenotypic (developmental) processes with the Second Law of Thermodynamics and to eliminate the common error of explanations that life can evolve and develop simply using energy arriving from the sun, Schrödinger introduced the new concept of “negative entropy” in place of energy. Leon Brillouin (1956) renamed it “negentropy” and merged Schrödinger’s physical explanations and models explicitly with Shannon’s theory of information. Even today, the common belief in the modified Posidonian view is that we get from the sun, perhaps not vital force, but negentropy or information which is generating information processes in living organisms.

The idea that negentropy is a measure of information (and therefore of a positive magnitude) and at the same time is opposite to always positive entropy is mathematical nonsense. But it can be fixed, for instance by introducing an alternative measure of information (Schroeder 2004). A more important deficiency of this perspective on life and its relationship to the Second Law of Thermodynamics and to information is that the actual process cannot be considered in the local, reductionistic way.

Equally important as the arrival of visible light from the sun (electromagnetic radiation of relatively lower entropy) is the re-radiation from earth of infrared electromagnetic waves (with higher entropy). It is a fact that radiation with twenty two times higher entropy, carrying the same amount of energy, is out-going compared to that incoming that matters. What is being carried by arriving radiation is irrelevant without consideration of what is sent back. Now, the overall process cannot be explained in a strictly local, reductionistic way, because the difference between in-coming and out-going radiation depends on the entire eco-system. If the surface of earth was devoid of life and consisted only of dry desert, the difference between in-coming and out-going radiation would be minimal, and therefore the same radiation in-coming today could not sustain any higher form of life (Schroeder 2007a).

To avoid confusion, it should be emphasized that there is nothing wrong or false in the local description of all metabolic cycles, genetic transfer of information, etc. This only means, that the description of these local mechanisms at the level of organisms, organs, and cells cannot provide a full explanation of what life is, since the most important process setting in motion the dynamics of life processes cannot be reduced to a scale below the level of ecosystem.

Even stronger arguments for the need for some form of holistic methods are related to a different, more specific aspect of higher forms of life, to cognitive processes and consciousness.

There is one characteristic of conscious experience which from the early times of psychological research has been distinguished, its uniformity or wholeness. William James described it in short: “The perception is one state of mind or nothing.” (James 1896) Even earlier, the unity of cognitive processes was expressed in the concept of apperception introduced by Gotfried F. Leibniz, which in the 19th Century J. F. Herbart made a central subject of psychological study, and which emphasized the view that mental experience is not composed of separate bits, but forms a unity.

One more step back takes us to Descartes and his center of common sense (*sensus communis*) integrating contributions of senses into a coherent perception, which of course has been inherited from Aristotelian study of common sense and common sensibles. Actually, we can go back to the beginnings of European philosophical tradition to find views similar to that of James presented by Xenophanes “If the divine exists, it is a living thing; if it is a living thing, it sees – for he sees as a whole, he thinks as a whole, he hears as a whole.” (Barnes 2001)

In modern psychology, the question of the unity of consciousness diverged into many more specific fields of study such as a cross-modal sensory integration, inherited from the Gestalt psychology question of the priority of the perception of a whole over the parts, face recognition, and so on.

William James, in his search for the unity of consciousness, which he characterized using the metaphor of a stream, has made quite extensive diachronic and cross-cultural study of the tradition of the one-many philosophy, which he identified with the opposition of pluralism and monism: “The alternative here [of the one and the many, *mjs*] is known as that between pluralism and monism. It is the most pregnant of all dilemmas of philosophy.” (James 1911/1948)

It is a natural question to ask how this unity can be expressed in terms of information or information processing. The awareness of importance of the unity of consciousness has accompanied all modern developments in psychology, but only quite recently first hypotheses of the possible models of information unity or integration have been presented.

The research on the unity of consciousness conducted by neuro-psychologists has not produced much material for theoretical considerations regarding the mechanisms responsible for the process. Gerald Edelmann and Gulio Tononi (1998) with their collaborators have provided evidence of the correlations between the firings of neurons and analyzed them in terms of informational entropy. However, the temporal correlations, or identification of the regions of the brain cooperating in producing conscious experience, do not tell us much about the mechanisms which are responsible for the correlation. Also, the fact that the processes can be described in terms of entropy does not constitute evidence for any specific form of information processing. At best, we may be convinced *that* integration of information happens in the brain, but we do not have any clue *how* it happens.

Another approach, purely theoretical, was based on the assumption that the cognitive processes must involve some unique physical phenomenon clearly involving integration of the states of its components, quantum-mechanical superposition. In the early 1970's several attempts were made to use quantum phenomena in the explanation of consciousness (Pribram et al. 1974; Hameroff 1974; Frohlich 1975). The problem was that quantum mechanical description applies to physical systems of a size much smaller than that of any potential functional units of the brain. Quantum description of one neuron does not make much sense due to its relatively big size, so considering that the cognitive functions of the brain involved activation of hundreds, thousands or millions of neurons, the situation seemed hopeless.

Hope was revived by the studies of the so called Bose-Einstein condensates which may exhibit quantum characteristics in volumes exceeding size of all human brain, but in conditions very different from those in the human organism (Marshall 1989). The recognition of the special role of synapses, relatively small spaces at the point of contact between axon playing the role of the output of one neuron and dendrite or soma of the next neuron, in the functioning of the nerve system and in particular in cognitive processes temporarily rekindled hope for a quantum-mechanical description of consciousness (Beck & Eccles 1992, 2003; Eccles 1994).

The approach, based on an assumption of quantum-mechanical mechanisms in the brain, culminated in the Hameroff-Penrose (1996) model of information integration in the brain. However, years have passed and there is no convincing evidence that the relatively large regions of the brain responsible for cognitive functions could be considered quantum mechanical systems maintaining coherence for long enough to influence consciousness (Tegmark 2000). The price for the apparent explanatory power of quantum mechanics in the study of the unity of consciousness was the mystery of applicability of this physical theory to the system which apparently belongs to the domain of classical physics.

The scope of this paper does not allow for more comprehensive documentation of all philosophical and scientific contexts in which holistic methods have been sought without much success. However, it would be incomplete without a short reference to the attempt in developing a scientific discipline exploring systems which require a holistic description. The General Systems Theory (GST) of Ludwig Von Bertalanffy (1950) generated great hope for a new chapter in the philosophy and methodology of science. It is no surprise that Von Bertalanffy was a biologist working on mathematical models of the growth of organisms. Yet, from the present perspective the attempt had some consequences which challenged holistic tendencies in science.

After a few years of great popularity GST started to degenerate into a cult of a few who could see the need for holistic approach, but who could not produce results which could convince the majority about the legitimacy of the methods proposed. This led to marginalization of the movement, which made any reference to holism repulsive for majority of researchers and attractive to those looking for sensational topics. Association with mystery hunters brought stigma, so in decent scientific company people avoid using the h-word and at the best are talking about "non-locality".

There seem to be two main reasons why the reception of General System Theory and the work of researchers identified with this program met such strong resistance. Both related to the confusion common among supporters and critics of this approach. The first is the mistaken belief that the use of the new conceptual framework and new language of inquiry is sufficient for success in solving fundamental problems, such as the question about the nature of life, while a consistent and comprehensive theory is necessary. The second is the divisive tendency to revolutionize scientific inquiry by cutting off ties with methodological and philosophical tradition. Instead of looking for the connection with accumulated knowledge and with existing tendencies, a need for radical change was overemphasized.

An example can be found in very interesting ideas of Robert Rosen who followed his teacher Nicolas Rashevsky in the development of relational biology. Rashevsky was trying to develop a new mathematical approach to biology, but he started by changing the language of biological discourse (Rashevsky 1965). His Generalized Postulate of Relation Forces was as follows: "The development of organismic set proceeds in such a manner as to maximize the total number of relations and the number of different kinds of relations during the total course of development." (Rashevsky 1972) Paul Cull in an article presenting Rashevsky as an "important figure in the introduction of quantitative models and methods into biology" asks "What does it mean?" and answers, "I'm not sure." (Cull 2007) The postulate is formulated in a new language and in a new conceptual framework, separate from a more general, existing philosophical background. The author attempts to create at the same time a new science of life and its new philosophy.

Rosen (1991a) explains Rashevsky's motivation for such radical separation from the mainstream of biological research in the recognition of the fact that the living organism is changing completely its material substratum in a short period of time, therefore it is the persisting higher level structure or organization of molecules which matters, not the matter itself. For Rosen it was a new and revolutionary idea.

Rosen's approach is similar, although he was referring to a more specific mathematical language of category theory (Rosen 1958). The leitmotif of his own research was self reference, which in the past was blamed for all the problems in the foundations of mathematics, and whose elimination was the main tool in the attempts to find solutions. Self reference, or more exactly loops in causal relationships, became for Rosen the main characteristic of complex systems, as distinguished from simple mechanisms studied in physics (Rosen 1991b). Rosen believed that using category theory he could avoid the logical consequences of self reference. After all, enthusiasts of that era's new and attractive language of mathematics had to deal with similar objections regarding logical inconsistencies. Staying within one category (**Set**) in writing about his (M,R)-systems modeling living organisms seemed to prevent more serious problems.

The problem is that the theory of categories and functors was developed as a tool to make possible transfer of methods between algebra, topology and combinatorics in terms of functors. If we decide to use just one category of sets, it could be compared to the development of a formalism for scientific theory using the set theory, but not involving the concept of a function. Thus, the use of category theory in the context of

(M,R)-systems gave a new and elegant language to the consideration of the organizational invariants, but did not constitute a development of a consistent theory of life in all its aspects. Category theory did not provide any new tools for solving problems which could not be solved in terms of set theory, but rather offered a convenient language for the presentation of solutions which could be obtained anyway.

Of course finding the best language for the construction of a theory is a part of the solution. Rosen went further in building the framework for his (M,R)-systems and found some results. But the disappointment was that he promised to provide a theory more general than that which could be provided by physics, in which physics becomes a special sub-domain of biology. And, it is difficult to find such a theory in his writings. Of course, there were many physicists who were equally enchanted by category theory as Rosen, and who tried to use it in re-writing physics (the present author was one of them, trying to find a better description of quantization thirty years ago). There are still physicists who believe that category theory is a perfect formal language for physics. But if it is so, it is because it offers the perfect tools to traverse between diverse mathematical theories.

There is, however, a much deeper deficiency in Rosen's perspective on scientific methodology and philosophy which is in surprising contrast to his unquestionable scientific erudition. He seems not to notice that what he considers a revolutionary insight of Rashevsky, challenging scientific tradition and especially physics, was already a commonly accepted paradigm of physics as a theory of invariants of transformations describing the transition between observers, i.e. as a theory guided by the requirement of intersubjectivity. He complained about the arbitrary choice of observables (Rosen 1987), as if he did not know that the special role of some observables (e.g. energy, momentum) is explained by Noether's Theorem. We select some particular observables to characterize physical systems exactly because they are invariant (or covariant) with transformations which make theoretical description coherent. Of course, the use of such a paradigm borrowed from mathematics and physics in biology may be revolutionary in biology (it wasn't at that time, as it was in some sense already present in Bertalanffy's "organicism"). But it cannot be claimed that the idea of looking for the structural invariants of transformations is a step ahead from physics.

The idea of searching for structural invariants was actually one of most important attempts in overcoming the limitations of reductionism. Its first significant manifestation was in the Erlangen Program of Felix Klein from 1872. At that time the issue was about the classification of geometries by the groups of their transformations, but the idea of the fundamental importance of the invariants of transformations was already present in the program.

Einstein's Special Relativity Theory, understood as a theory of invariants of the Lorentz group (in distinction from the Galileo group for classical mechanics), was the second crucial moment in the development of the methodology of the study of structures through their groups of transformations. The third stage was the classification of elementary particles. This step was important, because it was possible to link this theoretical approach with empirical results, when the existence of some particles was predicted based on expected types of transformations.

The success of the use of group theory in physics had important consequences for all domains of human activity in the 20th Century providing methodological patterns for at least some forms of structuralism. Jean Piaget (1968/1972) gave a comprehensive overview of this aspect of structuralism, including of course the role of INCS group in the genesis of intelligence and the works of Claude Lévi-Strauss which contributed to the popularization of the idea.

Obviously, the methodology of structuralism based on groups of transformations was related to holistic tendencies within scientific and humanistic reflection. The point of departure in structuralistic analysis is in the group structure of all transformations of the whole system whose invariants give identities to the local objects. But even in the forms of structuralism, which was never a homogeneous and coherent system, that do not focus on transformations, this holistic tendency is present. Alison Assiter (1984) in the attempt to summarize the most fundamental characteristics of structuralism across its diverse forms presents as the first of its four principles “A structure determines the position of each element of a whole.” It is not a surprise that Piaget (1968/1972) writes about von Bertalanffy as a pioneer of structuralism in biology.

It has to be emphasized that structuralism cannot be considered a philosophical foundation for holism, and group theory is not likely to be the appropriate mathematical language for its formalization. They do not provide the tools (conceptual or formal) to make distinctions between analytic or reductionistic, and synthetic or holistic methods. More likely we can find in them methods of crossing the division between the two orientations.

There is one more aspect of the attempts to build a General System Theory which had divisive consequences for the two methodological tendencies in science. It is the claim that without drastic changes in the understanding of causal relationships no holistic methods are possible.

Once again, an example can be found in the writings of Robert Rosen. His distinction of complex systems is based on the presence of closed loops of causal relationships (Rosen 1987). His concept of predictive (or anticipatory) systems is very interesting and innovative, but his conclusion that this way we can reintroduce final cause into the scientific methodology is very questionable. It seems that he is confusing the models of the future (based on the past experience, and therefore on the effective cause) with the future itself. Since there are no systems which can make absolutely infallible predictions, unless we believe in extreme form of mechanistic determinism which Rosen of course would not accept, the distinction between models of the future and the future itself cannot be ignored.

More disturbing is his revival of Aristotelian four causes without any justification, as if the three of them buried by Francis Bacon three hundreds years ago belonged to the usual concepts of modern science. It is true that he is doing it while discussing an important question, considered by many authors earlier in relation to the foundations of quantum mechanics, regarding the distinction of what constitutes a system, and what is its state. But his conclusion is astonishing.

Rosen proposes the tripartite division in which he is using metaphorical terms of a genome, environment and phenotype corresponding to physical concepts of a parameter, external variables, and internal variables. Thus far, the idea of the additional distinction between external and internal variables is very interesting. But, when soon later he writes “The partition of the arguments of an equation of state into genome, environment and phenotype turns out to be closely related to the old Aristotelian categories of causation; genome can be identified with *formal cause*, environment with *efficient cause*, and state itself with *material cause*” (Rosen 1987) it is difficult to follow his reasoning leading to apparently necessary consideration of the closed causal loops.

At this point someone could ask whether my own example considered above of the eco system is not an illustration of a closed causal loop. Life on earth is possible due to the entropic differences between incoming visible light and re-radiated infrared radiation, but this difference is influenced by the functioning of the eco system. However, the interpretation of this relationship as a causal loop would be a clear error as the closure of the loop appears only when we attempt to describe causal relationships within synchronic and local model of the eco-system understood as a collection of independent living organisms. If we use a diachronic, global perspective there is no need for any causal loops. What seems a loop is actually a helix.

This example suggests that holistic perspective may give us a solution to the problem of apparent occurrences of causal loops when a reasoning is restricted to the reductionistic, local perspective.

3 Information and Its Integration

Since the question regarding the meaning of the term “information” does not have a commonly accepted answer, it is necessary to provide a short explanation of how it is understood here, referring to earlier articles of the author for its more extensive presentation (Schroeder 2005, 2009). Information is understood as an identification of the variety, i.e. that which makes one out of the many. It presupposes some variety (many) which can be identified as a carrier of information, and some form of unity (one) which is predicated on this variety. Since the relationship (opposition) of one to many is relative, so is the concept of information understood in this way. Also, from a philosophical point of view, this opposition has a categorical character (and therefore is indefinable) making the concept of information built on it very general and applicable in a very wide range of contexts, but still firmly grounded in philosophical reflection.

The two most basic ways many can be made one are by a selection of one out of many (selective manifestation of information) or by a structure introduced in the many which unites it into a whole (structural manifestation of information). These are two complementary manifestations of information, not separate types of information, as either of them requires the presence of the other, although possibly with respect to a different information carrier, i.e. a different variety. If the elements of the variety are devoid of any structure, it is difficult to expect any information involved in the selection of one of them. The selection of one out of many is in this case purely arbitrary. On the other hand, every particular structure imposed on the elements of the variety can be considered an outcome of the selection of one of a variety of possible structures. In the first case, the original variety of the elements is different from the variety formed by the structural subcomponents of each of the elements. In the latter case, the original variety of elements bound into a structure is different from the variety of potential structures. Thus, the transition between different manifestations of information requires a change of the information carrier.

As a consequence of this understanding of information, two main characteristics can be identified. One is quantitative, referring to the selective manifestation. It is a measure of information reflecting the size of the variety and the level of determination of the selection, for instance using entropy, or to be consistent with the definition considered here, rather the alternative, but closely related measure introduced by the author (Schroeder 2004).

The other is qualitative (but possibly admitting a quantitative form) referring to the structural manifestation, a level of information integration which reflects the mutual interdependence of the elements of a variety (Schroeder 2009, 2011).

The orthodox study of information initiated by Claude Shannon can be easily interpreted as a study of the selective manifestation of information in the absence of information integration. This absence is reflected in the fact that the conditions of selection are described by a probability distribution defined on all (measurable) subsets of the probability space not equipped with any additional structure. Therefore, there is no risk that the specific understanding of the concept of information in the present paper can raise the objection of a loss of the accumulated toolkit of methods and results of information theory.

The concept of information integration does not have formal antecedents in information theory. It has been introduced by the author for the purpose of explaining how consciousness can be studied in terms of the general concept of information (Schroeder 2007b).

The point of departure of this approach is where the attempts to interpret consciousness as a quantum mechanical phenomenon at the macroscopic level have become stuck. The present author has proposed a different approach which incorporates quantum-theoretical formalism into mathematical structure modeling information integration in the brain, but without the necessity of assuming that the brain or its parts are actually quantum-mechanical systems. The approach is based on the assumption that, what is important is not the involvement of quantum mechanics as a physical theory describing the brain as a mechanical system, but the properties of the structure used in its formalism which can be used in the building of a model describing information integration. Since it is possible to identify a mathematical structure similar to that underlying quantum formalism in the models of information processing, it is possible to transfer the concept of quantum coherence into the model of information processing (Schroeder 2006).

In the earlier papers of the author on the theoretical mechanisms of information integration in the brain their models have been described in terms of information processing gates (called Venn gates due to some analogy to Venn diagrams). However, their function as theoretical devices for processing information is a matter of interpretation of the mathematical formalism. Thus, they may be considered mathematical models of information integration in more general sense.

4 Methodological Aspects of Information Integration

The formalism of information integration (Schroeder 2009) is formulated in terms of closure spaces (sets equipped with a general, not necessarily additive as in topology, closure operator) and complete lattices of closed subsets (Birkhoff 1967).

The level of information integration is determined by the algebraic properties of the lattice of closed subsets, which in analogy to lattice theoretic formalism of quantum mechanics (QM) in which it is called quantum logic (Jauch 1968; Piron 1976), can be called a logic of information system.

Purely quantum logic (i.e. without any superselection rules) is an example of a system which corresponds to complete information integration. This is the reason why quantum mechanical phenomena have been associated with consciousness. However, quantum logic gives only a very special instance of information integration. On the other hand it provides a good example of the source of mystification involved in interpretation of holistic aspects of physical reality.

The Superposition Principle expressed in the orthodox formalism as a superposition of wave functions describing states of a system seems exotic and mysterious. However, in the perspective of quantum logic formalism it is a very simple, although fundamental property of the irreducibility of the lattice describing the logic of a system. This simply means, that quantum logic cannot be represented as a direct product of component lattices. A purely quantum system (no such systems exist in physical reality) is completely irreducible, while purely classical system (Boolean logic) can be totally decomposed into (or reduced to) the product of trivial two element lattices (Jauch 1968).

The actual physical systems of quantum mechanics are somewhere in between. Their logics have a nontrivial reducible part (described formally as the center of the lattice) and sectors of quantum coherence which individually are irreducible. The center forms a Boolean sublattice corresponding to the lattice of all subsets of the phase space in classical mechanics.

Someone might object that this irreducibility may be a simple algebraic property, but that it reflects a mysterious property of the microscopic world. However, we have many examples of familiar systems described by direct product irreducible lattices. For instance, we can refer to the irreducibility of the lattice of closed subsets in the closure space formalism of geometry. This property, from the point of view of geometry as an information system, is experienced by us, humans as the unity of the space.

The next objection could be made, that using formal properties derived from quantum logic for modeling brain mechanisms seems artificial. After all, objects of our conscious experience are governed by classical mechanics. Why is classical mechanics with its Boolean (completely reducible) logic of all subsets of the phase space a non-integrating information system, while the brain which seems to be a system belonging to objects described by classical mechanics is supposed to perform information integration?

This can be answered by noting that classical mechanics is based on the idealization of its objects. The idealization consists of an assumption that the smallest objects within the system are points (i.e. they do not have internal structure requiring information integration) which have externally manifested properties measured as, for instance, mass. In classical mechanics, compound systems consisting of several (let's say 'n') points in three-dimensional space are represented as one point in multidimensional (3n-dimensional) configuration space. This way, objects are devoid of internal structure, and as such do not require any involvement of information integration.

The objects governed by the rules of quantum mechanics are overly influenced by the process of measurement to be considered devoid of any internal structure. This is why their description requires a formalism which considers the integrated information associated with internal structure, as well as disintegrated information related to their classically distinguished characteristics such as mass. Thus, it is not that the brain exhibits quantum behavior, but that the description of quantum objects such as elementary particles reflect the process of human comprehension of the world, or in other words it reflects characteristics of human consciousness.

From the mathematical point of view, the crucial point of the idea of information integration is in decomposability. It is an old strategy to investigate conditions of the reduction of complex structures into products of those irreducible. For instance, one of already classical research programs consisted of classification of simple finite groups. Once they are known, every finite group can be constructed from the simple ones. In this case, indecomposability of lattices and the structural characteristics of compound ones are used to characterize the level of information integration. The use of closure spaces gives the formalism a wide range of applications in multiple contexts. Finally, the formalism is closely related to the formalisms of quantum and classical mechanics, which gives examples of its application in the description of the physical world. Of course, it can be presented in the language of category theory, but it would be unnecessary, excessive level of abstraction.

5 Conclusion

The formalism which was presented above, in a very general way, without any specifics of mathematical concepts involved presented in articles listed in references, allows study of information and its integration in a very wide range of contexts. Geometry and its relation to processing information regarding the configuration of objects has been mentioned above. There is a very extensive body of literature regarding the closure space formulation of geometry, convexity, etc. Closure spaces have appeared in mathematics as generalizations of topological spaces, and this opens the way for the study of information in the context of topological properties. Closure space formalisms are fundamental for the study of the logical consequence operators initiated by Tarski. This approach to logical inference allows us to link logic (in the traditional meaning, as a discipline studying processes of reasoning) with information. There are many other mathematical theories using closure spaces as their basic concept.

The main open problem is in the transmission of mathematical concepts and results from the mathematical disciplines whose conceptual framework was used to develop classical quantitative information theory of the type initiated by Claude Shannon, such as probability theory, to a more general context of information systems defined by a large variety of closure spaces. There is no problem of generalization to quantum theory, as it can be understood as probability theory on non-distributive lattices. However, there are information systems which require more general closure spaces (geometry could be an example) in which probability measures cannot be defined due to the lack of a concept of orthocomplementation. The question is whether more general measures of information can be defined for this purpose.

The formalism presented above provides a theoretical tool for holistic methods going beyond simple declarations of the need to consider mutual interactions of the components of compound or complex systems. Actually, the formalism combines the analytic and holistic methodologies, as the distinction between them is based on different levels of information integration. Since in many cases we have systems which are neither at the level of complete disintegration (Boolean logic of information), nor complete integration (completely irreducible logic of information), the distinction into analytical and holistic methods is losing its antagonistic character.

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The Engine of Engines – Toward a Computational Ecology

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Abstract. Our knowledge related to the entailments of functionalities of different biological processes as they enable sentience to arise in the human is still limited due to the biological complexity of the body. There are two interrelated research paradigms that can be developed to approach this problem– one paradigm seeks to study the body and articulate its entailments (intra-functionalities) at multiple scales over time; the second paradigm seeks to glean knowledge from this study of biological processes and create new forms of computation to enable us to transcend the limitations of current computational modes. The nature and scope of the question necessitates an transdisciplinary approach to research through the development of a multi-perspective approach to knowledge production. Here, key solutions can in part arise at the interstices between disciplines, and potentially enable us to define and 'chip away' at the problem set. Central is observing the body as a distributed network of computational processes that function at different physical scales as well as across time-dependent, process-oriented accretive frames. We can articulate the study of the body by calling it an electrochemical computer— a computer whose deep functionality is not yet fully entailed. Historically the nature of the problem has been to isolate a biological system and study its entailments to ascertain its functionality. Yet, the nature of sentience asks us as researchers to take a more holistic approach, despite the complexity at play. These two paradigms then become a long-term problem set that a network of high-end researchers can collaborate on, by bringing different areas of expertise to the table. The notion of developing a biomimetic/bio-relational *Engine of Engines— A Computational Ecology* (Stengers 2005) derives from observing computational systems at work in the body and approaching them through observation— through technological, mathematical and/or computational abstraction. Where the body has been described as functioning as a computational system that transcends the Turing limit (Siegelmann 1999)(Maclennan 2003)(Penrose 1989) new approaches to computation need to be undertaken to reflect this deep complexity.

Keywords: analogue computation, digital computation, hybrid computation, bio-relational systems, computational ecology.

1 The Engine of Engines – Toward a Computational Ecology

In the words of von Neumann from The General Theory of Automata: "[…] It is a fundamental requirement of the scientific viewpoint – the so-called principle of the psycho-physical parallelism – that it must be possible so to describe the extra-physical process of the subjective perception as if it were in reality in the physical world – i.e., to assign to its parts equivalent physical processes in the objective environment, in ordinary space." (von Neumann, 1995)

2 Introduction

When we study the body we can consider it to function incorporating the architecture of different computational processes that are currently not fully understood, especially in terms of the interrelation of those processes over time functioning in concert with other biological functionalities. From this overarching perspective we can study the body as an ultra-complex time-dependent computational ecology. We ask, what are all of the salient computational processes on multiple scales that contribute to our sentience over the course of our lives that become operative within this biological network? It is imperative to develop new computational methodologies to approach this problem set. MacLennan, in his paper *Transcending Turing Computability* discusses "Hypercomputation" — "The Turing-machine model makes assumptions about information representation and processing that are badly matched to the realities of natural computation (information representation and processing in or inspired by natural systems)." (MacLennan, 2003). Research into the *The Engine of Engines* seeks to entertain such new methodologies by exploring two paradigms in an interoperative manner — 1) seeking to define the entailment structures of the body at different scales, at operation over time and 2) to explore new forms and approaches to computation, informed by paradigm 1, forming a biomimetic and/or bio-relational *Engine of Engines*. Exploration of these new forms should fold back in an ongoing expanding manner and further inform both paradigms. Seaman's concept of an "Insight Engine," a system to house related data and enable such a complex undertaking (Seaman 2009), embodies a multi-perspective approach that intermingles databases and discourse processes from the sciences, the humanities and the arts—potentially enabling a Koestler-like space for bisociation (Koestler 1964). In discussions with researcher Olivier Perriquet, it has become clear that such a multi-perspective approach enables one to understand any object of study in a multivalent manner resulting in different discourses on the same object or experience (Perriquet & Seaman 2011). This approach enables new ideas to arise at the intersection/juxtaposition of disciplines.

Seaman and Rössler in *Neosentience / The Benevolence Engine* (Seaman & Rössler, 2011) have been exploring the potentials for a related AI/Robotic branch of research. Many references from their book inform the writing of this paper. Seaman and Rössler's paper entitled *Toward the creation of an intelligent situated computer and related robotic system: An intra-functional network of living analogies* (Seaman

& Rossler, 2006) discusses the notion of articulating physical processes in the body and making analogical and/or digital abstractions of them in the service of this new AI/Robotic paradigm. *Endophysics and the Thoughtbody Environment: an Outline for a Neo-computational Paradigm* (Seaman, 2005) also frames some of the initial parameters of this discussion. Seeing the mind/brain/body/environment set of relations as being both analogue and digital, this research falls in relation to, yet differentiates itself from entirely discrete models of computation. (Zuse, 1969) (Wolfram, 2002) (Fredkin, 2005). One can see the value in the "discrete" approach and von Neumann pushed for this to get beyond problems of noise in early computation. Alternately, von Neumann discussed the mixed character of living organisms as being both digital and analogue, recognizing the potential of shifting the efficacy of neural processes via "humoral" media (von Neumann, 1995). Central to the research is seeing the body as an ultra-complex electrochemical computer that has mixed distributed analogue and digital computational qualities (Seaman and Rössler, 2011) that contribute to the arising of sentience.

This new research starts with the body as being conceived (bringing together different code potentials); growing up— nested in the environment over time, unfolding biological potentials via the code-based processes enabled through DNA and RNA; building up knowledge of environment via the senses and through coupled interaction with environment— the embodied/embedded paradigm (Clancey, 1992) (Froese, 2002), as well as through introspection; the acquisition of natural language; moving in space; having a deep multi-modal understanding of changing context; learning and anticipating; being creative; and interacting with others as part of a larger intellectual, social and cultural ecology. Froese in his paper *On the role of AI in the ongoing paradigm shift within the cognitive sciences* discusses related embodied/embedded approaches under the rubric of "enactivism"…which "radicalizes the embodied-embedded approach by placing autonomous agency and lived subjectivity at the heart of cognitive science." (Froese, 2002) How do the low level systems enable the high level processes of being sentient to arise? Undertaking a multidisciplinary, multi-perspective approach to knowledge production is here essential. The central concept is to create and study analogous computational systems and interfacing methodologies to those at operation in body, and to explore bio-relational approaches to further illuminate aspects of human computation.

3 The Body and Computation

It was Descartes who first understood the body to be a special variety of machine. Rashevsky pointed to early ideas surrounding analogue two step neural processes of excitation and inhibition (Rashevsky, 1940); McCulloch and Pitts (Rashevsky's student), shortly after the publication of Rashevsky's seminal book, *Advances and Applications of Mathematical Biology*, began to articulate computational potentials based on their notion of the Neural Net (McCulloch and Pitts, 1943). Rashevsky's critique of the neural net was essential as well as his approach to articulating logical processes (Rashevsky, 1948). Von Foerster early on talked about cognition as computation (von Foerster, 1973). Turing discussed notions of "input" and "output" organs. (Turing,

1986) Elsewhere Seaman has discussed the notion that we learn and accretively gain our intelligence via experience in the world in part through a series of sense-based pattern flows (Seaman, 2005). Hebb's law (Hebb, 1949) (Wiles et.al., 2010) here is central. Yet, what different computational processes in the body contribute to the ability to register patterns flows of sense perturbations? What computational processes enable the building of the biological systems in themselves? Von Neumann's notion of the self-replicating machine from the *Theory of Self-reproducing Automata* here comes to the fore. (von Neumann, 1966) (Stevens [no date given])

Entailment of the body as an ultra-complex system, seeks to map and understand the role of all of the contributory processes to sentience production as a long-term goal. Another "fine grained" approach includes the research of Penrose and Hameroff (Penrose & Hameroff, 1998) and in particular Hameroff's discussion of microtubules and quantum level processes in the brain. (Hameroff, 1987) The central hypothesis in our research is that there is a machine-like biophysics behind all processes in the body relevant to sentience production. This can be seen as a different attitude to that of Rosen as discussed in *Life Itself* (Rosen, 1991), who did not want to see the body as a machine. One goal of the research seeks to more fully entail distributed aspects of the body's functionality. Seaman sees the body as a *not yet fully entailed biomachine* of ultra-complexity — an electrochemical computer with related sensing/volition mechanisms (Seaman & Rössler, 2011). It is interesting to also note that Rosen, like Pitts studied under Rashevsky and is perhaps best known for his work related to category theory, (Rosen, 1958) another approach relevant to our research.

Rössler's approach, *Endophysics* is central to the study of these processes from the perspective of a "physics from within" (Rössler, 1998). His concept is to use simulation strategies such that one can become a superobserver of the system, although his study focuses on a more "point" like interface (Seaman in discussion with Rössler). The *Engine of Engines* research seeks to enable embodied study of differing biocomputational modalities through the generation of analogous computational processes, as well as via high-level computational modeling operating in concert with advanced scanning methodologies, functioning in the service of entailment. Cognitive science works with "a complex 3-way analogy among the mind, the brain, and computers. Mind, brain, and computation can each be used to suggest new ideas about the others."(Thagard, 2011) Expanding on this notion points to the potential of exploring biomimetic and bio-relational systems to better come to understand the distributed computational inter/intra functionalities that are at operation in the body and how they become relevant to brain/mind functionality. Thom's early approach to emergence via catastrophe theory and topological theory (Thom, 1975) also plays into our discussion, where thought can be seen to be an emergent property arising out of this mixed computational nature. Certainly the writings of Conrad (Conrad, 1992) Zauner (Zauner, 1998) and Adleman (Adleman, 1994), related to molecular and DNA computing, as well as the writings of Patee (Patee, 1969) related to molecular messaging, become important pre-cursors to our research, as does the seminal discussion of analogue processes by Smale— exploring functionality through the rubric of dynamical systems (Smale, 1963; 1967) e.g. if we think of neural transmitters, manufactured in different parts of the body, and their contribution to thought processes, we can discuss a protein shape code and how this code, when in operation, shifts the efficacy of the firing of the synapse.

4 Divide and Concur— Breaking Down Problem Sets and Having Differing Kinds of Computers, Both Analogue and Digital, Work on Them in Cooperation

One seeks to define a network of processes mathematically that can reflect specific biological qualities as they are mapped to different mathematical problem sets. In terms of non-conventional computers one could point to different focused qualities relevant to each computer as they are applied to different kinds of problem solving. This is very different in approach to the ideas surrounding the "universal" Turing machine. Siegemann's has discussed the potential of analogue computation. In her book *Neural Networks and Analog Computation: Beyond the Turing Limit* she discusses the notion of a Church-Turing-like thesis which might be applied to analogue computation, featuring the neural network instead of the Turing machine. In particular she feels that on a mathematical level the exploration of analogue neural networks "enriches" the theory of computation. She feels that the potential for the development of supra-Turing computational theories can arise from the scope of this analogue perspective, (Siegelmann, 1998) and that such an approach "explicates the computational complexity associated with biological networks, adaptive engineering tools, and related models from the fields of control theory and nonlinear dynamics." (Siegelmann, 1998) She states that "when analog networks assume real weights, their power encompasses and transcends that of digital computers… our model captures nature's manifest 'computation' of the future physical world from the present, in which constants that are not known to us, or cannot even [currently emphasis Seaman] be measured, do affect the evolution of the system." (Siegelmann, 1998) Given this discussion it follows that the focused exploration of analogue systems may help contribute to a more full understanding of how the body functions in terms of the emergent nature of biological computations that contribute to sentience production. It follows that the specific interfacing of differing computational systems, based on biomimetic and biorelational approaches, may provide new knowledge about sentience production.

5 Drawing on these Distributed Processes in the Body in Terms of Their Contribution to Natural Computing

Entailment processes must be articulated across different scales found at operation in the body. It is interesting to note that as we fully articulate entailment (biofunctionality), we shift a process from the designation of being "emergent" to that of being entailed (understood)[discussion with Perriquet]. As a research strategy we can seek to map a series of mixed analogue and digital processes that contribute to the arising of sentience over time as well as to define their intrafunctionality. This in part relates to the notion of *Natural Computing* articulated by Rozenberg: "Natural Computing is the field of research that investigates both human-designed computing inspired by nature and computing that takes place in nature, in terms of information processing…(including, emphasis Seaman) neural computation inspired by the functioning of the brain. (Rozenberg, 2012: forthcoming) A number of new definitions for computation in this area seem to be under construction, as they pertain to information change over time. (Fredkin, 2005) (Wolfram, 2002) There is certainly a debate surrounding the discrete vs. continuum-based "understanding" of the world. I see computational processes in the body as being of a mixed analogue/digital nature as discussed by von Neumann above (von Neumann, 1995), functioning across a continuum. I can also understand that this continuum can be successfully parsed at different scales to contribute to differing discrete computational 'articulations' of biological mechanisms. There is still debate concerning the actual lowest level of this discrete parsing as it pertains to the physics underlying biological functionality. Negotiating/debating this potential definition of a new constant also folds into this research. Alternately, in terms of entailment mapping it also makes sense to have different scale discrete parsings that are 'set' [articulated by researchers] which are highly focused to particular regions in the body, and are observed/compared in a time-based manner as they relate to the unfolding of particular biological processes functioning at different scales.

Dodig-Crnkovic has been working to define her own particular approach to computation in relation to information. In her paper entitled *Info-Computationalism and Morphological Computing of Informational Structure* (in this volume) she points to the fact "that knowledge is generated bi-directionally, through the interaction between computer science and the natural sciences." She aptly points out that "While the natural sciences are rapidly absorbing ideas, tools and methodologies of information processing, computer science is broadening the notion of computation, recognizing information processing found in nature as (natural) computation. (Rozenberg & Kari, 2008); (Stepney et al., 2006)"…"This new concept of computation allows for nondeterministic complex computational systems with self-* properties. Here self-* stands for self-organization, self-configuration, self-optimization, self-healing, self-protection, self-explanation, and self(context)-awareness. Dodig-Crnkovic in (Dodig-Crnkovic & Müller, 2009) argues that "natural computation (understood as processes acting on informational structures) provides a basis within info-computational framework for a unified understanding of phenomena of embodied cognition, intelligence and knowledge generation." (Dodig-Crnkovic, 2011) How can we define and articulate a relationality between "processes acting on informational structures" (Dodig-Crnkovic, 2011) and other historical approaches to computation, both analogue and digital? Here we can look at "all" process-change in nature as discrete computation (for the sake of ease of mathematical discernment), as in the thought of Friedkin exemplified in his paper on *A Computing Architecture For Physics* (Fredkin, 2005), yet, I am suggesting that the body achieves focused biological functionality through specific "varieties" of computational processes as they function in conjunction with other biological process distributed across the body, mixing analogue and digital methodologies. These processes are "interfaced" internally or run at a distance (or function on different scales of space and/or time) inside of the body, as well as become interfaced with focused computational processes that run both internal and external to the body, that can be intentionally explored in the service of knowledge production, social interaction, as well as the focused study of biological functionality.

The body functions as an autopoietic unity (Maturana & Varela, 1980), summing these different computational processes. A debate continues concerning the seeing of the body as a hierarchy and/or dynamic heterarchy under particular extreme biological conditions. (McCulloch, 1945)(Pattee, 1973)(Seaman & Rössler, 2011) This will be further discussed in a subsequent paper. We must seek to develop new models to reflect the true complexity of our biological systems as they function over time in relation to different environments, as well as in relation to deep structural changes (sometimes catastrophic [pun intended]) (Thom, 1975), that can affect the autopoietic unity. This also includes the implanting of devices that transcend traditional notions of this biological unity e.g. cochlear implants et al.

The focused study of the relationality between different forms of computation is essential to the *Engine of Engines'* two interrelated research paradigms. Here we see an integration of biological processes as they enable distributed computational processes discussed as "natural computing", which can be seen to nest other "concepts" or "varieties" of computation, both analogue and digital. We must also remember any analogue process can be modeled (to a particular degree of accuracy) via a discrete computational system, and also become part of our ecology.

Alternately, the notion that the body functions as a self-observer (as mentioned by Dodig-Crnkovic) becomes important— an observer that can differentiate and frame different notions of computation, and be introspective about this framing. Thus the human computer functions as one of the "computers" in the network ecology. When we draw a distinction between well articulated differences in the (re)definition of computation, we can include notions of "Morphological" computation (Dodig-Crnkovic, 2011) as a *different level of computational functionality* that enfolds and nests other computational functionalities in the body— a pattern of information patterns changing over time. Dodig-Crnkovic discusses a number of issues surrounding information and computation in her paper entitled *Dynamics of Information as Natural Computation*. (Dodig-Crnkovic, 2011b) Here we must seek to negotiate a stable definition of 'information' especially as it subtly migrates across different research domains from physics, to biology, to mathematics, to computation. The notion of sharing careful definitions across transdisciplinary fields is essential. Also the difference between the functionality of physical/analogue codes [e.g. protein shape codes] and how they become operative, versus how digital code functions as a physical system in the light of "Natural Computing", is by no means trivial. One could also research how different varieties of analogue/digital codes could be simultaneously running at different scales and across differing time frames within the body, especially as it falls in relation to the larger environment. (Dodig-Crnkovic, 2011b)

6 Computational Processes at Operation in the Body

Seeing these biologically networked computational processes as relevant to human biocomputation, one thus seeks to extend the current model of the Neural Net to enfold other relevant distributed biocomputational and/or bio-relational processes. We can discuss the body as having a number of processes on differing scales contributing to thought and action where mind and body are seen as co-arising via physical processes as articulated by von Neumann above (von Neumann, 1995). Yet, at this moment it is difficult to parse exactly what computational processes in the body are at operation, and in particular how they contribute to neural computation. Here we can take stock of some of the processes that might be considered to contribute to its mixed "computational" nature. These might include: neural flows (mixing analogue and digital processes) including: a. neural transmitters (protein shape communications); b) circulating frequencies – that also function to regulate bodily processes and change synaptic efficacy (Kumar & Mehta, 2011); synapse flows (changing efficacy in part in relation to a. and b. above); genetic processes contributing to growth and the formation of the systems themselves (DNA); nanoscale processes regulating molecular change and biological communication; flow processes (acting as analogue computation) or vehicles enabling distributed biological processes; quantum processes in nanotubules and other locations; and other biological functionalities still under research (volume transmission) (Agnati et al., 1995). Additionally the notion of multi-modal sensing and embodied experience becomes an important operational mechanism both in the human and in artificial polysensing environments that might enable a machine to build up knowledge about environment. (Seaman & Verbauwhede [date not set]) (Seaman & Verbauwhede [date not set]b). From this list of human/biological computational processes the research field has spawned many biomimetic and bio-relational computational approaches. This includes analogue and digital manifestations e.g. neuromorphic chips (Folowosele, 2010). Such computers include: protein computers (Biomatic.org Wiki); DNA computers (Landwber, 1999); quantum computers (Hagar, 2011)(Markoff, 2010); embodied sensing systems informing computation/learning systems – polysensing environments (Seaman & Verbauwhede, [date not set]); analogue flow computers (Pask, 1982); analogue physical computers, wind tunnel computers, blood flow computers (Parrish et al., 1959); electrochemical computers (Kahn, 1992); (Seaman, 2009); nano computers and related nano sensors (Blomberg, 2011); (Brumfield, 2011); and neural nets of differing kinds (Whittle, 2010).

7 The Engine of Engines as Computational Ecology

By networking these many different kinds of computers via the development of new forms of interface, we seek to draw upon the quantitative characteristic differences that make each unique. Many of these computers push "Beyond the Turing Limit." (Siegelmann, 1998) Perhaps each with a special attribute that enables it to perform "particular" kinds of computational processes, or that exploit a particular quality inherent to their physics and/or to their analogical substrates. Yet in almost every case these computers are currently interacted with via von Neumann machines (or human computers, that re-encode information gleaned from these machines, translating their output into a form that is compatible with von Neumann machines). The challenge of future research is in the development of new interfaces that bridge from the analogue to the digital; new forms of cross functional operating systems that can enable information exchange with the greatest acceptable accuracy; and new forms of communication across scales.

The body achieves a unity bridging multiple scales of computational processes as they become operative in conjunction with other networked biological operations. Certainly Simeonov has charted a new science of mathematical relations separately covering many of these areas of research in his paper entitled: *Integral Biomathics – A Post Newtonian View Into the Logos of Bios (On The New Meaning, Relations and Principles of Life in Science)* (Simeonov, 2010). One could also work toward emulating these intrafunctional systems in von Neumann machines; yet, given the impetus of exploring mixed analogue/digital systems where particular substrates enable new varieties of communication and functionality, it seems important to explore the potentials of mixed analogue/digital computation. Here we encounter two related questions: 1) biologically, how are such processes in the body currently interfaced so that they become inter/intrafunctional at different levels and scales? And, 2) in the development of new modalities of computation can we articulate new forms of interface that enable a transfer of relevant data, without a "significant" loss of the precision and/or specific functional attributes of the individual mechanisms involved, informed by our study of biological entailment? By linking disperate computers using a von Neumann machine as a "pivoting" hub, and/or by developing specific biomimetic and/or bio-relational forms of functional inter-system interfaces, we can potentially point at and better come to understand complex forms of biological functionality. We can, in some cases divide up problems to be tackled on the computational machines that might best achieve particular focused "mathematical" goals. Not only can we interface with the von Neumann machine, the long-term goal is to facilitate unique interface development between the differing systems. To articulate such an *Engine of Engines* one will need to enable a dramatic "Convergence" between disparate researchers. (Sharp, et. al., 2011) (Angelica, 2011)

In the context of the body functioning as a unity, how can the interfacing of all of these biocomputational processes best be reflected upon? Our long-term research goal focuses on formulating a clear set of methodologies to come to understand how disparate informational structures and biological processes enable the propagation of unique computational qualities that function in the service of sentience production. Through this research, biomimetic and bio-relational computation is spawned in an ongoing manner to extend the understanding of the body's entailments, while it simultaneously enables us to better reflect on the body's functionality as a system of systems — *an Engine of Engines*.

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Seaman, B.: (October 20, 2011)

Ten Autobiographical Stepping-stones towards a Comprehensive Theoretical Biology Comprising Physics

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Abstract. A chronological listing of ten scientific insights obtained by a theoretical biologist over half a century is presented. The circle spans many fields of science (engineering, chemistry, physics) exploring and exploding many accepted concepts. What is only touched upon is the assignment of the Now as the only place at which anything can be done and appreciated in our private qualia.

(September 15, revised September 18, 2011)

Keywords: theoretical biology, theoretical physics, endophysics, chaos theory, cryodynamics, neuroscience.

1 Ten Findings

1) A nonlinear energy-saving “carrier-proportional-to-voice" amplitude modulation; made distortion-free through negative feedback (demodulated high-frequency output signal fed back to microphone input) - 1957
2) Origin and evolution of life made predictable as a runaway self-inhibition of energy dissipation (manifest as a growing automaton) – 1961 pp.
3) Epigenetic personogenesis (the uniquely human smile-laughter indistinguishability enables the invention of the suspicion of benevolence by the mirror-competent toddler) – 1964 pp.
4) Brain equation (enables best local solution to the traveling-salesman-with-alarm-clocks problem) – 1973
5) Non-planar limit cycles (with spiral chaos, screw chaos, hyperchaos and superfat attractors) – 1975 pp.
6) Transfinitely-exact classical indistinguishability: implies h via the observer’s Sackur cell - 1984
7) VX-diagram: proves validity of Everett’s theory of quantum mechanics at the expense of the Copenhagen interpretation – 1988 pp.
8) Finite observer diameter: implies c via classical indistinguishability – 1989 pp.
9) WM-diagram: proves validity in the Einstein equivalence principle of the Telemach theorem which implies that black holes are necessarily non-charged and nonevaporating – 1998 pp.

10) Cryodynamics, sister discipline to thermodynamics: explains Hubble law and implies an infinite regenerative Boltzmannian cosmos – 2003 pp.

2 Ten Remarks

1 (Distortion-free distortion): My teacher in the Radio Amateurs' Club of Tubingen was Mr. Lennartz who had lost both hands. He helped me obtain my radio amateur's license precociously at age 17 and had a lovely daughter. [1]

2 (Noninhibitable evolution): A juxtaposition made by Ludwig von Bertalanffy between a burning candle and a mouse, each placed into a box with holes in it, as being both indistinguishable in terms of chemical inputs and outputs, triggered (via rust placed in between as a mental catalyst) the following intuitive insight: Existence of a preformed infinite chemical network, with a few constantly replenished (red) pool substances on the left. Then one sees a lawful creeping-in from the left of red color into the at first colorless vinyl tubules which make up the preformed infinite tree of reactions, including recurrences that lead to over-regeneration. This veined picture split itself up into two equally valid descriptions: thermodynamic and kinetic. The first pointed back to Teilhard, the second forward to Prigogine, but the full picture ("recursive evolution") was novel - being developed in parallel by Stu Kauffman, Joel Cohen and Robert Forward. It earned me the early support of C.F. von Weizsäcker whom I had written a letter because of his book "The History of Nature" in which he had come close. He would launch me from medicine into science. R.W. Kaplan and Bob Rosen then became my guardian angels and Manfred Eigen for a while my largest adversary which, too, turned into grace. [2]

3 (Levinasian smile): Here my teacher was a doomed young pediatric patient in a surgical unit who - like me at the same age - had optimized his smile in an orphanage. Not being allowed to adopt him to save his life for my being unmarried, I later published the theory I had learned from his smile as a therapy for autism. The therapy mimics the unique epigenetic condition of human beings (that smile and laughter look the same). It allows one to spread personhood across the cosmos to other bonding mirror-competent creatures ("galactic export"). This can be started on earth with a young white elephant or dolphin as partner. The key is to have the caretaker produce an acoustic smile (bonding signal) whenever about to break out into a hearty laughter. In this way, the physiological smile-blindness is acoustically overcome. I once saw a living case study on TV: A still smile-blind hairdresser inadvertently healed by his mother at age 7: He woke up, reported, when she sat behind him holding him on her lap while he was trying to scribble letters. In my mind's eye I heard the tender noises of pleasure she made whenever he succeeded (Stern TV, January 29, 2008).

The theory, which formally goes back to two 1947 papers by Nicolas Rashevsky and Anatol Rapoport, respectively, found the approval of Gregory Bateson and Niklas Luhmann, but was never taken up to the best of my knowledge, to the possible detriment of millions. [3]

4 (Brain equation): The idea grew out of discussions with Konrad Lorenz: An automated automobile has several types of tanks that each need refilling at a green, blue, red or yellow filling station, respectively, each color independently dispersed in space much as in reality. The crucial parameter is the ratio of color-specific (all equal, say) maximal traveling radius between refillings, over mean distance between filling stations of same color (all equal, say). Before this ratio approaches unity from above, the solution becomes infinitely complex. The problem is mathematically equivalent to the famous ordinary traveling salesman problem, as Garey and Johnson later proved in their book "Computers and Intractability." The brain equation approximates the best “local” strategy and thus is necessarily suboptimal, but when combined with a “universal simulator” (VR) becomes arbitrarily efficient in principle. Miraculously, the traveling salesman possesses Gödel's tiling problem as a limit. [4]

5 (Chaos): My penchant for visual thinking earned me the early friendship of Art Winfree (via Wolfgang Engelmann). He introduced me to chaos in 1975. The transfinite mathematical beauty of chaos was first seen by Anaxagoras. Chaos is a matchmaker for lifelong friendship including John L. (Jack) Hudson and Christophe Letellier. Georg C. Hartmann is co-responsible for the “flare attractor” of economics found after we had come in contact with the late Richard M. Goodwin, discoverer of the limit cycle (pork cycle) in mathematical economics . [5]

6 (h): “An estimate of Planck’s constant” appeared in 1985. Classical indistinguishability goes back to the Leibniz-Clarke correspondence of 1716. Hans Primas introduced me to Hermann Weyl’s “Philosophy of Mathematics and Science” in the context of indistinguishability. Otto Sackur in 1913 had re-discovered h empirically in a radiation-free gas, and theoretically on the basis of Gibbsian indistinguishability. The classical Sackur-Tetrode equation contains h only as a system-specific unit action, not as the empirically universal action. The implied classical explanation of spin was spotted only 14 years after, jointly with Michael Conrad. [6]

7 (VX diagram): John S. Bell, on seeing the diagram (the letter V standing for the two mutually departing correlated photons, crossed in an x-shaped fashion by two different simultaneities valid at the two measuring stations placed into mutually receding spaceships) commented graciously “this idea is completely new to me” and corrected the resulting paper. Roger Penrose and later Anton Zeilinger with Antoine Suarez arrived at the same experimentally testable idea, Susan J. Feingold was the first. [7]

8 (c): Microscopically sharp “assignment conditions” naturally complement Newton’s dichotomy between “laws” and “initial conditions.” The name Endophysics (for "physics from within") I owe to David Finkelstein.

The observer diameter – obtained heuristically by inserting h and c plus T (the observer temperature) into the Sackur-Tetrode equation of the brain - is 7.4 micrometers, a typical cell diameter in the reticular formation. That the latter’s cells can be interpreted as the "momentary seat of consciousness" is an admissible conjecture. [8]

9 (WM diagram): The diagram (again both letters superposed) lies at the root of Einstein's gravitation theory. Height is pointing up, time points right on two levels: faster upstairs, slower downstairs. Light rays go up and down in a zigzag, cutting out different time lengths (the shorter bijectively matching intervals being downstairs)**.** My students co-responsible for the diagram, Dieter Fröhlich and Heinrich Kuypers, still have not been granted their deserved PhDs. The main consequence – lack of Hawking radiation and hence unsafeness of the LHC experiment at CERN – remains non-falsified. The United Nations had to be asked to convene the requisite safety conference. [9]

10 (Cryodynamics): The theory goes back to Fritz Zwicky and Subrahmanyan Chandrasekhar ("dynamical friction") in 1929 and 1943, respectively. It was re-discovered in 2003 in Tubingen. A first numerical demonstration was obtained in 2010 in a formally 1-D two-particle (of strongly unequal masses) Newtonian system in a T-tube configuration, by Klaus Sonnleitner. The implied eternal-recurrence interpretation of the cosmos involves validity of point 9 above. It is empirically falsifiable. [10]

3 Conclusions

Pure thought sometimes leads to ridiculous hypotheses. For example, regarding point 6 above, my late friend Joe Ford wrote an anonymous referee report to a physics journal that started out on the following sentence: "Dear Otto, please, do not publish this paper." The method of non-peer reviewed publication has since ceased to be attractive altogether, in our current Mark Gable Foundation age. "The Mark Gable Foundation" is a chapter written in 1948 of a famous science-fiction book by former bomb-inventor, bomb-advocate and bomb- revoker (in vain) Leo Szilard titled "The Voice of the Dolphins," of all things [11]. He there proposed all the currently en vogue instruments allegedly promoting science (like large cooperating groups, huge prizes, evaluation committees manned by the most accomplished scientists, big grant agencies) – as an unrecognizable means to slow scientific progress down. Nevertheless the old and in his eyes so dangerous inexpensive way of doing science by imaginative thinking (in a light-house keeper's existence as propagated by his mentor Einstein) remains our only hope, as I had to learn reluctantly. For its abrogation is even more dangerous, given the already existing instruments that those opinion-averaged groups are given to play with while necessarily lacking the critical instinct that only the old system of self-responsible individuals can breed.

Today I attended the funeral of my friend Valentin Braitenberg (author of "Hirngespinste" – roughly: crazy spider-web brain). His kindness and his "simple thinking" – with doctoral students up to his turning 85 – was lauded in a moving sermon by the pastor in the full-packed church, and afterwards from the same pulpit by our joint secular friend Niels Birbaumer. Braitenberg was the inventor of the "thought puppet" so I learned: that an idea needs to be played with exactly as a child plays with his puppet looking at it in any possible mental and hands-on way.

I dedicate this short note to Valentino.

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Part V

INBIOSA White Paper

Stepping beyond the Newtonian Paradigm in Biology

Towards an Integrable Model of Life: Accelerating Discovery in the Biological Foundations of Science

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Note: This White Paper is not a concise report on the research program we seek to elaborate in INBIOSA. It has been conceived as a 'living' document, progressively developed along the months by discussions among scientists with differing formations and states of mind. We have chosen to respect their personalities, at the risk of some lack of homogeneity and repetitions between different passages. Also, incompleteness, inconsistences and antagonisms could not be completely avoided.

This document is not intended to question the goals or the validity of Systems Biology or its approaches. However, it is necessary to clearly differentiate what our Integral Biomathics community is attempting to do from what systems biologists are already doing.

The best of science doesn’t consist of mathematical models and experiments, as textbooks make it seem. Those come later. It springs fresh from a more primitive mode of thought when the hunter’s mind weaves ideas from old facts and fresh metaphors and the scrambled crazy images of things recently seen. To move forward is to concoct new patterns of thought, which in turn dictate the design of models and experiments.

Edward O. Wilson,
The Diversity of Life, 1992.
Harvard University Press,
ISBN 0-674-21298-3.

Summary

The INBIOSA project brings together a group of experts across many disciplines who believe that science requires a revolutionary transformative step in order to address many of the vexing challenges presented by the world. It is INBIOSA's purpose to enable the focused collaboration of an interdisciplinary community of original thinkers.

This paper sets out the case for support for this effort. The focus of the transformative research program proposal is biology-centric. We admit that biology to date has been more fact-oriented and less theoretical than physics. However, the key leverageable idea is that careful extension of the science of living systems can be more effectively applied to some of our most vexing modern problems than the prevailing scheme, derived from abstractions in physics. While these have some universal application and demonstrate computational advantages, they are not theoretically mandated for the living. A new set of mathematical abstractions derived from biology can now be similarly extended. This is made possible by leveraging new formal tools to understand abstraction and enable *computability.* [The latter has a much expanded meaning in our context from the one known and used in computer science and biology today, that is "by rote algorithmic means", since it is not known if a living system is computable in this sense (Mossio et al., 2009).] *Two major challenges* constitute the effort.

The first challenge is to design an original general system of abstractions within the biological domain. The initial issue is descriptive leading to the explanatory. There has not yet been a serious formal examination of the abstractions of the biological domain. What is used today is an amalgam; much is inherited from physics (via the bridging abstractions of chemistry) and there are many new abstractions from advances in mathematics (incentivized by the need for more capable computational analyses). Interspersed are abstractions, concepts and underlying assumptions "native" to biology and distinct from the mechanical language of physics and computation as we know them. A pressing agenda should be to single out the most concrete and at the same time the most fundamental process-units in biology and to recruit them into the descriptive domain. Therefore, the first challenge is to build a coherent formal system of abstractions and operations that is *truly native* to living systems.

Nothing will be thrown away, but many common methods will be philosophically recast, just as in physics relativity subsumed and reinterpreted Newtonian mechanics.

This step is required because we need a comprehensible, formal system to apply in many domains. Emphasis should be placed on the distinction between multi-perspective analysis and synthesis and on what could be the basic terms or tools needed.

The second challenge is relatively simple: the actual application of this set of biology-centric ways and means to cross-disciplinary problems. In its early stages, this will seem to be a "new science".

This White Paper sets out the case of continuing support of Information and Communication Technology (ICT) for transformative research in biology and information processing centered on paradigm changes in the epistemological, ontological, mathematical and computational bases of the science of living systems**.** Today, curiously, living systems cannot be said to be anything more than dissipative structures organized internally by genetic information. There is not anything substantially different from abiotic systems other than the empirical nature of their robustness. We believe that there are other new and unique properties and patterns comprehensible at this *biological* level. The report lays out a fundamental set of approaches to articulate these properties and patterns, and is composed as follows.

Sections 1 through 4 (preamble, introduction, motivation and major biomathematical problems) provide the background. Section 5 describes the issues affecting Integral Biomathics and Section 6 -- the aspects of the Grand Challenge we face with this project. Section 7 contemplates the effort to formalize a General Theory of Living Systems (GTLS) from what we have today. The goal is to have a formal system, equivalent to that which exists in the physics community. Here we define how to perceive the role of time in biology. Section 8 describes the initial efforts to apply this general theory of living systems in many domains, with special emphasis on cross-disciplinary problems and multiple domains spanning both "hard" and "soft" sciences. The expected result is a coherent collection of integrated mathematical techniques. Section 9 discusses the first two test cases, project proposals, of our approach. They are designed to demonstrate the ability of our approach to address "wicked problems" which span across physics, chemistry, biology, societies and societal dynamics. The solutions require integrated measurable results at multiple levels known as "grand challenges" to existing methods. Finally, Section 10 adheres to an appeal for action, advocating the necessity for further long-term support of the INBIOSA program.

The report is concluded with preliminary non-exclusive list of challenging research themes to address, as well as required administrative actions. The efforts described in the ten sections of this White Paper will proceed concurrently. Collectively, they describe a program that can be managed and measured as it progresses.

Keywords: integral biomathics, theoretical biology, biological mathematics, theoretical physics, endophysics, semiotics, observer-participation, developmental biology, neuroscience, natural computing, biocomputing, category theory, logic, positivism, scientific revolution, determinism, non-deterministic chaos, first-person perspective, complementarity, emergence, complexity, holism, reductionism, information, information integration, communication, change, development, hierarchies, scale and hyperscale, self-organization, autopoiesis, internalism, mechanicism, vagueness, class identity, individual identity, biological time, mind-body problem, non-locality, virtualization, distribution, genetic transcoding, neural systems, memory, cognition, consciousness, quantum effects in biology, life.

1 Preamble

Fundamental assumption: all natural objects and phenomena have representations in the language of mathematics. Biology is a subject concerned with the organization of relations. Life is not primarily characterized by its underlying physicochemical structures, but by its entailment relations – by what the physiochemical structures do, and to what end.

Organisms are not man-made machines. Life is not a specialization of engineering; it is an expansive generalization of engineering, subject to regulations of internal origin. To answer biological questions, it is therefore insufficient to follow the reductionist strategy derived entirely from the Cartesian metaphor and Newtonian mechanics. Such a 'watchmaker' approach is often limited to breaking down a complex entity into simpler pieces, to examine the pieces themselves, and then to attempt to understand the organism from a parts-only perspective. It is necessary to revive efforts to advance science beyond such reductionism; its failure is due to the inability of a small surrogate representation to exhaust the real world's complexity. The limits of physicochemical and mechanistic dogma are specific examples of the restrictiveness of self-imposed methodologies. The resulting artificial 'limitations' on science and knowledge are due to the non-generic nature of the methods and their associated bounded microcosms.

The obstruction of the advance of science beyond such limitations is not merely a problem within science; it has left societies floundering in the face of what are now called 'wicked problems', problems that cannot be dealt with by the old forms of science.

Classical computing, framed today in third person descriptions, is often based on unambiguous known algorithmic or rote procedures; it is this lack of ambiguity that makes it precisely suited to modeling mechanisms. A living system is impredicative and self-referential: this is what makes it more than a machine. We might call it a new variety of machine, perhaps a relational machine, as yet, not fully entailed. The introduction of the *self,* the *subject* in addition to the *object*, makes the participation of first person descriptions inevitable. The precision of conventional classical computing makes it unsuitable for modeling impredicativity and its natural entailment of ambiguity. Ambiguity is by no means an infamy: it is a great asset to biology in its redundancy, its ubiquitous degeneracy properties and survivability. INBIOSA will shed light not only on third person descriptions of biology, but also on first person descriptions for both organisms and machines. For computation to be a successful tool in biology, it must go far beyond any strict limitation of currently known algorithms. However several properties of living systems, including impredicativity can be computed, for instance by using typed (polymorphic) programming languages (Mossio et al., 2009).

While we often speak of "mathematics" and "computation" in this INBIOSA White Paper, these terms are not intended in a narrow, classical sense[1].

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[1] In particular, computation belongs to the modern philosophical view of reality in which information assumes place of substance, and computation of the dynamics of its transformation (Collier, 2004).

2 Introduction

The goal of the INBIOSA support action is to devise a long-term research program for naturalistic biocomputation. There are two problematic areas in this enterprise: mathematical techniques, and their ability to enable reflection on biological processes. Currently available mathematical techniques appear to be insufficient to deal with the complexities of biology, and biological processes do not easily lend themselves to traditional mathematical analysis.

The central target of INBIOSA is to devise ways in which these two initially independent domains may be resolved and integrated into a common framework. There are a number of different regimes within which this integration may be attempted. A major theme of INBIOSA is to critically consider each of these regimes to see where common ground may be found. It is not initially obvious how biocomputational integration must, or can take place, but the evidence of the natural world is that such integration is itself natural. While an easy starting place would be to try to extend the reductionist position to include biology, this is likely to be unsuccessful or at least incomplete, and we will almost certainly need to step beyond the Newtonian paradigm (Ulanowicz, 2009; Simeonov, 2010a/b) in search of success. One alternative approach, for example, could be based on a general theory of entangled coherent complex systems, both non-living and living, from quantum computers (e.g. Monz et. al., 2011) to the human brain (e.g. Ehresmann & Vanbremeersch, 2007). Karl Pribram (Pribram, 2001) has proposed that one kind of quasi-quantal neural processing takes place within the 'axonite mesh' between neurons. The associated presumption would be that if entangled quanta can 'calculate' by methods more powerful than Boolean algebras, then entangled nerves can also 'calculate' at a higher level than individual ones. Multicellular systems (animals, hearts, kidneys, brains, etc.) work as unified entities, and exhibit emergent effects, which are not immediately obvious from the properties of their constituent cells.

Biological systems are integrated through their complementary functions and structures, so that they can only be treated *properly* as causally integrated systems. Our mistake until now in biology has been to treat them as if their causal integration matters less than their syntactic integration (as in computer programs). To understand and explain how biological systems work is the task of Integral Biomathics (Simeonov, 2010a/b) and of the INBIOSA project. In the distinction between living and non-living systems, and the consequent generation of *meaning* (Rosen, 1991; Cottam et al., 2005; Gare, 2008; Louie, 2009), the basic questions we ask about *computation* from a revised conceptual framework are:

i) What is computation within the biological context?

ii) How useful is computation for living systems, where usefulness is considered from the viewpoint of the entity performing the computation?

iii) To what extent can a computation be carried out in an organism or an ecosystem with the available resources?

Returning to the quantum mechanical domain, the underlying central question, which may indeed deliver breakthrough answers, is:

> *What can serve as a cohesive factor for making biological beings as they are?* *Can we take quantum entanglement and superposition models from physics and apply them to biology and, vice versa, can we use models of integrated biological systems to model quantum entanglement and superposition? How can we relate the occurrence of a cohesive factor unique to biology to nonlocal simultaneous correlations available in physics in general and in quantum mechanics in particular?*

One associated area of investigation, which has up to now received little or no attention is the possibility that biology makes use of quantum logic without the implication of physical quantum systems (Schroeder, 2009; 2011). We will come back to this issue in sections 5.8 and 7.4.

It is not entirely beyond the bounds of reason that biological processing may rely on large-scale quasi-entanglement. In this case we could postulate that individual cells in an organism are entangled to work in a coherent way. The key question would be to understand the *meaning* of this biological computation and entanglement of the whole organism. But this and other similarly specific questions should be tackled in the context of the two initial difficulties we cited – those of mathematical viability for biology, and of biological process suitability for mathematics. We will address these two aspects in the following sections of this document. We must also come to understand how lower level quantum processes affect other biological processes unfolding on differing scales in the body, flowing up to the level of consciousness and behavior in the lived environment over time. This will be discussed in section 5.2 *Scale and Hyperscale* and in section 5.8 *Quantum Effects in Biology.*

3 Motivation

In the history of science it is noted that Laplace had a checkered career. He seemed to work on physics or astronomy for several years and then drop this and switch to studies of pure mathematics for a few years; then suddenly, he would switch back to physics or astronomy, and so forth for decades (Gillispie, 2000). Laplace was such a productive scientist and mathematician because the two fields were completely integrated in his mind. He derived his mathematical problems from his astronomical and physical researches and his astronomical and physical problems from the regions in which existing mathematical methods failed. So in practice, what Laplace did was to study a physical process, develop a model for the behaviour of the system that would, in turn, yield a set of equations describing the model. More often than not, because Laplace focused on processes that had no adequate physical explanation, he would find that it was impossible to solve the equations needed to model the system. Being a first-rate mathematician, he would therefore refocus his efforts on deriving from first principles the new methods necessary to solve the sets of equations he had invented. This effort often took him several years. Once he had satisfactorily set that new area of mathematics to rights, he would go back to his astronomical or physical studies, apply his new mathematical insights to his models, and see what kinds of new problems these revealed. This story is important in devising a new field of biomathematics: those undertaking the work should understand that, historically, both science and mathematics have provided each other with fruitful problems and methods. Laplace was not a mathematical physicist or a physical mathematician, but both, simultaneously. This integrated (or back-and-forth) view of the relation between science and mathematics is quite at odds with the dominant (and long-outmoded) Comteian positivistic philosophy of science that still predominates among scientists and mathematicians today.

Positivism explicitly posits the notion that science is founded in logic, and mathematics drives progress in the rest of science, so that it is possible to rank-order the scientific reliability of a field by the degree to which it has become mathematized. The increase in "positive knowledge" is always from mathematics through physics to the "softer" sciences. There are two errors in this positivistic philosophy. One is that even pseudoscience[2] can be expressed in terms of equations, (making the pseudoscience no more 'true' than it was when expressed only in words). The other error is to mistake the purpose of mathematization as being primarily a means of validating scientific research. To the contrary, mathematics can provide novel tools for exploring scientific problems. But that said, existing mathematics does not contain all the possible tools that scientists may need. Like Laplace, present-day mathematicians are likely to find fascinating and valuable mathematical problems by learning enough biology to understand where existing mathematical tools fail. From this perspective, mathematics is useful to any given science only to the extent to which it is appropriate to addressing the problems posed by that science.

Simply mathematizing biology using existing methods does not add anything to our understanding of biology unless the mathematics illuminates points that non-mathematical statements of the same models or theories cannot address. Unfortunately, many scientists make their models conform to existing mathematical methods rather than doing what Laplace did, which is to devise an appropriate model and then invent the mathematics to describe it. Thus, historically, "mathematical biology" has not yielded many deep insights. The history of science suggests a second reason that mathematics has not been as useful in the biological sciences as in the physical sciences. Scientists tend to ascribe the power of physical sciences to their mathematization, but the real power has come from the ability of astronomers and physicists to define their problems accurately and precisely enough for mathematical methods to be valuable. The emphasis here is on problem finding and defining. Historically, chemists, biochemists, biologists, and social scientists have rarely been able to define their problems with the precision and accuracy of the physicist or astronomer, making the mathematical investigation of their relatively "fuzzy" problems difficult. Thus, one reason for the lack of mathematics in biology is that the lack of well-defined problems has made the field less amenable to mathematization than, say, physics. Recognizing that categories

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[2] Pseudosciences are often promoted by sects as true sciences with the support of mathematical modeling, thus misleading even serious researchers including biologists.

in non-physical systems are often ‘fuzzy’ is, in fact, what led Zadeh to invent his theory of ‘fuzzy sets’, a major advance for both mathematics and modeling in biological and social sciences (Zadeh, 1965). The degree to which we can define our biological problems accurately and precisely enough to intrigue mathematicians will determine whether we make progress in developing biomathematics, e.g. in working toward defining new forms of dynamic relational sets.

The third reason that biology has so far failed to benefit from mathematization to the degree that physics and astronomy have, is that the mathematics that is used to describe physics and astronomy developed hand-in-hand with those sciences but has not developed hand in hand with biological problems. Laplace is hardly unique in having had hands in both mathematics and physics simultaneously – think of Descartes, Leibnitz, Lagrange, Fourier, Poincare, etc. Unfortunately, the mathematical methods developed to model physical processes do not (in general) illuminate biological problems. Biology is not chemistry, which is not physics. Simple hierarchical reasoning states that we can recognize a new level of organization when the principles, properties and models that worked for the previous level of organization can be reinterpreted and harnessed by the higher level (Weiss, 1971).

Chemistry becomes chemistry (and not physics) at the point where we can ignore the physical properties of the components carrying out the chemistry. We don’t need an understanding of nuclear physics to describe the kinetics of a chemical reaction; we don’t need to know the movements of every molecule in a gas to measure its temperature or volume; we don’t need an understanding of electron shells to explain how DNA encodes genetic information. Similarly, biology becomes biology and not chemistry when we can ignore the chemical properties of the components carrying out the biology. For example, Mendelian genetics was invented without any concept of the structure of a gene, let alone what macromolecular structure encoded genetic information. Darwinian evolution by survival of the fittest does not rely upon any chemistry at all! This is not to say that biological systems are not comprised of chemicals or to deny that they obey the laws of physics, but rather to make the point that biological systems are recognizably biological because they have organizational properties that allow them to carry out processes that cannot be accounted for purely on the basis of the physics and chemistry of their individual components. So, what we need is new mathematical notions and a new concept of computing, but also a number of new mathematical tools, that permit us to model the emergence of new properties resulting in the carrying out of novel processes as a result of innovative forms of organization within complex systems. Or, put more simply, a mathematics which will be appropriate to biology must be motivated by problems that are biological in their origins and nature, just as mathematics appropriate to physics was physical in its origin and nature.

Thus, to develop a new field of biomathematics, we would propose that we behave as a community as Laplace and his colleagues did, by going back and forth between the science and the mathematics, letting each inform the other. Biology has much to contribute to mathematics, especially to the development of new forms of mathematics appropriate to solving the kinds of problems that make biology different from physics or astronomy. And biology-inspired mathematics can be expected to return to biology the same kinds of gifts that physics-inspired mathematics returned to physics. Indeed, not until we abandon the Comteian idea that mathematics should drive science, will biology benefit as it should from mathematics. Reversing the equation, and permitting biology to drive the mathematics (at least half of the time!) may yield us new insights as important as those generated by Laplace and the other physicist-mathematicians who founded their fields. Moreover, it may revolutionize mathematics itself, just as the focus on physical problems motivated many of the great mathematicians of the past.

But Integral Biomathics is not going to be a purely theoretical discipline. Because "simulation" is not only running a discretized differential equation on a computer, and visualization is not only graphical imaging and animation, it will also explore the creation of *new simulation and visualization paradigms* and techniques for biological phenomena. The reason behind this multi-perspective, quantitative-emergent approach is that there are certain emergent features of fundamental processes that cannot be easily described/captured by closed form, differential or any currently known mathematical object or expression. A good example can be found in molecular dynamics (MD). For instance, if we want to computationally assess a macroscopic constitutive parameter such the permeability of a cell membrane with respect to a given molecule, then much insight can be gained by simulating the dynamics of a large number of molecules of the different species involved, whereas trying to find some elegant mathematical equation that will answer the question may currently fail. The same holds for instance in astrophysics where simulation techniques such as smooth particle hydrodynamics are used to study the formation of complex astronomical objects such as a galaxy. In both these examples the emergent complexity is assessed via simulation in which the mutual interactions between the objects themselves are described by simple laws (e.g. Newton's law of gravitation and those of classical electrodynamics). Cellular automata, e.g. (von Neumann, 1966; Wolfram, 1994; Wolfram, 2002; Miller & Fredkin, 2005) are another example of how a simulation tool can produce emergent behaviour by simulating the dynamics of agents that follow simple rules.

Therefore, we consider the development of *new kinds* of biologically inspired simulation and visualization methods as part of the INBIOSA research program from which emergent features can be rigorously analyzed. They constitute part of the intermediate steps towards the discovery of new abstract mathematical tools enabling virtual experimentation, and enable with systems to study complexity and emergence.

4 Major Biomathematical Problems

What kinds of well-defined biological problems exist that seem not to be amenable to current mathematical approaches, or have simply been overlooked by mathematicians who already have the kinds of novel approaches that would open up these biological areas to formal analysis? INBIOSA's collaborators and colleagues have been struggling with *six such areas*, all of which are general enough to have broad implications both in and beyond biology and are therefore potentially worth the effort of a mathematician to explore. All of them, in one way or another, share the common feature that the systems that need to be described combine some type of continuous function with some type of discontinuous function and some add the fillips of vector/tensor, relational and geometrical aspects as well. The mathematical challenge is how to analyze biological problems that currently exist in two or more of these domains thought to be unrelated in orthodox mathematics.

The first problem concerns the modeling of a cell as a dynamic process. The cell itself is a discrete object yet the flow of materials in, out, and through a cell is continuous[3]. Moreover, if one asks at any given time what defines the cell, the details of this description will differ from those at any other time. For example, when a cell replicates, it breaks down its Golgi apparatus, its actin fibers, and various other cell organelles, into the molecular constituents from which they are assembled. These molecular constituents are randomly distributed into the two daughter cells. Both of the resulting cells are still cells of the same species as the parent cell, yet neither has exactly the same number or even exactly the same proportion of cellular constituents as the parent cell or as each other. So clearly there is "variance" in the absolute numbers and in the proportions of the constituents of a cell within which the cell can still function as a cell. Moreover, the rates at which these constituents turn over, are replenished and excreted also vary from cell to cell and from instant to instant. Now, this variance[4] is clearly open to experimental manipulation. One can dehydrate cells and find out how little or how much water they require or can sustain and continue to live. One can destroy particular cellular constituents, or block particular receptors or transporters, and see how these modifications affect the proportions of other cellular constituents in relation to whether, and how, the cell continues to function. So we can obtain plenty of quantitative data. But what do these data mean in terms of what the interactive variances in constituents can be within a living system? The problem becomes even more complicated when we start playing with cellular structures and macromolecules. While there are so many molecules of water or glucose or ATP in a cell that it might be acceptable to model cellular dehydration as a continuous function, one cannot vary the numbers of actin fibrils, Golgi apparatus, mitochondria, chloroplast, ribosomes, nucleoli, centrosomes, chromosomes, etc. as continuous functions. These are discrete variables, with variances that are measured in discrete units.

The mathematical problem therefore becomes one of finding means to utilize all of this information, both continuous and discrete, in an integrated model that lets us understand what the limits of variance, and the limits of life, are for a functioning cell[5].

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[3] The flow of material is actually a flow of discrete particles, but the time flow may be considered continuous. In fact, the discrete/continuous duality does not reflect a fundamental modeling necessity, but the consequence of observer's perspective, (s. section 5.4) and modeling choice.

[4] Under steady-state conditions the cell's total mass must remain constant otherwise it would increase or decrease in size (which is the case when a cell is dividing or differentiating). Barring statistical fluctuations changes over time of some cell products like hormones depend on the context (e.g. signaling from other cell types) that explains (at least partly) the variances.

[5] In this *First Problem* there are actually three sub-problems, where the first one is somewhat unrelated to the other two: i) combining discrete with continuous quantities, ii) explaining their variances and their interrelatedness, iii) discovering the cells' functioning (and non-functioning) parameter ranges. Regarding the third sub-problem, dynamic systems theory, sensitivity analysis and bifurcation theory seem to provide some tools to tackle it.

Secondly, posing the question of what constitutes a cell in this way has provoked interest in set theory as a possible basis of a new biological mathematics. But the current state of set theory seems inadequate in two fundamental ways. First, cells are autopoietic – they form themselves. Indeed, evolutionary theory asserts that cells evolved from primordial aggregates of self-organizing compounds built from even simpler interactive modules, back to the primordial soup. Sets, at least as they exist in mathematical forms, are not autopoietic. Existing set theories use axioms which limit the way sets are defined, for instance by limiting the expressions describing their elements to avoid self-reference, which in turn is a critical property of living systems. Development of a set theory suitable for such systems could be attempted, for example allowing sets to be defined by dynamic rules, including self-referential ones, so as not to produce paradoxes, but to permit autopoiesis[6] (Maturana & Varela, 1980). This is, in a sense, what complexity theory is about (e.g., Kauffmann, 1993), but complexity theory does not incorporate most of the useful features of set theory. Could a mathematics that described autopoietic sets through complexity-like theory exist? Might it shed light on the evolution of the "sets" we call "cellular life" by permitting us to describe continuous functions that produce rules that then limit the entry and exit of possible components of the set, and that can undergo transformations (metabolism) within the set? After all, this is what cells do. So why not develop a mathematics that describes what nature can already do? Another way in which modern set theory cannot be trivially applied to tackle biological problems is because biological sets have the variance property described above. Any given cell must have chromosomes, but their number can vary (as they do in cancers and parthenogenotes) and still be viable; they can have many or few ribosomes and mitochondria and still live; they can accumulate certain amounts of toxins or lose a certain amount of key ions and still function; etc. So in addition to inventing autopoietic sets, is it possible to invent sets that are not defined by specific numbers of constituents, but by variances within which all of these constituents must exist. A bacterial cell that becomes dehydrated may die, or it may sporulate. How can some form of set theory be devised that models the process of switching between stable states when certain variances are exceeded? What, in general, does such a state-sensitive, mathematical set look like? How does it behave? What properties does it have that sets, as currently defined in mathematics, do not? How might these new set properties inform living systems and perhaps even our understanding of social processes, supply chains, and other useful functions? Since the origin of the first protocells/autocells is imaginable, this approach appears reasonable. But since we have no idea about the origin of the genetic apparatus where does that get us?

So one thing that is needed in our new biomathematics is a way to model self-emergent sets (origins of first cells; self-assembly of viruses, etc.) But these self-emergent sets would seem to need the ability to carry out functions (selecting/rejecting

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[6] The mathematics necessary to cover/explain autopoiesis may *not* necessarily require "autopoietic" sets but self-referenced objects. An alternative approach could be to define an object by the transitions rules (predicates) that hold over pairs of objects. This allows under certain circumstances a (static) mathematical description of an object that would self-replicate in simulation space. However, we wish to go beyond these limits.

among possible components; minimizing what a physicist thinks of as free energy; etc.). One possible focus of a new biomathematics would be to invent an appropriate theory of self-emergent sets that can carry out functions within variances. Such a theory would preferably incorporate the work that has been done on understanding hierarchical systems' emergent properties, complexity theory and so forth. Such a mathematics would therefore be extraordinarily integrative, a point to which we will return.

Thirdly, a biological problem related to set-like properties is that organization strictly limits variance through the formation of modules in a manner that requires diligent ways of using probability theory. Imagine a clueless, blind "watchmaker" of the sort that Richard Dawkins likes to put in charge of evolutionary processes. But let this watchmaker carry out a process first investigated by Herb Simon in one of his little known and under-appreciated essays on evolutionary processes (Simon, 1981).

Combining Dawkins's and Simon's watchmakers produces the following scenario that exemplifies one of the critical problems that needs to be addressed in the origins and evolution of life. Imagine two watchmakers, the first of whom must randomly assemble 25 parts in order to put together a "watch". This completely ignorant watchmaker must explore every possible combination of the 25 parts he has in front of him, which is to say 25! or about 1.55×10^{25} possibilities! If it took a single minute for each of these possibilities to be explored, our watchmaker would not succeed in making even a single watch within the lifetime of the universe! Moreover, because he's just a random assembler and cannot learn from experience, he has to explore all these possibilities each and every time he tries to build a watch! Clearly, such an entity working by such a process would, for all intents and purposes, never succeed, making *de novo* evolution of life virtually impossible.

But what Simon first recognized, and Root-Bernstein has developed (Root-Bernstein & Dillon 1997; Hunding et al., 2006), is that an equally clueless, blind and random watchmaker who uses stable modules built on the principle of molecular complementarity would succeed, and astoundingly quickly! Simon's model assumed that the watchmakers knew how to make a watch (a clearly un-biological assumption), from which he derived the following equation: the time required for the evolution of a complex form from simple elements depends critically on the number and distribution of potential intermediate stable forms. In particular, if there exists a hierarchy of potentially stable 'sub-assemblies', with about the same span, s, (i.e., the number of parts or components required to form each stable subunit) at each level of the hierarchy, then the probability that a subassembly process will be completed within any given time, T, can be expected to be about $1/(1 - p)^s$, where p is the probability that the assembly process will be interrupted during time T. Clearly the less stable each step is in the assembly (i.e., the greater p is) and the larger the number of components that must be assembled to achieve a complete assembly (s), the less probable any particular assemblage is to evolve. Conversely, the more stable each step in assembly is (i.e., the smaller p gets) and the smaller the number of components required to produce a completed assembly (s), the greater the probability an assemblage is to evolve (Simon, 1981, p. 203).

The implication of Simon's model is that we should therefore expect evolution to be characterized by the selection of semi-stable modules arranged in a hierarchical fashion that minimizes wasted time, effort and resources. This is precisely what we do see. But Simon's model is not an accurate portrayal of the biological problem.

The problem with Simon's model is that evolutionary watchmakers do not know how to make a watch and must search randomly for stable modules. Fortunately, molecular complementarity between compounds naturally forms such stable modules, so these come into existence in just the kind of random fashion that needs to be assumed. So once again assume our modular watchmaker needs to make a watch from 25 pieces, but also assume that she makes her watches in five stable sets of five ordered parts. Stable five-element modules could be built by exploring only 5! possibilities or just 120 combinations. Then our modular watchmaker would need to explore randomly the 5! possible combinations of these five modules, or another 120 possibilities. Altogether, the modular watchmaker explores only 720 = 6! possible combinations, which, if they could be explored at one possibility per minute, would yield a watch every two hours. Quite a difference from 1.55 x 10^{25} minutes to explore the original 25! combinations! The impossible becomes highly likely[7] (Root-Bernstein, 2012)!

Now, obviously the advantage of modularity is not as great as just stated for a real, molecularly complementary system. Firstly, stable modules might not result from any given set of five components so that our modular watchmaker may have to explore more sets than we have assumed. Secondly, the specificity of module building is not perfect and some non-functional modules will also likely be stable, confusing final assembly. We can also assume that the proper modules will out-compete the improper ones in producing complete watches, but this may not be the case if improper modules, inefficient at assembly as they may be, so out-number the proper ones as to swamp them. Finally, there is no biological reason to assume that stable modules have five components – the number could vary from two or three to two or three dozen per module. And this is exactly the point at which current probability theory is improperly applied. How do we model the kind of system we have just proposed in which modular sets are formed in a reversible manner, may contain variable numbers of components, and compete with each other in a probabilistic scenario? Again, such a kind of mathematics must exist, since Nature already performs these functions, but what does that mathematics look like? Perhaps it is not a matter of the non-existence of certain types of mathematics, but rather that the appropriate type of mathematics has not been applied to these questions. We do not know. What matters is that these questions are still looking for mathematical answers.

The importance of being able to address this modularity-probability problem is illustrated by the fact that the formation of complementary module building within complex systems can prune out huge numbers of possibilities at each step of hierarchical assembly. In general, the greater the number of pieces, and the more modular steps involved in the process, the more efficient the process becomes. Given the mathematics of these probabilities, there must be some optimal number of pieces per module, and an optimal number of modules per functional unit and an optimal stability that must be attained. All of these variables must be optimized so as to maximize

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[7] However, it is necessary to pay attention to the principle of minimum of three levels of modules in hierarchy theory (Salthe, 1985): more is fine, but fewer – logically unworkable.

the rate at which functional modules are generated while minimizing the number of possibilities that must be explored. Our assumption is that nature has already solved this problem. Analyzing naturally occurring modular hierarchies for rules of optimization might therefore have vast implications not only for understanding the evolution of life, but also, as Simon (1981) notes in his original essay, for the most efficient design of chemical, technological, and even human systems of organization.

We have already alluded above to various biological problems that require working at the interface between continuous and discontinuous functions. One might posit that most of biology consists of sets of problems existing at this continuous-discontinuous interface. For example, chemical neurotransmitters (working continuously) release a single electrical discharge (occurring discontinuously); individual organisms can potentially interact more or less strongly with other individuals by means of chemical messages (continuously variable) that determine whether they develop as many individuals or transform themselves into a single super-organism (a biofilm). How can we mathematically handle interactions that may vary continuously but act on a small set of definable individuals? These are not amenable to modeling solely using mathematics that assumes continuous functions. We are particularly interested in these continuous-grainy problems from the perspective of complementarity. Any given species of molecule may interact more or less with any other type of molecule, so that in a very diverse mixture of molecules, a large number of weak interactions may overwhelm a small number of strong ones. The same can be true among sets of cells or in species or social interactions that involve what Csermely has called ‘weak links’ (Csermely, 2006) and Root-Bernstein calls ‘complementarity’ (Root-Bernstein & Dillon, 1997; Root-Bernstein, 2011). There appears to be no orthodox way to model such systems mathematically, yet such systems occur at every level of biological complexity. Again, since biological systems are able to integrate units with continuous functions, surely there is a mathematics that is appropriate for modeling how biological systems do so.

A fourth set of problems relates to the key properties differentiating a living system from a non-living one. Living systems involve directional processes[8]. Their physical environment, however, is characterized by non-directional properties. In other words, we have two different models at the same level one for living and one for non-living matter. One doesn't need vectors to describe chemical reactions in a test tube, but one does need vectors to describe biochemical networks. Hence, a characteristic feature of biological systems is that some of their properties involve transformations from scalar to vector quantities. Some very interesting and important problems lie at the interfaces between the physical world and the biological one; they require mathematical means to describe how vector processes interface with scalar ones. For instance, how does

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[8] For clarity, in what follows in this paragraph and in the next ones, we will often name by "vector" the directional properties and by "scalar" the non-directional ones, discarding that we are outside the required mathematical context in which these terms are usually defined. Thus, the use of these terms and several other ones should be understood from our context rather than from the algebraic one. Furthermore, it should be obvious when the terms refer indeed to the mathematical context.

random diffusion get converted into directional ion transport? We need a single integrated model, but not different ones for each domain.

We know from elementary algebra that multiplying a scalar by a scalar gives a scalar; and multiplying a scalar by a vector gives a vector; and multiplying a vector by a vector gives a scalar (V.V) or vector (VxV); but how does one get from purely scalar quantities to a vector one? Is this another kind of tensor *transformation*? How do racemic mixtures of chemicals give rise to chiral handedness in living systems? How does a chemical neurotransmitter signal (scalar diffusion) become a directional electrical signal? How does one evolve from random diffusion (scalar) to facilitated transport systems (vector)? How does one evolve from all possible reactions occurring (primordial soup, laboratory bench) to reaction pathways (vector/tensor)? In all these cases (and many more) scalar processes result in vector ones, yet mathematics generally treats *either* scalar quantities *or* vector and tensor quantities, but not the transformation of scalar to vector and vice versa. In differential geometry, scalars, vectors, tensors and matrices are considered as examples of multilinear maps, and so are graphs in the usual definition with only one arrow between 2 vertices, which is easily translated into a tensor or a matrix. Could a new operator be adapted for living systems? Or we need a new mathematical formalism for this purpose? Or should we still approach problems in differentiated way? Perhaps we may well need to apply different types of mathematics than are currently applied. Recall that the tensor concept emerged out of the necessity to have vector transformations. The issue with matrices and determinants used to solve systems of (polynomial and differential) equations is similar: they all emerged out of the necessity to solve particular problems. Mathematicians like Newton, Leibniz, Gauss and others were clever enough to discover the repeating pattern and simplify the solution. Now, we have another set of biological problems, e.g. in the domain of genetic regulatory networks, where one can trace a complex map of enactions and transitions between certain protein chains (objects) – well modeled by directed (hyper)graphs – but then at a certain point in time these objects suddenly turn into processes or entire networks of them (autopoiesis!?) revealing some hidden variable operational semantics (Bohm) that completely inverts the picture, so one has a "jump" or gap in the overall description. How to explain that? The object becomes a process, and then again the reverse situation at some point later. What we may need is a mathematics in which one assumes that every scalar quantity is actually a pair of opposite vectors (or tensors) that normally sum to the null vector (or tensor). For example, in all vector/tensor systems in biology of which we are aware, an inflow of one kind of molecule is always balanced by an outflow of another; selection for right-handed sugars occurs only where there is concomitant selection for left-handed amino acids. So is it possible that in fact the overall balance of vectors/tensors in a biological system is always conserved and that the local manifestation of one half of a vector/tensor pair (e.g., inflow) is always balanced by the expression of the opposite vector/tensor pair (outflow) in the opposing process? Is there a mathematics that can help us investigate the rules that might govern such processes by integrating vector/tensor reasoning into the kinds of set thinking postulated above so we can understand how molecules move directionally through cells as a result of metabolic processes, etc.?

The fifth type of problem involves the linkage of form and function. Biologists who deal with almost any level of biological organization have recognized that natural selection attempts to optimize forms to carry out particular functions, but since novel functions evolve from existing forms, these attempts may be seriously limited. The mathematical challenges involved in attempting to model these form-function interactions are far from trivial. Knot Theory (Manturov, 2004) allows study of the form of proteins, in particular protein folding (Kauffman & Magarshak, 1993; Taylor, 2000; Martz, 2000), but we do not have good geometrical tools that can easily model complex processes in embryological development. Fractals and other forms of mathematics that generate lovely images that look like the final products of some of these processes (e.g., the branching structure of the bronchioles in the lungs) but share nothing of the actual biological processes that give rise to these structures. But the very fact that the final outcomes of these images look similar suggests that they do share something in the functional and structural organization, even if we do not understand what it is. Our mathematical geometries generally do not illuminate the processes that give rise to biological geometries, but only their outward forms. More importantly, the interesting thing about biological forms is not their geometries per se, but the ways in which these forms are reifications of the biochemical *processes* they carry out or make possible. For example, it has become evident that the folding of chromosomes is a prerequisite to bringing together genes that would otherwise be spatially separated; and that spatial proximity permits the rapid diffusion, and control of interactive gene products that would otherwise be unable to interact in a reasonable biological time frame across an unfolded genome (Junier et al., 2011).

But what kind of mathematics would make it possible to model simultaneously the effects of geometry (spatial structure) on continuous functions such as diffusion, that in turn regulate on-off gene regulatory switches that act discontinuously or digitally? Similarly, in developmental biology, we now have excellent data concerning the sets of genes that must be turned on and when they must be activated or inactivated in order to produce proper embryological development (e.g., Carroll, 2005), yet the discrete information generated from combinations of individual genes is expressed as a continuous flow of proteins and hormones that produce gradients which must be reified as organized groupings of cells that have a specific form. So once again, embryology is stymied by the lack of mathematical approaches that can link discrete, continuous and geometrical information.

Conventional approaches to these sorts of problems rely on modeling one aspect of the problem with one form of mathematics, switching to another sort of mathematics to address the next aspect, and to a third one to describe yet another. All this switching is an indication of how difficult it is to apply our mathematical tools for addressing these problems. Biological systems function at all of these levels simultaneously, so why cannot our mathematics?

We maintain that it is not the biology that is too messy to be modeled in these cases, but the application of orthodox mathematics that is inadequate, because it is inappropriate for addressing these sorts of biological problems. This is why we need a new biomathematics! Indeed, we speculate that complementarity might be the solution to both the biological and the mathematical problems here. What we seem to need are the means to describe all of the biological problems listed above as manifestations of a single problem that can be examined using a single, (new) type of mathematics.

To summarize, our contention is that the reason that biologists have failed to develop a viable set of mathematics methods appropriate to solving biology's problems is that we have relied too long on mathematics developed to model physical problems that are intrinsically different. The assumption has been that biology can be reduced to chemistry and eventually to physics, and therefore that a physics-derived mathematics should be sufficient. But hierarchy theory suggests that reductionism can never explain how novel properties and processes emerge. Biological entities have properties that are different from chemical and physical ones and that require novel mathematics for their description.

Thus, what we need is not more detailed physical models of biological systems that can handle greater and greater amounts of detailed data from increasingly fine-grained studies of the components of systems, but ways of identifying the biological properties that are as unique to such complex conglomerations as temperature is to a set of molecules. What we have lacked, in short, is a uniquely evolutionary mathematics that deals with the emergence of organization from non-random selection among replicating variations within complex populations.

The challenge to a novel biological mathematics, or biomathematics, is to invent new mathematical tools (or to make effective use of existing ones), which are able to handle such emergent properties and organizations. This will allow the development of a biologically relevant theoretical framework integrating concepts of continuous mathematics with discrete mathematics, algebraic formalisms, abstract calculi, logics and topological/geometrical principles in a novel biologically relevant framework we call **Integral Biomathics.**

The sixth and final type of problem deals with multi-scale integration of mathematical models and the study of emergence. It is concerned with the development of a set of theories that cut across multiple spatio-temporal scales of organization. In fact, such a kind of mathematics, which is capable of unifying the different domains of mathematics, already exists: Category Theory (cf. Section 7.6.1). It allows an approach to the five types of problems mentioned above. We believe, as Charles Ehresmann noted in 1966, that mathematics "is the key for the understanding of the whole Universe, unifying all human thinking" and that "the theory of categories seems to be the most unifying trend today" (Ehresmann, 1966). In the past 50 years new branches of Category Theory (CT) have been further developed: monoidal categories which generalize tensor calculus and are used for instance in Categorical QM Semantics (Abramsky, 1996; Abramsky & Coecke, 2007) and Quantum Picturalism (Coecke, 2009); higher categories and sketches which Charles and Andree Ehresmann introduced and were later modified and developed by others (incl. their research students) leading to completely new sub-domains of category theory with applications in computer science and in the foundations of physics. Some of the above problems are raised in the Memory Evolutive Systems (MES; cf. Section 7.6), (Ehresmann & Vanbremeersch, 2007), which are based on a *dynamic* theory of categories incorporating time. Indeed a MES is "not" a category, but an "Evolutive System", i.e. *a family of* *categories indexed by time*, with transition partial functors between them modelling the changes over time, each category representing only a snapshot of the configuration of the system at a given time. The transition functors allow consideration of the dynamic aspects. Thus, Evolutive Systems can be called "changing category" with time. What makes MES adapted for modelling living entities is not just that they are ES (it could also be the case for "mechanisms"), but their multi-agent multi-temporal self-organization, with the interplay among their agents (called Co-Regulators, CR) and its capacity of learning based on the formation of a flexible though robust and plastic memory[9]. However for MES to become a good formal methodology it needs to evolve like a living system itself, otherwise it would be a dead end. Further, it is already a living system itself, thus able to be enhanced and adapted to reflect the nature of the most recent findings in biology in order to prepare for the discovery of new ones. This will be also the case in future, for we are challenged to build Integral Biomathics on solid foundations. So, even in the best cases, MES will not remain the same in the future. We may also experience some surprises on the way. Thus, the sixth and last type of problem outlines some ideas, which give the INBIOSA incentive a push toward a real (and probably completely different) theory of living systems, cf. section 7. We are aware that the above arguments are perhaps not sufficient to firmly underpin our position prior to discussing the above six major problems within this short 12 months project. Usually, scientific discussions of that kind take years. We will need time to systematically analyse all proven theories, postulates, facts and assumptions underlying this rough outline of a research program in order to "clearly state" (as some of our discussants requested) the INBIOSA "roadmap". Or the roadmap may need radically redrawn, because of new insights encountered along the way. The reader may also criticize the many overlapping issues in this section, since

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[9] The above mentioned transformation from scalar to vector could correspond to the 'jump' from process to object, and vice versa, done in MES to construct the landscape of a CR, and later realize the selected procedure. Indeed, the landscape of a CR at a given time t is a category which has for objects the links f of the system which transmit information to the CR around t: thus the passage from the system to the landscape of a CR transforms information processes f into objects. And conversely, the procedure that the CR selects is an object Pr (in the memory), which is realized through its commands to effectors, thus transformation of an object Pr into processes. Let us note that categories consider both objects and processes (as links between the objects), and, through the colimit operation, transform patterns (= subnetworks) into higher objects. The situation is still more complex in 2-categories, where the same element can be seen either as an object or a process. A 2-category K is a category in which the sets Hom(A, B) of links from A to B are equipped with a composition law transforming them into categories (with some coherence axioms). Thus an *object g* in the category Hom(A, B) is at the same time a link from A to B in K, hence can be seen as a *process* between them. Thus, depending on how it is looked at, g 'jumps' from being considered as an object to a process and vice versa. However, there might be other explanations for such phenomena, e.g. the WLI's shuttle/netbot duality principle (Simeonov, 2002), which is closely related and complementary to MES.

usually major problems of ambitious programs are defined as disjoint (although related, as e.g. in (Hilbert, 1902)) entities. But this is really entered "terra incognita" and only recently started. Thus, elaborating the details of the above six problems will be continued in a future follow-up project.

In conclusion, we feel compelled to think that **Integral Biomathics** may revolutionize mathematics itself by proposing mathematical models based on a recently developed domain of mathematics (Category Theory) that integrates (through fundamentally simple insights) disparate areas of both mathematics and the sciences. Since we have to think about biological systems in all of these ways in order to model them, and since biological processes are intrinsically carried out in these integrated ways by Nature itself, it seems logical that real and useful connections must exist within the mathematical formulations of these natural processes as well. Indeed, as we have indicated, we believe that biology is just one of many such sets of emergent properties resulting from spontaneous organization within complex systems. As a consequence, the principles that are derived from our studies of biomathematics should apply to an understanding of how novel properties can emerge in complex systems of any kind, whether ecological, social, behavioural, technological or economic. Thus, just as the Scientific Revolution provided us with physics-based mathematics that made possible the investigation of whole new realms of science, so can we expect the development of a biology-based mathematics, **Integral Biomathics** (Simeonov, 2010a/b; Simeonov et al., 2011), to have equally far-reaching and revolutionary effects.

5 Issues Affecting Integral Biomathics

There are a large number of specific issues or difficulties, which impact directly or indirectly on the development of Integral Biomathics. The following list is not exhaustive, but provides an important starting point in constructing the boundary conditions within which a mathematical description can be formulated.

5.1 Complementarity

Possibly the primary defining character of biological systems is complementarity. This, in itself, is sufficient to emphasize that biology must be treated differently from physics or chemistry, where although complementarity can and does exist, it is less critical. Mathematically, complementarity will provide the biggest challenge in the conception of **Integral Biomathics**.

One sort of complementarity is methodological, enabling relational data to emerge through dialogical processes that juxtapose different mathematical approaches (both static and dynamic), as embodied within new simulation and visualization methodologies. The complexity of biological functionality necessitates the employment of a multi-perspective set of mathematical approaches. Such approaches can be realized by articulating a set of relations and interactions between the differing branches of mathematics that come into play, as well as by developing new forms of mathematics driven by the biology at hand. Another kind of complementarity is that of investigated objects and processes. It is comparatively rare in biological settings to find a process or phenomenon, which is independent from all others and the forms in which complementarity appears are many and varied. When we observe the ways that molecules and systems interact to create complexes, whose emergent properties are unpredictable from their individual components, then complementarity resembles Escher tillings, in which each line defines two forms, and the overall design is different from the sum of the parts. Another way complementarity can appear is more like the way physicists use the term, where something can be described both as a wave and a particle. It is important to remember that Niels Bohr's position was that ideas of complementarity should not be restricted to particle-wave duality. Complementarity reminds us that we must cohesively integrate actor-centered first person descriptions and impartial third person descriptions in any overview of biology.

Any successful formulation of **Integral Biomathics** must take account of apparent dichotomies like that at the intersection of reductionism and holism. Ideally, such a formulation would be capable of re-casting this, and other dichotomies, as complementarities, thus avoiding inherent or unintended paradoxes. An important aspect of this relates to individuals, groups and evolution. Is there a way to look at natural selection from both individual and group selection perspectives that yields a new complementary model more powerful than either of them alone[10] (Fodor & Piattelli-Palmarini, 2010)? And could this lead, as it did in quantum theory, to fascinating new conundrums – such as a 'Heisenberg's uncertainty principle for biology' – in which, for example, it would only be possible to explain microevolution based on individual selection and macroevolution based on group selection, and that a population consisting of both individuals and groups would be amenable to both types of analysis, but could not be completely described by either?

5.2 Scale and Hyperscale

Confusion abounds as to the character of system *scale*. Most usually this concept is uniquely associated with its counterpart of *size*, but this often results in a complete misunderstanding of the role of scale and of its implications for system operation and function. Unfortunately, in the information sciences, the idea of scalability refers to a capacity to change the size of a system or network without running into unforeseen or undesirable situations – without any scalar effects appearing.

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[10] For instance, the Multiplicity Principle, MP (Ehresmann & Vanbremeersch, 2007) represents such a kind of complementarity: the same function can be realized by non-isomorphic complexes with the possibility of 'switches' between them. It is at the basis of the emergence of complex interactions between complexes A and B not reducible to interactions between the components of A and B. And the existence of complex links is the characteristics for the emergence of non-reducible objects of complexity order >1, i.e. complexes that have emergent properties unpredictable from their individual components but dependent on the global structure of lower levels.

Unfortunately, once more, the isolated Boolean nature of purely digital systems explicitly eliminates any local-to-global effects: in their instantiation as information processors, digital systems *never* exhibit real scale, no matter how big they may become. Much is made of the possibility that a global intelligence could develop, or be developed, *within* the Internet. This is, unfortunately yet again, formally excluded for the same reasons, although it *could* be – and possibly currently *is* – a reality for the extended global system of {Internet + users}. Intelligence is a vitally important feature of any biological system. It constitutes at the very least a capacity to operationally relate the lowest organizational level of an organism to a higher organizational level, and/or levels, in support of the organism's survival. Leaving aside for the moment *how* a higher scalar level of an organism may emerge, this transition is always associated with a reduction in the available degrees of freedom, and it naturally takes place through a region of state space (or, rather, *scale space*) of great complexity[11].

Consequently, it is virtually impossible to model mathematically a *single* ('local') scale-change in an organism without also taking account of its global properties. Although the operations characterizing an organism at a single scalar level, e.g. that of biological cells, may at first sight appear intractable, the *real* challenge is to somehow model the relations between even adjacent scales. The inter-scalar 'regions' of an organism are archetypically complex, and multiply fractal. Accordingly, any approach to their understanding requires close attention to complexity theory. If we assume that individual scalar levels can be at least approximated by Newtonian representations, then the inter-scalar regions are more closely related to quantum-mechanical superposition-and-collapse: first a superposition of all the 'possible emergences' (Yardley, 2010), followed by a collapse to the most suitable one. In an information-processing context this *birational* character may be ubiquitous. Pribram has suggested a related model for the interaction of neuron groups (Pribram, 2001), where the neural dendrites and nucleus may be represented by some kind of (classical) summation of information, and where the axonite distribution of the result is transmitted to following neurons by a '(real) simulation' of quasi-wave transmission and 'collapse'. Another interesting theory of fractal space-time and scale relativity for biology was presented by Nottale and Auffray (Nottale, 1993; Auffray & Nottale, 2008; Nottale & Auffray, 2008).

Living systems develop into multiscalar assemblies whose organizational structure has much in common with conventional ideas of both *hierarchy* and *heterarchy*. However, where the usual concept of hierarchy imposes one of two forms – *scale hierarchy* or *specification hierarchy* – living systems appear to develop into a form which can most usefully described as a *model hierarchy* that has been described as "a

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[11] By 'complexity' here we refer to Rosennian complexity of real systems, and not the Kolmogorov complexity, which appears in digital information processing. However the Kolmogoroff complexity can be generalized to hierarchical systems such as biological systems to measure the 'real' constructive complexity of a component; and it has been shown that the Multiplicity Principle (formalizing the degeneracy properties of living systems) is necessary for the existence of such higher complexity (Ehresmann & Vanbremeersch 2007), which contradicts a "pure" reductionism.

specification hierarchy constructed in terms of scale"[12] (Cottam et al., 2003, 2004). Here, each level of the (quasi-)hierarchy represents the entire organism at a different scale. Whereas scale and specification hierarchies are usually referred to as *abstract* human constructions, a model hierarchy appears to successfully represent what a living system *itself constructs*. Each level of such an assembly is partially enclosed and partially in communication with its neighboring scales, and the entire assembly forms a 'self-correlating' whole of partially autonomous scaled 'sub-systems'. This type of structure not only subsumes the idea of *hierarchy*, it also subsumes *heterarchy* through the variable nature of its partial inter-scale communication and consequent variable scale autonomy. The 'traditionally' problematic aspect of hierarchy is how to represent the *emergence* of a structure's new higher scale level by 'upscaling' from a lower one. This 'transitional' upscaling in living systems appears to be a generic form of quantum error correction[13], where local system information is added to a description of the initial level to focus targeting on the higher one. Close examination of the properties and features of living systems over the last two decades has indicated that this type of Newtonian-plus-quantal 'two-stage process' characterizes *all* 'transitional' upscaling processes, whether in biotic or abiotic 'systems'[14]. This must, then, constitute a central issue in any approach to creating a mathematical scheme for biology *per se*.

However, as it stands this is insufficient, for it offers no advice at all about how changes in one level may impact on its lower neighbor. If we take Rosen's sole reference to scale systems as a lead, it is unclear exactly how a suitable mathematical scheme may be formulated, because to do so requires us to address how to mathematically differentiate or integrate a complementary pair! Nevertheless, more elaborate categorical tools (such as sketch theory and its application to the complexification process) can provide some answer to this question (Ehresmann & Vanbremeersch, 2007).

At the very least, any representation of a living entity, for example of a biological cell, must take account of these aspects of scale. Although many informational properties of a cell may be derived from experiments with cellular cultures, this in no way addresses the cell's internal workings, and a great deal of expertise and imagination will be required if we are to 'construct' a link between these two, even if only conceptually rather than mathematically. As seen from outside, an organism will always appear to be a set of properties which operate at a number of different scales, and although we can attempt to model these in a 'global' representation, our 'access' to internal scales will always be partial in nature and dependent on the extent to which our informing experiments disrupt the organism's 'closure' (Cottam et al., 2000).

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[12] A citation of Stanley Salthe, who also added here when reviewing this paper: "Some have proposed that diachronic processes, like evolution or development can be represented using the specification hierarchy, while any stage picked out for examination would have scale hierarchy form".

[13] A suggestion originally made by Walter Schempp.

[14] Technically, all 'systems' 'include' life, and we must be careful how we refer to abiotic 'systems' within their abiotic/biotic environment.

In our daily lives we view entities in our surroundings in a similar manner – as a loose conglomeration of both 'visible' and 'imagined' multi-scale properties and processes. Here again, two decades of research have indicated that this *hyper-scale* 'picture' (Cottam et al., 2006) is not only characteristic of the way we view an entity, but that it is intimately associated with the way an entity itself builds up its very nature. Not only are the different scales of an organism only indirectly accessible from an outside platform in a 'vague' manner, their internal inter-correlation is *itself* vague – the result of 'integrating' its different scales across a number of internal levels. Thus, scale, and this difficulty of inter-scale transit, must occupy a prime position in any attempt to model biosystems. The viability of any mathematical approach must be judged by its ability to address scale issues as they unfold in time. It is far from clear that this will be possible from either a purely physics-based approach or a purely biology-based approach. Life itself appears 'automatically' within Nature, and consequently it should appear 'automatically' from any realistic model of Nature. Rather than beginning from a purely biological ground, it seems that the best route would be to first create a modeling framework, which is independent of any 'biotic or abiotic' distinction – to create a framework, which is not restricted by the constraints of either physics or biology. Such an enterprise, therefore, must encompass two quasi-independent features in relation to a specific target: first, a foundational framework within which Newtonian and quantal viewpoints, and their more local derivatives, can successfully coexist; second, a mathematical formulation which addresses features of current interest. It is most unlikely that a single general mathematical formulation will be sufficient for all purposes[15]. Instead, panoply of different techniques will need to be interlinked in **Integral Biomathics** through the foundational framework, to provide access to a useful range of system properties. In particular, defining operative sets of relational properties, drawn from the juxtaposition and future unification of differing mathematical approaches, applied across multiple scales, will become a focus of articulating methodological complementarity.

5.3 Class Identity vs. Individual Identity

Biology is grounded on the maintenance of molecular organization *(class identity),* at the cost of constant variation in the constituent molecular subunits. Low-level biological processes do not follow a rule of 'one molecule, one effect', but 'one continuation of molecular presence, one effect', where individual molecular presence is often very short-term. For instance, consider a biological organism such as a human egg cell, containing about 30,000 genes, which encode protein molecules. Roughly 3,000 genes encode specific proteins called transcription factors that regulate RNA transcriptions. These transcription factors uniquely determine when genes will be turned on, for their expression, and turned off, while at the same time orchestrating an exquisite network of transcription-sequence regulation. How is it possible for one transcription-factor molecule for every ten genes (on average) to adequately

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[15] Rosen has pointed out that 'real' complexity could only be accurately addressed through an infinite assembly of formal techniques.

regulate the expression of each one of those ten genes in the succeeding developmental process?

A clue to the answer to this question can be found in the observation that typical genomes in cells contain extensive non-coding, regulatory regions, and that these regions can act as enhancers, silencers, insulators, and promoters of the genes. If the expression of each gene is regulated by a combination of many different transcription factors, the accompanying combinatorial control may be competent enough to form a consensus among the participating transcription factors as to whether or not the gene in the target will be expressed, and when.

The flow of time involved in the developmental process can be made explicit by referring to the input-output relationship between transcription factor concentrations and the rate of protein production from downstream genes. Although noise latent in the transcription factor molecules in the input is random and rapidly varying, due to the stochastic nature of each biochemical reaction involved, this does not imply that similar randomness and rapidity would also apply to the rate of protein production of the output downstream. A relevant experimental model indicates that fluctuations in the output level of the protein molecules are much slower than those of the input level of transcription factor molecules (Rosenfeld et al., 2005; Pedraza & van Oudenaarden, 2005). This suggests that there must be some robust scheme for generating such slower fluctuations, in which the underlying organization can serve as a standard to which the passage of time in the form of fluctuations can be referred.

The binding interaction between the transcription factors and the DNA molecule to be transcribed is rather weak (of the order of 4kJ/mol or less) due to the underlying van der Waals forces. Consequently, a transcription factor molecule can easily be detached from the DNA by thermal fluctuations at ambient temperature. If there are sufficient transcription factor molecules in the neighborhood, however, the binding site can easily be ‘replenished’ by another similar molecule. The functional unity of the binding site is thus effectively maintained in an uninterrupted manner, even though the individual transcription factor molecules are constantly exchanged (‘touch-and-go’). This functional unity may help to suppress the rapid fluctuations associated with the frequent exchange of input transcription factor molecules.

This kind of the ‘touch-and-go acrobatics’ is ubiquitous in biology, making *class identity* far more relevant than the *individual identity*, which characterizes typical physics or chemistry investigation (though class identity plays a role in statistical physics and in thermodynamics). *Class identity,* corresponding to the ideas put forward by Elsasser (Elsasser, 1981) and Bateson (Bateson, 1972, 2002), must become a cornerstone of Integral Biomathics.

5.4 First Person Perspective

Classical science is based entirely on a third-person perspective of Nature. This is the basis of its objectivity, as a way of developing representations of reality, which are both independent of human observer and reproducible. This is arguably the central strength of *science* and of its child *technology*, and it depends on the central assumption that the entities or processes which it studies are incapable of initiating action, that they are unconscious and to that extent inert.

The picture obviously changes when we move to the examination of human affairs, where we assume that ‘free will’ based on first person perspective is extant (or at least there is something which from outside resembles ‘free will’). This is a major problem, which faces practitioners of the social sciences, that although reliable data may be obtained for populations, this is not the case for individuals. Here again, *class identity* is of overriding importance.

The question which now faces us is whether, in developing an **Integral Biomathics**, we should permit the inclusion of first person perspectives or not? Historically, the study of biology has taken the same line as physics and chemistry, in insisting that third person perspective alone should be taken into account. Philosophically, this has corresponded with the view that mankind is unique in its ‘free will’, and that consequently the non-human first person perspective could be ignored. We can permit ourselves no similar luxury. Clearly we should include first person perspective at the level of complete organisms: but at the level of biochemicals? Integral Biomathics will need a well thought out internal framework to take account of differences in the importance of first person perspective right across the multiple scales of biology. The example of clock-control by *cyanobactrium Synechococcus* cited below suggests that care must be exercised even at low levels of organization.

Why do we need a First Person perspective?

Probability theory is a branch of mathematics concerned with assigning a numerical value (a probability) to a possible event. There are two main approaches to this problem, on the one hand, the frequentist view which studies probabilities as frequencies, i.e. the ratio of the times the event occurs over a test series, and on the other hand, the Bayesian view, in which probability is a measure of the degree of belief that an event will occur (Jaynes, 2003). While the first approach is externalist, it measures a "hard fact", frequency, which is "out there in the world", the Bayesian approach to probability is inherently internalist (mental) because the probability of an event is always conditioned by the prior knowledge we have in the moment we make the prediction. Thus, the Bayesian or mental approach to probability is on the basis of both the information we have (degree of belief) and the information we lack (uncertainty), rather than as the outcome of a repeated series of experiments. The frequentist view of probability can work in those situations in which everyone has the same information, for example when we are told that the probability of flipping a coin with the result head is 50%, it is possible to perform that experiment a number of times and arrive at the conclusion that 50% is the limit value, so the more times one flips the coin, the closer will be the outcome to the 50%. But for statements like "the probability of rain tomorrow is 50%" the frequentist approach objectivist point of view is ill suited because it cannot be tested. There is only one "tomorrow", so we cannot make ensembles of tomorrows in order to find the limit value of the outcome. This kind of probability relies on prior beliefs already present in the forecaster’s mind. To put it simply, when the "game" cannot be repeated, the probability of an outcome reflects the fraction of paths leading to this outcome. Our capacity to understand the dynamics and the sensitivity to the initial conditions of what is encoded in the internalist approach to probability (Sornette, 2000) is limited. To sum up, Bayesian (internalist, subjectivist or classical) probability is not restricted, as the frequentist or objectivist view is, to situations in which the repetition of large numbers of equiprobable events is viable. It must be said that while a purely Bayesian approach may pose computational problems for large models it may always be used as an insightful guiding principle, that can result in explicit ways to model internal knowledge in, for example, neural systems. In this line, the paper of Fiorillo in this volume (Fiorillo, 2012) provides a new perspective to information processing in neural systems that relies on first-person Bayesian approach. In addition, Gomez-Ramirez and Sanz, also in this volume (Gomez-Ramirez & Sanz, 2012), formally define "The Internal Model Principle" and postulate it as a guide for investigating how much knowledge a biological system has of itself.

5.5 Biological Time

The Flow of Time

There are two quite different versions of the flow of time. One is the flow of time exclusively in the present tense, which Newton took as a serious matter as demonstrated in his propositions made in the present tense in *Principia*. Another one is the flow of time crossing different tenses, say from past to present to future, which has been the main concern of philosophers including Aristotle and McTaggart.

The idea of the uniformity of the flow of time can be applied to Newtonian time because of the ubiquity of the presumed homogenous fluxionum in the present tense. Nonetheless, the uniformity has already equipped itself with the arrow of time implicitly since the flow has originally been conceived of based on the constant rotation of the Earth that is totally empirical.

Yet, at the quantum level micro-time reversals are also at play. Rössler in his discussion of *Endophysics* suggests that "there is a macro dynamics (the coarse-grained responses of the dissipative structure called the ‘observer’), and there is an underlying, much faster microdynamics". Even the most rapid macro change in the observer lasts several orders of magnitude longer than a micro time slice does. The micro time slices therefore are necessarily "integrated over" from the macro point of view (Rössler, 1998).

Physical laws remain invariant under the inversion of time. However, it would be next to impossible to properly comprehend how the flow of time conceived in the present tense alone could be reversed without referring to past and future. If both past and future are referred to when the direction of the flow is addressed, it will not be the flow of time unique to the present tense. Hence, a challenging question is how to conceive of the flow of time crossing different tenses. In other words, time itself is already dynamic in its capacity of integrating different tenses. Physics has unwittingly dismissed the presence of such question. Thus we also need to address mathematical approaches to hyper-scale issues, where the lowest level has different properties to other scales. Alternately the nature of biological change over a human lifetime needs to be enfolded. An additional time-related factor is the Libet's delay and how it impacts cognition and environmental response.

How should we study time in biology? The nature of *biological* time is of fundamental importance to the formulation of **Integral Biomathics**. As usual, whether for time or any other parameter, to measure differences we need an invariant reference. In the scheme of classical mechanics, Newton, following Ptolemy, conceived of the invariant "clockwork" of celestial bodies as a reliable reference, and posited the flow of time based on repeated cycles of the celestial clockwork motion. The flow of time derived in this way has been treated as being specific to the physicist instead of to the clockwork itself. A serious question now arises: is it only human beings that experience the flow of time in nature?

A Lesson from Cyanobacteria

One empirical response is the circadian oscillation observed in *cyanobactrium Synechococcus elongatus* – the most primitive photosynthetic bacterium (Kageyama et al., 2006). Cyanobacteria can move and read the circadian clocks they carry. The essence of the circadian oscillation is in a monomer shuffling of the protein called KaiC hexamer. The experimental background of the monomer shuffling is of a predecessor hexamer K-K-K-K-K-K being alternated by the successor K*-K-K-K-K-K, then by K*-K*-K-K-K-K . . . and so on, where K is a monomeric KaiC unphosphorylated subunit and K* is the similar phosphorylated subunit in the presence of ATP as the phosphate source. When the hexamer reaches K*-K*-K*-K*-K*-K*, it starts dephosphorylation back to K-K-K-K-K-K. What is peculiar here is that although the KaiC hexamer does not undergo the monomer shuffling during the phase of dephosphorylation (from K*-K*-K*-K*-K*-K* to K-K-K-K-K-K), the phosphorylation phase (from K-K-K-K-K-K to K*-K*-K*-K*-K*-K*) *does* require the monomer shuffling in the sense that the hexamer recruits the monomers to be phosphorylated from the outside and lets the unphosphorylated ones disperse. This has been experimentally confirmed (Kageyama et al., 2006). The KaiC hexamer remains as it is, even though the monomeric KaiC subunits are constantly exchanged. This means that the KaiC hexamer sets itself to be an invariant reference to specify time constantly passing away, in sharp contrast to Newtonian time.

Although Newton could not move celestial bodies, the KaiC hexamers in cynanobacteria can both read and move its clock. The *class identity* of the hexamer outlives the individual identity of each monomeric subunit within that hexamer, as an invariant reference.

Alternatively, if we focus upon the *individual identities* of the monomeric KaiC subunits both entering and leaving, these can be associated with the flow of time. The agent responsible for implementing the flow here is cyanobacteria themselves, instead of the physicist as in the case of Newtonian time.

Integrating Mathematical Symbolism and Physical Internalism

Once the flow of time is naturalized, the material substrate supporting its carrier will become a *sign*, that is, something having the causal capacity of relating itself to something else. Rudimentary types of sign have already been available in physics, but have so far failed to receive due attention. A case in point is found in thermodynamics.

Consider, for example, Boyle-Charles law of the ideal gas in the form of the equation $PV=RT$, in which P is pressure, V is volume, T is temperature and R is the gas constant. The equation by itself is under-complete, in that if any one of the three variables is fixed, there is ambiguity in specifying the values of the remaining two variables. The situation is different, however, if all three variables in whatever natural settings are fixed in the course of time. Although the physicist may say that the three variables are determinable as a matter of principle once thermodynamics is grounded upon statistical mechanics, the minimal specification of thermodynamics as a fundamental ingredient of empirical sciences remains independent of statistical mechanics. But even at the minimal specification level, each variable is 'competent enough to determine its own value' in relation to the two others to fulfill the Boyle-Charles law. Each thermodynamic variable has the capacity of detecting the others *internally* and specifying its own value accordingly. This is equivalent to saying that a thermodynamic variable is a *sign* on its own – always referring to the activity of something relating itself to something else.

The likelihood of the action of *signs* in the empirical world now opens up a novel vista within which mathematical expertise could be extended to meet the challenge of how signs could be symbolized.

Summarizing, we conclude the following:

i) biological systems have internal clocks, and processes synchronize with them, and
ii) physical variables affect each other – particularly in a complex way within (or among) living things – so we can refer to them as *signs*, for they have a deeper meaning for an individual organism, and their understanding demands better interpretation schemes.

Underlying this perception is the appraisal of first person descriptions. The presence of an internal clock in each biological system lends it a self-supporting temporal identity, and a self is unquestionably related to first person descriptions, which we cannot then avoid. Physical variables which affect each other, like the three thermodynamic variables of the Boyle-Charles law, are not mechanistically controlled from outside, but from inside through the agential activity of detecting and fulfilling the law. Such an agential capacity can be approached through relation to first-person experience.

A crucial question here would be how to accommodate signs perceivable in first person descriptions with third person descriptions, the latter of which are inevitable to any explanatory model. One prerequisite when entering the symbolization of a sign is to specify the sign's concrete material nature. A relevant example here is the synthesis of meta-stable products in chemical evolution as attempted in the laboratory.

A meta-stable product (as the material partial carrier of the preceding reaction) is a material embodiment of past memory, and at the same time it directs the succeeding reaction to a limited extent. Such a meta-stable product is nothing but a sign, which relates the preceding reaction to the succeeding one. The action of signs is already operative in the successive synthesis of meta-stable products, unless it is methodologically eliminated by integrating each individual action in the statistical ensemble of the similar individual actions, as is often attempted in statistical mechanics. *In this sense, meta-stable products may serve as a mediator between non-life and life.* Meta-stable products themselves are already the material embodiment of history and memory. The relevant question at this point would be to evaluate how rich the individual action of a sign could be in its content.

5.6 Memory

The functioning and survival of living systems necessitates a kind of long term "memory", which can be purely innate or may develop over time for better adaptation. For instance, bacteria engage in metabolic activity, reproduce and repair damaged DNA. All these activities are autonomously controlled by their genetic 'program', which serves as a memory of the organism's ancestry. An animal with a rudimentary nervous system, such as a fish or a lizard, receives information/stimuli about its environment and its internal states (e.g., hunger or pain), and may remember them for later recognition; it has some innate behaviours, but is also able to learn new skills and behaviours, and to evaluate them. More highly developed animals (mammals, birds, octopi) are capable of developing a semantics, which may modulate their actions according to their circumstances and allow for communication.

An organism’s memory plays an essential role in the dynamics of the system, by allowing it to recognize objects and events which were met previously, and to select procedures that were already used, while taking into account previous results. Such a memory is not rigid like a computer memory, but it is robust (meaning that it maintains its contents in spite of disturbances), and plastic enough to adapt to the context. Its 'records' can be innate or they can be formed, for example, when triggered by an event to remember features of the environment. Other triggers may take the form of internal configurations, or situations the system does not recognize, along with the procedures it develops to react to a situation in an adaptive manner. These ‘memory’ records can be more or less complex, and their internal organization may vary to facilitate adaptation to more or less approximate situations.

5.7 Vagueness

We create models of the world, which are as fully explicit as possible, but the real world that they represent – or our perception of it – is always to some extent vague. Models can capture very well any generic or coarse aspects of a phenomenon, but do not capture the details so well. Some of these details, however, may be very important, and may even trigger emergent behaviour. Observed systems will be vague when they can be affected by small-scale events which occur during experimental observation, and which can be obscured by historical contingencies, where these are not embodied in the models' boundary conditions.

This means that we must be very aware of the scale of our observations with regard to that of an observed system and of how that may be impacted by events at other scales. Our observational frame is imposed upon an observed system, and this makes the interaction less than objective; our observations may deform the observed system, marking it. How should this be taken into account, most specifically in the case of biological systems? In addition, the observed system may be in the process of changing at a scale which is greater than that of our observational time-frame, in which case we may well carefully and accurately measure aspects of the observed system that are ultimately of little relevance, even though these measurements provide values for variables in our model.

Biological phenomena in particular will be vague with respect to our models of them because they are affected by history and because they will usually be changing at time-scales both smaller and larger than our observational timeframe. Models are limited generally; they cannot be constructed so as to maximize accuracy, precision and generality. In particular, "models proposed by those who enter biology by way of physics often sacrifice realism to generality and precision" (Levins, 1968). Thus, any aspect of the system being modeled that is not in the focus will remain *vague* in the view of that model. This especially applies to complex systems, which are subject to many different sorts of modeling.

5.8 Quantum Effects in Biology

The grounding of any embodiment of a biological system lies within Quantum Mechanics (QM) (Ball, 2011). At first sight we might expect that quantum effects and biology would occupy completely different worlds. We cannot, however, blindly eliminate quantum effects from our investigations of biology without good reason. Here again, the question is primarily one of scale. It would be fatuous to investigate the biochemical basis of life without even *considering* the relevance of QM, but should this also apply to descriptions of the ways in which organs or complete organisms operate? A first consideration is clearly the size of the entity we are thinking about: it would be natural to assume that it is only small things that are influenced by QM, even though some evidence of large scale entanglement has been published (Ghosh et al., 2003). A second consideration is the nature of the processes we are considering. If inorganic chemical reactions can be described without recourse to QM, why would organic chemical reactions be any different? But, are interactions involving enzyme catalysation as simple as inorganic reactions? The principle of macromolecular self-assembly was first used by Michael Conrad to construct a quantum molecular computing model (Conrad, 1992).

Suspicions of the influences of QM in biology abound, but it is difficult to obtain conclusive hard data. Many birds navigate by using the Earth's magnetic field to direct their migrations. It is known that their magnetic sensors are affected by the incidence of light on their retinas, and the suggestion has been made that the result is an entangled pair of electrons (Ritz et al., 2004) with a coherent lifetime of tens of microseconds (Gauger et al., 2011). More prosaically, QM effects in biomaterials are now of great significance to the electronics industry, where nature-inspired organic semiconductors are of growing importance (Smits et al., 2008; Glowacki et al., 2011). Prime examples of the links between quantum coherence and entanglement with photosynthesis at the biophysical and biochemical level, providing a base for ‘green’ quantum computing and ‘green’ photovoltaics, can be found in (Engel et al., 2007; Lee et al., 2007; Sension, 2007; Scholes, 2009; Sarovar et al., 2010; Panitchayangkoon et al., 2010; Collini et al., 2010).

However, a central question concerns the extent to which mathematical descriptions must themselves be based on QM. The difficulties in finding mechanisms responsible for the phenomenal experience of consciousness based on classical mechanics, in particular its unity, attracted many researchers to the possibility of quantum mechanical explanation. Several authors proposed quantum mechanical explanation of consciousness or cognitive functions of the brain in the 1970's (Pribram et al., 1974; Hameroff, 1974; Frohlich, 1975). The attempts to apply quantum mechanics have been hampered by the relatively large size of the functional units of the brain, so long as this role was given to the neurons. Hameroff's idea was to identify as units much smaller microtubules, and this raised hope of applicability of quantum descriptions. In cooperation with Penrose, whose writing for the general audience greatly contributed to popularization of this approach (Penrose, 1994), Hameroff developed a model of consciousness based on such description (Hameroff & Penrose, 1996; Hameroff, 1998). The main obstacle to becoming acceptable for the majority of those interested in consciousness studies, was the difficulty of justifying physically unrealistic assumption of maintaining quantum coherence for sufficiently long period of time at realistic temperatures. More than a decade later, only sporadically has the issue of coherence and the model returned to discussion.

However, more recently the relationship with QM has been examined from a different perspective. Schroeder (2009) proposed considering a model of information integration[16] in the brain based on the assumption that the mechanism is exhibiting the formal characteristics of coherence expressed in the mathematical structures used in QM, but without the assumption that the brain or its functional units are quantum mechanical systems. This formal characteristic (direct product irreducibility) is a common property of the structures describing geometries, as well as many other systems, which do not have any relationship with QM. Moreover, in this perspective it is not the brain, which exhibits quantum-mechanical properties, but quantum mechanical description which reflects the cognitive functions of the brain.

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[16] Information integration has become the central theme of Tononi's concept of consciousness. However, all that he and his collaborators contributed so far were either very general statements referring to phenomenal experience of unity of consciousness (Edelman & Tononi, 2001), or to identifying the integration with statistical synchrony of neural firings in terms of entropy, (Laureys & Tononi, 2008). There were some recent efforts in investigating the theoretical and empirical evidence of information integration (Seth et al., 2011; Barett & Seth, 2011), but neither they, nor Tononi, or anyone else, incl. (Sloman & Chirsley, 2004) provided any model of integration or any idea of how it can be implemented.

There are also other possible ways of developing new perspectives on the relationship between QM and biology. In particular, in a categorical model such as MES (Ehresmann & Vanbremeersch, 2007; cf. Section 7.6) quantum entanglement can be modeled as a special form of categorical colimit. Such colimits impose constraints on the lower logics (up to the molecular level), where they play an important role. At the higher levels, entanglement can play a role only through lower order processes; indeed, during the interplay of the logics, there is a risk of decoherence because of the variety of higher constraints.

At these higher levels, what is important for living systems is the existence of multiform components, which can operate through two non-connected decompositions (this "degeneracy" property is formalized in the Multiplicity Principle). MP allows for the emergence of structures and processes of increasing complexity order in MES and provides flexibility and robustness to the system (cf. Section 7.6). Now, MP is itself a consequence of QM (Ehresmann & Vanbremeersch, 2002). Indeed QM implies that MP is satisfied at the lower particle-atom level, from which higher levels have evolved by iterated complexification processes. As complexification preserves MP, it is also satisfied at higher levels, hence in living systems. It explains how quantum properties (entanglement, non-localization) allow, through the MP, for the emergence of higher and higher processes up to consciousness.

To conclude, entanglement has its role at the lower levels, but the characteristics of life depend more on the (somewhat 'opposite') degeneracy/multiplicity principle, which is itself deduced from QM properties at the lower level. However if there is any evidence implying constraints on the higher levels that realize entanglement through higher order processes, we should take it into account in our model. Our general point of view must be an open one, permitting investigation of QM relevance at every level of mathematical representation.

5.9 Biotic vs. Abiotic Systems

If we wish to move beyond the issues raised by Salthe, who noted that "Today, curiously, living systems cannot be said to be anything more than dissipative structures informed internally by genetic information. There is not really anything substantially different from abiotic systems in them other than greater stability due to this internal information.", we need to decide on a level at which to start. If we think in terms of independent living entities (ignoring viruses, prions) then what these have in common is that they are based on the cell. Thus we become interested in characterising the living cell. Cells stand at a particular level: they are omnipresent in animals and plants (from the single celled amoeba to all plants to all classes of animals): indeed they are just about *all* that is omnipresent, and they are constituents of multicellular animals. So our first actual suggestion for a biomathics is that it should reflect this. But what does that actually imply?

We can characterize a cell by its boundary, B. This provides a division of space: we have in(B) and out(B), and we have B itself. We have mechanisms for crossing this boundary both from in(B) to out(B) and from out(B) to in(B). We then need to consider the nature of B, in(B), out(B), crossings from in(B) to out(B) and out(B) to in(B) might usefully be: as matters stand, it is difficult to imagine anything simpler (as it stands, it's quite like Spencer-Brown's *Laws of Form* (1972), which implies that it can be used a basis for logic). The system needs much in addition (at least): events, time, mechanisms for examining what's happening inside the cell (which might well be based on the same abstraction), mechanisms governing movement and transfer across the cell membrane, and mechanisms for putting cells together. In this area, the work of Cardelli (2005, 2008) provides one possible way forward, although it is more oriented towards a purely computational approach. At a lower level, there are internals that can cope with (e.g.) protein/protein interactions in the style of Hong (2005a/b), as well as abstractions that can stand in for diffusible chemicals, concentration gradients, perhaps gravity, and other physical issues, and at higher levels there are multi-cellular organisms. Inside the cell, we have protein interactions, as well as influences from energy changes (etc.) from outside the cell. These are unlikely to be precisely defined or replicatable: protein interactions rely on reactive surfaces being brought into close proximity with each other, while they are moving in aqueous solution, and having their shapes influenced by local electric fields caused by other proteins and external forces.

One can argue that cells perform information processing (deciding to move, or to engulf a particle, or create a protein), however, it is not necessarily possible to separate out what the cell does in order to survive and live, and what it does from an information processing viewpoint: we need to be careful not to enforce our own narrow interpretations of their activity too strongly.

Thus, there is a whole level (or indeed several levels) inside the cell that we could conceivably put together to determine the activity of a cell. Yet while the cell lives, its behaviour appears to possess a unity that (in some sense) belongs to the cell, and not to its numerous constituents. At a higher level, the same is true for multicellular organisms: they possess a unity that belongs to the organism, and not its constituent cells, or their constituent elements. At death, this ceases to be true. Cells appear to have a more purposeful behaviour than, say, a protein. Whatever the cell is doing, its behaviour is always subordinate to its main goal: survival. This holds for all higher levels of cellular organization up to communities, societies and nations. Clarifying/rendering a "crisper" notion of purposeful behaviour is part of the early research agenda of INBIOSA.

6 The Grand Challenge

This section addresses three major questions or grand challenge issues in the sciences of complexity that underlie biology and the related study of living entities. The first issue is the relevance of a more complete understanding of biological complexity and the increasing complexity of artificial (engineered) systems to the progress of science.

The second question is why a paradigmatically radical shift in methodology is critical to progress in biology. The third issue is the potential impact of a revolutionary advance in biology on all sciences and technologies involving life-like or life-enabled complexity. A discussion of these issues is followed by a recommendation for a new strategic collaboration *framework* to support the advancement, articulation and development of new theoretical and computational foundations for biology.

6.1 The Relevance of Complexity to the Problems of Science

We begin by examining the historical trajectory of science and how that changed dramatically with the invention of mathematical physics. Next we examine the current impasse in the progress of biology and other sciences involving life-like complexity or life-enabled complexity. We then conclude with the role of mathematics in the development of complexity sciences.

6.1.1 The Trajectory of Science: The Transformation of Methodological Paradigms from Descriptive to Mathematical

The following scheme is a sequential model of science:

Observation of new phenomena → **speculative concepts/ hypotheses/ theories → new mathematical formalisms → predictive conjecture →** empirical demonstration and verification → theoretical foundation for practical applications

The schematic trajectory of science presented above is a simplification of much more complex system. A more complete model of science, as a highly complex system of thought, a noetic system in itself, would illustrate how the process is simultaneously cyclic, recursive and unpredictable in the sense of generating novel emergent structures (predicting new phenomena) from its own mathematical grammars. The power of mathematics (mathematical language and its grammars) to transform the methodological paradigm of physics was first demonstrated by James Clerk Maxwell with his revolutionary use of the differential equations that effectively *described* electromagnetic field phenomena to *predict the existence* of electromagnetic waves and the electromagnetic nature of light, both phenomena then unknown to experimental physics (Arianhod, 2006). The subsequent experimental observation of radio waves enabled the modern world of telecommunications and the concept of the radiation of light led to the science of quantum physics. The paradigm shift in physics from concrete models to mathematical imagination created the methodology of modern mathematical physics.

The science of biology awaits a similar transformation. Biology needs a new mathematics allowing for a new form of computing that will permit us to model the emergence of new structures carrying out novel processes as a result of innovative forms of organization within complex systems. At that point, we will be on the verge of a transformation in biology as profound as that in physics. In other words, the transformative paradigm shift in biology requires the development of mathematics appropriate to biology that is motivated by problems that are biological in their origins and nature, just as the mathematics appropriate to physics was physical in its origin and nature (Root-Bernstein, 2012).

6.1.2 The Impasse in Biology and the Need for Convergent Theoretical Synthesis

Much progress has been made in biology. The last fifty years have generated a huge amount of information on life processes. DNA, the genome and systems biology have had huge success in extending our understanding of many of the basic processes in living cells and tissues. But in recent years, research seems to have concentrated on more and more detailed molecular understanding of these processes, without managing to pull these together across scales of space and time, without increasing our overall understanding of the nature of these processes, or of how they make living organisms actually live. Developing a set of theories that cut across these levels aims to fill that space.

The sciences of living systems are stalled at the most basic stages of observation and speculative ontologies/hypotheses/theories. The energetic and optimistic application of the highly successful Newtonian and von Neumann paradigms of physics and computation have not really enabled a breakthrough in the understanding of living systems as *distinct* from non-living matter. Mechanistic models are still dominating biology and science. To make new inroads into biological study we must move to new forms of dynamic relational models that enfold multiple mathematical approaches.

Funded research is producing ever more detailed reductionist descriptions of biological systems, but failing to produce the understanding and insight that would be necessary for real progress. The central idea behind our proposal is therefore to develop theoretical foundations that can bring together the huge range of biological (genetic, molecular, protein-based) knowledge by developing theories that cross boundaries. Mainstream research appears to be about building up more and more knowledge in the hope that one day it might be altogether made sense of. In Physics, there is a strong belief in clear underlying principles that drives fundamental research. In Biology, such principles seem to be more difficult to find, and are often seen as less important, if only because clinical work has different aspirations from pure science.

6.1.3 The Evolution of Mathematics in the Development of Science

There are many scientific problems a new mathematics of biology (biomathematics) would have to address. How to model self-emergent sets (origins of first cells; self-assembly of viruses, etc.) How to have such self-emergent sets carry out functions selecting/rejecting among possible components; minimizing what a physicist thinks of as free energy. How to create a mathematics that can simultaneously deal with continuous variations in chemical kinetics yet yield information about modular probabilities within complex systems to prune out huge numbers of possibilities at each step of hierarchical assembly. The new mathematics would preferably incorporate the work that has been done on understanding hierarchical systems, emergent properties and complexity theory.

Current approaches to these sorts of problems rely on modeling one aspect of the problem with one form of mathematics, switching to another sort of mathematics to address the next aspect, and to a third to describe yet another. Such switching is an indication of how inadequate our mathematical tools are for addressing these problems. Biological systems function at all of these levels simultaneously, and so must our mathematics. A new mathematics would therefore be integrative.

In a nutshell, mathematics will be required to expand its descriptive capability. The traditional mathematical disciplines have been well versed with monologic discourses and formalization in an unsurpassed manner, while the real processes operating in biology are dialogic in maneuvering a wide variety of resource explorations and exploitations among the participating material agencies. A major theme of the upcoming biomathematics we call **Integral Biomathics**, should be how to reach monologic discourses, starting from the dialogic dynamics anchored upon the real material world without being entrapped by easy static or statistical artifacts. One breakthrough that might be expected is extending the scope of category theory as a mediator integrating the primitive nascent categories in the dialogic dynamic domain into the full-blown formal categories in the monologic descriptive enterprises.

6.2 The Radical Paradigm

We suggest a new collaborative pathway in this section – convergent theoretical synthesis – as a paradigm shift and an alternative to the current heavy emphasis on empirical research in order to accelerate progress in these sciences. The envisioned research program is not an extension of the existing paradigm in which the principles underlying the successful models, philosophical assumptions and computational approaches of physics are assumed to apply as the foundations of biology. It is not that we are suggesting that the laws of Physics do not apply to biology! However, we propose that there are additional deep laws that apply to biological systems *as well.* The current paradigm has failed in substantial ways to advance life sciences. The understanding of living processes has not been amenable to orthodox mathematical modeling and logic despite enormous advances in computational and experimental tools. Von Neumann computing is practically unable to address the complexity of interactions involved in even the simplest molecular expressions. Therefore, INBIOSA focuses on challenging the central reductive and simplification assumptions of classical science.

6.2.1 A New Trajectory: Towards Theoretical Foundations for Biology

This concept is best expressed as a transposition of the modeling assumptions that enabled the emergence of the Newtonian paradigm, which forms the base of biological theories today:

Non-living systems (Newton):
    Apparent *complexity* of observable phenomena →
    Modeled effectively by *simplistic* minimalist formalisms
Living systems (Darwin):
    Apparent *simplicity* of observable behaviour and development →
    Require modeling of ultra *complex interacting structures*

Nevertheless the physical sciences have led to the development of new observational, analytical and computational tools applicable to modern experimental biology. This has in turn enabled the collection of a vast highly detailed new repository of data at all levels of complex living systems.

Observation of new phenomena → speculative concepts/ hypotheses/ theories → new mathematical formalisms → predictive conjecture → empirical demonstration and verification → theoretical foundation for practical applications

These technologies have in turn enabled the evolution of many disciplines and subdisciplines of biology founded upon a wide variety of paradigms, hypotheses and theories based upon specific (narrow) evidential bases. There is great need for convergent theoretical syntheses (Kant, 1999) to reduce the number of plausible theories and to synthesize across paradigms. **Such tests of convergence have been the pillar of scientific advance in astronomy, geology and biology** (Donald, 2004).

In biology theoretical integration and synthesis will enable more precise conceptual models for the newly observed key processes of complex systems.

Observation of new phenomena → **convergent theoretical synthesis** → new mathematical formalisms → predictive conjecture → empirical demonstration and verification → theoretical foundation for practical applications

These new conceptual models in turn will enable new mathematical formalisms to be developed for each process with a possible integrated mathematics from which all processes can be derived (Root-Bernstein, 2012). Thus, computation can be part of convergent theoretical synthesis.

Observation of new phenomena → convergent theoretical synthesis → **new mathematical formalisms** → predictive conjecture → empirical demonstration and verification → theoretical foundation for practical applications

In particular, there could be a possible paradigm change to development, not evolution as the basic orientation of biology. The groundwork was laid by A. I. Zlotin in the 1960's in Russia (Zlotin, 1972). It is thought of (if at all) as a 'dismal science', as it is based in thermodynamics and focuses on the processes of senescence (Salthe, 1993) and complexity (Salthe, 2005a). Developmental Biology is not informed by this possible theoretical basis, and has, indeed, no theoretical basis of its own. This approach is grounded in a basic perspective opposite to the 'growth ideology' of our culture, and it would be truly a radical departure.

Actually, developmental and evolutionary biology represent a complementary pair. Development is the process underpinned by genetics. It is genetics that determines the response to an event, at a certain level, since it determines what the protein structures will be, that will detect the changes that constitute events, as well as determining the reaction cascades that eventually result in action after an event.

6.2.2 The Entailments of Complexity

The traditional aim of science and the technological tools and processes that it enables, is the increase in our control over matter. This power rests entirely in the predictability entailments of the sciences, as we know them today. An understanding is scientific according to its power of predictability. Our historic understandings of the world around us (including our more recent understandings of human language, thought, consciousness and foresight) are based on the canon of predictability. That canon together with the mathematical innovations that enabled precision in predictability have been highly effective as we advanced our understandings in the traditional domains of physics, chemistry, biology, neuroscience, economics and in the varied technological and engineering domains that are derived from those sciences and upon which our material, economic and social progress have depended.

We are entering a new era, however, in which we seek to make even further interventions in the ways of nature and expand the potential for yet further material and social progress in the man-made world. What we have discovered is that we now have to address real complexity rather than an apparent complexity that can be reduced to simpler manageable and hence predictable entities. We are not surprised that nature presents such challenges, but we are realizing now that the pervasive and information-intensive infrastructure of our built worlds (at all scales) is exhibiting the same features: **unpredictable** interaction between components and sub-systems of exceedingly complicated systems.

The extraordinary capacity of all living entities to restructure themselves in order to address both internal and external stresses in ways that evade understanding is based on the canon of predictability. Biology as the study of living entities is the science that has faced the complexity phenomenon from its outset. Physics took somewhat longer to confront irreducible and irresolvable complexity in its formulations of non-equilibrium thermodynamics to account for its theories of the emergence of matter from energy and of life from matter (Chaisson, 2002).

The problems in biology and other fields of life-enabled complexity are not about the energy-budgets of structured matter, as physics might be concerned with but about the complex of processes that enable life and its continuing evolution in human culture and technology.

The bottom line is that even understanding complexity will not allow us to avoid the emergence of unpredictable properties or the illusion that we can manage the outcomes of emergence.

How essential it is then to understand the conditions, under which emergence of new properties occurs in biological systems (natural and synthetic) and in technologically complex engineered systems. Our challenges will be how to manage emergence and perhaps to shape the envelope of possibilities. The canon of predictability (the old sciences) will not apply. We have entered a new era in science.

6.2.3 Bridging the Complexity-Based Disciplines

The theoretical syntheses and mathematics that are derived from transdisciplinary studies of the above five grand scientific challenges have the potential to be applied to an understanding of how novel properties can emerge in complex systems of any kind, whether ecological, social, behavioural, technological or economic (Root-Bernstein, 2012). There are therefore many opportunities to advance understanding simultaneously by transferring new insights from a simpler kind of complexity to advance research in higher complexity regimes. We give our highest priority therefore to research spanning and integrating the insights to be gained from both engineered and natural systems of complexity.

INBIOSA proposes the development of bridges with EU Future and Emerging technology (FET) programs addressing the design of complex interacting engineered systems. Adoption of the INBIOSA institutionalization agenda (summarized below) can greatly assist FET programs that are beginning to address the problems of emergence of undesirable properties in what may be considered extremely complex engineered systems[17]. These efforts would benefit from the innovative perspectives of those who have articulated theories for a wide variety of emergent phenomena in biology, which involve much greater complexity than those in human-designed technologies. Mapping a new generation of bio-inspired emergence theories to complexity issues in engineered systems would accelerate design solutions as rapidly as new mathematical formalisms were developed and tested. Conversely, **adoption of an internalist perspective** involving our reflection upon the process of creating and operating a vast network of human-intelligence driven self-organizing engineered systems might give us some insight into how biological complexity in nature works.

The salient aspect of this argument was captured by Simeonov's Flagship Proposal (Simeonov, 2010a):

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[17] The FET consultation on evolvability raised further concerns that FET research projects pursuing advancements in collective adaptive systems are failing to address deeper fundamental issues in complexity engineering involving: the long-term controllability of autonomous artificial systems; artificial chemistries that may have the ability to re-write the operating system, or control system in which it is embodied; the need to understand emerging complexity in modern-world systems at the level of interaction between artificial systems; and ways of controlling emergence in artificial systems (Kernbach et al., 2009).

> "… we cannot truly rely on these machines to autonomously discover and explore new worlds which are impenetrable for us. They simply lack the ability to grow, develop and evolve under the two other fundamental capabilities that living systems possess: effectiveness and innate adaptability/learning (**without any human intervention**). "

However if we include the capabilities of effectiveness and innate adaptability/learning available through human intervention we might have much to learn from such biosynthetic complexity. Take for example telecommunications networks. We have entered an engineering era distinguished by an entirely new systems phenomenon: exceedingly complex interactive networks of computers and communicating devices. Such complex systems provide a new observational platform enabling the opportunity to explore, **from the inside out**, how exceedingly complex systems develop new properties. While not natural emergence as in the case of living systems, it is observable engineered emergence, the manipulation or re-configuration of technological capabilities towards an overt human purpose. Pioneering research on "recommendation architecture" has challenged von Neumann computer architecture as the way towards higher-performance global telecommunications infrastructures and at the same time provided theoretical insights into neural cognitive processes otherwise unavailable to experimental biology. INBIOSA believes that the time has come to discover universal "emergence" principles in the interaction between the human mind and its engineering goals for complex systems of all kinds through the new observational platforms being offered by complex engineered systems at many scales.

6.3 Institutionalizing the Lessons from the First Scientific Revolution

We believe that convergent theoretical synthesis and innovative mathematics hold the keys to transformative progress in biology and the other sciences and technologies of complexity. How then do we propose to create the conditions for focusing resources and talent upon these processes in the context of extreme disciplinary specialization and the massive commitment of resources to observational, clinical and experimental methodologies? The first principle that we propose as a foundation for transformative research is that of universality: that there is a commonality, a transdisciplinarity, an integrative view of what can be perceived by human intelligence that must assimilate the knowledge gained from research in all disciplines. Hence, our proposals recognize the variety and theoretical complementarity of complex systems, i.e. there are many kinds of complex systems, from relatively simple ones to ultra-complex ones. What they have in common is the ability to develop novel (i.e. unanticipated) properties from their own self-organizing capabilities. We can currently identify at least seven distinct kinds of complex self-organizing systems based on their distinct forms of semiosis, i.e. classes of communicating meaning with signs (Logan, 2007):

Kind of Self-organizing System/Discipline	**Form of Semiosis (communicating meaning through signs)**
molecular biology	digital transmission of information by DNA
cellular biology and ecology	process by which receptors of prokaryotes interpret signals from the environment
developmental biology	epigenesis of the phenotype from the DNA influenced by signals from the environment
neurocognitive science	biosemiosis of learning by virtue of the emergence of a central nervous system in animals
cognitive evolution	transition from percept-based thought to concept-based symbolic thought that emerged contemporaneously with human speech
distributed cognitive evolution and sociology	human culture, a symbolic thought based phenomenon
Semiotics	science, mathematics, technologies and economies, as products of the human mind generated through signs both spoken and notated

Focusing on biology, INBIOSA has identified five principal phenomena in biology towards which efforts at theoretical convergence and the development of an innovative mathematics should be focused in the immediate future:

1. the autopoiesis (self-construction) of cellular life;
2. the emergence of modules of hierarchy in all complex systems;
3. the varieties of modalities of communication within and between hierarchical levels of living systems;
4. the transformations of information processes from scalar to vector/tensor quantities; and
5. integrated mathematical approaches that can link discrete, continuous and geometrical information simultaneously.

6.4 A New Strategic Collaboration Framework

INBIOSA is the first formal attempt to provide a collaboration *framework* to support the advancement, articulation and development of new theoretical foundations for biology. We have drawn together a community of researchers to provide guidance on both the scientific and institutional steps required for a continuing scientific deliberation of paradigm shifting alternatives.

It is clear however, that the disciplinary structure, vocabularies and inertial belief patterns of academic research invite premature closure to cross-disciplinary debate and paradigm-transforming challenges. INBIOSA therefore proposes that FET continue to provide an institutional setting conducive to the research agenda we have proposed to address fundamental questions relevant to the broader field of complexity sciences. The FET program itself recognizes the acute need for a continuing process enabling scientific deliberation of paradigm shifting theoretical research. The EC report on the Future Internet[18] makes the extra-ordinary and rarely recognized point about the contingency of future progress at the economic enterprise level on "*new scientific foundations to produce Enterprise Systems offerings that are rested on and subject to the rigour of science*":

> "*More fundamentally, a science base is required for the development of the next-generation Internet-based Enterprise Systems able to cope with a new set of complex issues and requirements, while at the same time ensuring reliability, flexibility, scalability and other qualities that have made the Internet such an indispensable tool for businesses and society.* "

The existence of such a process will help to overcome a historic weakness in enabling challenges to orthodoxies, strengthening the climate for new paradigms and enabling new cross-disciplinary and inter-disciplinary syntheses in support of convergent paradigms. A first step in this direction was made in the panel discussions during the iBioMath 2011 workshops in San Jose (California) and Paris and the ACIB-11 research forum in Stirling, UK. The broad range of disciplinary response to these workshops demonstrates the latent interest of a wide range of research communities involved with theoretical and practical development of complex systems of all levels.

INBIOSA therefore proposes an expanded program of consultations and collaboration with relevant scientific and engineering communities focused on three objectives:

1. Identifying the scientific challenges in biological and artificial systems information processing;
2. Confirming support for the relevance of INBIOSA Grand Challenge Goals to the research objectives of their expert communities;
3. Commitment to joint development of an integrated research agenda.

INBIOSA suggests consideration of a conceptual model for such an institutional framework based on the concept of emergent complex systems itself. In other words, to mimic in the larger world, the thought processes and structures that enable the emergence of new ideas in the human mind. The table below lists potential fields of research addressing complexity issues. The institutional challenge is to recreate the individual thought process of performing the necessary convergent synthesis of theory underlying the complexity of living systems at the scale of the total societal effort in the relevant sciences. In other words, the co-ordination (but not the control) of the many modules of thought that could be, but are not being brought together into a more coherent model of life itself.

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[18] Future Internet Enterprise Systems (FInES). Position Paper on Orientations for FP8. Final Version. 18 March 2011.

This would involve co-coordinating efforts through FET programs and academic interdisciplinary collaborations guided by the principle of synthesis. Implementing such co-ordination is the institutional challenge. The form of structure and communication that would most benefit this process is not known yet. What is known is that existing processes of collaboration and disciplinary integration and co-ordination do not support such synthesis and mathematical innovation.

The following table summarizes the fields to be engaged, the problems identified for joint activity and the focus of specific research proposals.

The Reflective Collective Intellect: A preliminary schematic framework for enabling the emergence of a new scientific discipline of the complexity of natural and engineered systems – Integral Biomathics

Discipline/Organization	Knowledge Problems	Required Interdisciplinary Science Research Activity
Theoretical biology	Understanding how different levels interact (molecular, genomic, intracellular, extracellular, multicellular, organ level, whole organism level, ecosystems)	Development of multi-level/multi-temporal modelling synthesizing all levels and time scales
Biosemiotics	Understanding the different nature of all levels of abiotic, biotic and symbolic communications relevant to self-organizing entities	Process-based modeling (Mathematical, computational).
Mathematics	How to formalize biological problems that currently exist in two or more essentially unrelated domains of mathematics	a) Develop mathematics beyond autopoetic sets along the line of category theory and MES theory, using recent domains able to unify probability theory, hierarchy theory, network theory, vector/tensor calculus, logic, topology and others. b) Invent new mathematical methods and tools beyond a)
Systems engineering	Potential instability of highly complex systems as they increase in scale and complexity	How do biological systems integrate across multiple levels to produce long-living robust systems with clear goals?

Telecommunications engineering	Reconfiguration approaches to meet increasing flexibility in demand patterns and system reliability	As above
Health sciences	The lack of theoretical advances, the adoption of a naive immune inspired approach and the limited application of Artificial Immune Systems have limited immune systems research. Devise multi-scale models of pathologies and human anatomy/physiology accelerating therapeutic research; discovery of new pharmaceuticals and medical devices fostering an integrative approach to health care.	Similar to theoretical biology, but with an emphasis on pathogenesis and the means to eradicate/reverse the degeneration processes with minimal side effects while mobilizing and enforcing natural resources such as the immune system.
Cognitive science	How could the self emerge? What could be the material requirement for the emergence of the most primitive cognitive unit?	How could consciousness be related to cognition? Is cognition equivalent to measurement?
Synthetic biology	Knowing how to build synthetic biology systems; Understanding how to control a synthetic biological system in order to take advantage of its capabilities	Using the Mathematics and semiotics to help create systems for controlling (programming) these systems.
FET Projects	Unpredictability of self-replicating, high plasticity and self-healing and programming functionalities Complex Systems Unconventional Computing	New studies of heterogeneous systems. Studies of information processing in living systems: re-interpretation of biological computing.
Other (economy, finances, other complex technology disciplines.	Reducing dialogic movement to monologic discourse	Constantly transforming temporal categories

7 Towards a General Theory of Living Systems (GTLS)

This section describes the effort to formalize a general theory of living systems from what we have today. The eventual result will be a formal system, equivalent to that which exists in the physics community.

7.1 Objective

We focus on *evolving integral* models of life as an integration of both descriptive and explanatory models. An advantage of recruiting descriptive models amenable to first-person experience is to go beyond being entrapped by easy syntactic integrations unique to explanatory models limited to third-person descriptions, i.e. non-reductionist and both endo- and exophysical approaches to the emergence and development of dynamic, ordered hierarchical systems. These are facets of biological systems that no one can model at present. The elements we want to address have applications to "intelligent systems" of all kinds, including AI/ALife systems and emergent ecologies, etc. All these systems can be demonstrated to have similar features and functions (albeit at different levels of organization).

To address these issues, we postulate the development of a 'dynamic model’ of the entangled system 'in the making', trying to size up the successive specifications of its logic and semantics over time (Ehresmann & Vanbremeersch, 2007). At each time, we assume the overall ('global') logic of the system to result from the interplay among a hierarchy of 'local' logics and process event driven non-local crossovers, each with its own temporality, complexity and multiform components. Furthermore, this interplay is reckoned to become flexible through 'switches' between different decompositions of multiform components, allowing for a kind of fitness selection between them to preserve as much as possible of the local logics. While the local logics resort to 'classical' computations, the real challenge is to deal with their interplay, in particular how to handle switches between different possible decompositions of a multiform component, and with their non-local 'quantum' entanglements (Ehresmann & Vanbremeersch, 2002). The INBIOSA initiative suggests a radical approach to theoretical biology, biomathematics and bio-computation in the long term that can be supported by a transitional strategy in the short and middle term by addressing looming problems in complex interacting artificial systems that deserve attention according to the FET program (Kernbach et al., 2011).

7.2 Background

This section explores the reasons why the core question stated in the previous section has long been dismissed in the traditional scheme.

The history of science is a constant tension between those who would understand the world by examining its pieces (Democritus) and those who would understand it by studying its processes (Heraclitus). Erwin Chargaff wrote a very insightful (and unpopular) book about this conflict as it applies to molecular biology called *Heraclitean Fire* (Chargaff, 1978). The importance of making this distinction is that this book at present reads as if molecular biologists are studying cascades of molecular processes/changes, but in fact they are not, because these are only a small, low level part of the organism, and they ought to be examining the whole system. At least they have moved beyond simply looking at specific molecules, but they still make the often-repeated error of thinking that if they can isolate parts of the system that participate in the processes, the processes themselves will become clear. This is the epitome of the reductionist fallacy. The individual pieces of a clock do not predict or explain its "clockness", which resides instead in the way its organization permits it to carry out a specific process. The importance of making this distinction is that the mathematics used to model most biological processes have likewise developed from reductionist approaches, having been developed to model a Newtonian "clockwork universe". Reading the clock is irrelevant to a Newtonian universe since every inhabitant in the universe is no more than part of the single gigantic clock available there.

Despite the unquestioned success of the "omics" revolutions the paradigm shift in biology comparable to those invoked by the theory of relativity and the quantum theory in physics has not yet been achieved. Addressing the issues of parts of a clock, clockness and reading clocks discussed earlier may provide a key to engineering such a change in view.

How can we describe the synchronization of two adjacent clocks without relying upon Newtonian time? Just as physics has adopted novel forms of mathematical modeling that explicitly reject mechanistic reductionism, so must biology if it is to deal with similarly complex systems comprised of components that have multiple states and vary constantly in number and composition through time.

Another point that needs to be made explicitly is the necessity of taking into account hierarchies of organization. Biology is not chemistry, which is not physics. Chemistry becomes chemistry and not physics at the point where we can ignore the physical properties of the components carrying out the chemistry. Biology becomes biology and not chemistry when we can ignore the chemical properties of the components carrying out the biology. Yet, this is not reductionism. Simple hierarchical reasoning leads us to conclude that we can recognize a new level of organization when the principles and properties and models that worked for the previous level of organization can be ignored[19]. This is not to say that biological systems are not comprised of chemicals that obey the laws of physics, but to say that biological systems are *recognizably biological* because they have organizational properties and patterns that allow them to carry out processes that cannot be accounted purely on the basis of the physics and chemistry of their individual components. Here we often have interspersed interactions from higher layers of organization.

Consequently, what we need to describe and explain this "native biology" is the application of areas of mathematics not previously applied to it and the development of new ones, as well as of new forms of computing that permit us to model the

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[19] We don’t need an understanding of nuclear physics to describe the kinetics of a chemical reaction; we don’t need to know the movements of every molecule in a gas to measure its temperature; we don’t need an understanding of electron shells to explain how DNA encodes genetic information, but sometimes we need to invoke reasoning based on lower levels.

emergence of new biological properties and patterns resulting in the carrying out of novel processes as a result of innovative forms of organization within complex systems. This kind of mathematical formalism is expected to enable us to answer the question: "What exactly is so typical and unique for living systems that does not occur in non-living ones?" We do however recognize that attacking this question should proceed under the constraint of the impredicativity. That is equivalent to practicing whatever theoretical synthesis is to be framed in third person descriptions without forgetting about inevitable interferences from first person descriptions.

The reason that biology has failed to develop a viable set of mathematical theories is therefore a result of having attempted to treat its universal, hierarchically-unique, organizationally-derived processes in terms of reductionistic principles derived from studying the chemical particles upon/from which these processes emerged. Additional confusion comes from the usage of wrong and mixed-up definitions. We wish to know how the reaction cycle could emerge.

In fact, the reaction cycle, as a higher level organization compared to the constituent individual molecules, raises a serious question of how the identity of the higher level can come to outlive the identity of each constituent molecule in the lower level. Once it emerges, what kinds of problem would remain? Hierarchy theory suggests that reductionism can never explain how novel properties and processes emerge[20].

What we need is not more detailed models that can handle greater and greater amounts of detailed data from increasingly fine-grained studies of the components of systems, but ways of identifying properties that are as unique to such complex conglomerations as temperature is to a set of molecules. In short, what we lack is a uniquely developmental mathematics that deals with the emergence of organization from non-random selection among replicating variations within complex populations of living entities. Could it be possible to have a type of mathematics that may support the robust transformation from non-cyclic to cyclic reaction network (Yardley, 2010) in a sense approachable empirically? What then would the mathematics of emergent properties and organization look like? Biology is only one case of such emergent properties resulting from spontaneous organization within complex systems. Political and economic systems are two others.

Josephson's emergence approach suggests how to join mathematics and biology using signs/symbols (semiosis), along the same path that the fundamental concepts of natural numbers, Euclidean geometry, algebra and logic were developed: "By retreating into symbolism one escapes inconvenient facts about the world and is able to create a system that has a certain resemblance to the world even though there is no exact correspondence." (Josephson, 2012)

The principles that are derived from our studies should apply to an understanding of how novel properties can emerge in complex systems of any kind[21], whether ecological, social, behavioural, and possibly even technological.

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[20] They still have underlying causes; however, looking at them may obscure their higher-level important properties.

[21] Including future Internet infrastructures, virtual communities and extra-terrestrial life.

Among other things, we would conjecture that such a new mathematics would not be related to digital computation. Biological systems invariably involve weak interactions and complementarity between molecules and systems that are in dynamic motion. Such systems have characteristics shared with analogue systems as well as digital ones in the light of appreciating a novel source of cohesion. The analogue side of computing, while not entirely novel, has largely been ignored since the digital revolution. We will not make progress in modeling and understanding complex, emergent *living* systems until we have computational systems that are based on similar principles.

Again, many systems besides biological ones are analogue[22]. Most functions describing weather, economic indicators, etc. are also analog. It might therefore be possible to create a revolution in modeling across many disciplines by focusing on developing analogue modeling tools for biological systems.

However, the replacement of digital by analog might not provide the ultimate solution for biology. INBIOSA is in favor of integrative approaches combining the benefits of both worlds, but we need to turn our attention to analog computation and its derivatives, which appear to be more adequate for explaining biological phenomena. Yet, we should not forget that analog modes of operation can be also reductionist. So, a major question on the way to answer is: *Where is the border between reductionism and holism?* How can we find out whether a model entails all necessary variables and constraints?

How could we evaluate the roles of indefiniteness or potentiality and transform the indefiniteness? Perhaps we should make sure that such a model is capable of evolving and include more components approaching the real world situation in a series of iterations.

7.3 The Road Ahead

One possible breakthrough for cultivating the central task of INBIOSA research further may be in sight once we pay attention to the exchange of material, (ubiquitous in biology), as a demonstration of the interplay between first and third person descriptions. A helpful example is the monetary economy. A unique property of the monetary economy is the occurrence of something called *paper money* as an institutional means capable of paying for any kind of debt. To be sure, the paper money is by itself of no value as a physical body and cannot serve even as a substitute for a soft facial tissue, while some interesting figures are printed on its surface in many cases. Nonetheless, paper money used in the process of exchanging its ownership does serve as a means of being exchanged for whatever goods or services of equal value are printed on the paper.

The paper money keeping its designated value right in the process of exchanging its ownership is a prerequisite to the operation of the monetary economy, and the

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[22] In fact, everything is analogue at a Newtonian level. At a lower level systems may be grainy (discrete), but one needs to realize what advantage have accrued by using digital systems with very small discrete graduations.

monetary stock in the hand of each economic subject is merely a consequential derivative from the process (Matsuno, 1978). When one tries to address the monetary economy computationally or from the perspective of experiencing the monetary transactions internally, we need to pay attention to the dynamics of the monetary flow in the exchange. Furthermore, since no one except the central bank sanctioned by a nation state or a sovereign union can issue and destroy the paper money, each economic subject other than the central banks is under the inevitable constraint of fulfilling monetary flow continuity from each participatory perspective. Fulfilling monetary flow continuity is the computational task each economic agent must assume. What upholds the computational task is the identity of the body facilitating the exchange of the monetary ownership, rather than the identity of the paper money itself. Thus, the basic dynamic predicate coping with the monetary economy computationally must be the monetary flow rather than the monetary stock, the latter of which may be regarded as merely an instantaneous snapshot of the flow variable to be recorded. The appraisal of the priority of monetary flow necessitates the involvement of first person descriptions, since referring to the active agency (assuming first-person status) maneuvering the monetary flow from within is required there. Each economic subject is always busy with and serious about how to maintain monetary flow continuity by any means.

In essence, the keeper of a retail store is busy in managing his day-to-day business so as to clear the draft to be expired by the end of month, while a certified public accountant (CPA) is quietly vigilant in observing whether the double-entry bookkeeping to be prepared by the storekeeper by the end of month would actually let both the ends literally meet. Here, the storekeeper's activity is in first person descriptions, whereas the CPA's observation of the bookkeeping is in third person descriptions.

Both of them are involved in computation in one form or another. Above all, the computation specific to the storekeeper is definitely in first person descriptions.

Once it is properly perceived, the monetary economy in the making should be accessible in first person descriptions, while the record is also legitimately approachable in third person descriptions. Despite that, third person descriptions alone cannot be good enough for appreciating the priority of the flow variables since the simultaneous participation of the stock variables would also be made inevitable there. Computation in terms of flow variables as the most fundamental predicates thus makes the distinction between first and third person descriptions indispensible.

What is concretely at stake is computation underlying the implementation of empirical flow continuity processing various flows as the most fundamental dynamic predicates. The occurrence of the exchange of material in the empirical world is a necessary condition for the likelihood of letting the flow variables be irreducibly fundamental. This perception suggests to us that such computation in terms of the flow variables accessible exclusively in first person descriptions could have been operative even ever since the verge of the origin of life on Earth because of the ubiquity of the exchange of material. The remaining problem may be how to implement the scheme in an explicit manner as reminding us of the distinction between first and third person descriptions.

We are all economic agents; all of us participate, in some way or another, in trading, producing or consuming goods and services. It goes without saying that this poses an unprecedented problem in terms of dimensionality and complexity in modeling of systems such as national economies.

The mechanistic view of economy assumes that agents and the economy performed by them can be separated. In this classical view, the economy, for example the market economy, pursues a natural course towards equilibrium. The equilibrium hypothesis is needed in order to be able to obtain the analytical solutions to the complicated models formulated in ordinary or partial differential equations.

This approach, by emphasizing idealistic conditions (perfect competition, perfect knowledge of all agents etc.) in order to make the modeling problem tractable, sacrifices a more realistic account of how complex systems, like consumers, banks or institutions, adapt and react to the dynamic patterns that they create through their interactions.

This is one of the reasons why economic science has a layer of complexity that natural science does not have: agents elaborate purposive actions and strategies that try to cope with potential outcomes of their own actions, as they interact with other agents. For example, when an agent e.g. Goldman Sachs, predicts patterns in stock prices, that prediction is drastically modifying the pattern itself because other agents will try to adapt to the potential outcome of that action. It is known that herding behaviours like panic or euphoria may produce qualitative changes of regime in the systems that seem to be related with financial booms and busts. With this example we want to suggest that Economic Science, as any other social science that wants to model behaviour of complex systems (humans), is in sorely need of a new methodology.

Therefore, we need a **complex organic approach** able to revisit and elaborate, inside a new theoretical framework grounded in empirical data, concepts such as meta-stability/meta-instability, catastrophes and bifurcations.

7.4 The Junctions

7.4.1 Back to Aristotle?

The forerunners who recognized the significance of irreversibility latent in time include Heraclitus and Aristotle. In particular, Aristotle made a remark on irreversibility when stating "The now in one sense is the same, but not the same in another" or "While passing away constantly, time remains as time" according to Heidegger’s translation. This statement may look contradictory in the light of the principle of contradiction whose significance Aristotle certainly recognized. The principle says that one cannot both affirm and deny the same thing in the same respect at the same time. The remedy Aristotle came up with was the infamous entelecheia or telos at which when reached all of the likely contradictions would disappear in a wholesale manner. Although Aristotelian physics based upon entelecheia has lost its influence since the advent of Galilean physics, this does not mean that the irreversibility itself, noted by Aristotle, would also lose its significance. Quite the contrary, Aristotle’s remark on subjective irreversibility sets a critical criterion on explicating our conception of time in the first place.

7.4.2 Back to Plato?

When searching for new mathematical formalisms in biology it might be beneficial to take into account the paradigm change imposed by the discovery of the universal machine and the mathematics associated with it so far: that is, recursion theory and theoretical computer science. This might be useful independently of the mechanist hypothesis in the sciences of life and/or mind. If the mechanist thesis is correct, we can assume that the formalism we are searching for is already part of the very rich mathematics of computer science taking the word in a broad sense. If the mechanist thesis is refuted, then a good understanding of machines and their limitations can only help in developing another, better formalism for non-mechanically emulable processes. Indeed, the larger part of computability theory is already a study of the infinite ladder of non-computable functions, and the study of degrees of non-algorithmic solubility. In fact, "computability theory" is really the study of the non-computable functions and processes, and the very existence of the notion of universality is made possible conceptually by the fact that programmable processes have intrinsically non-computable effects, as Turing's non-halting machine problem already illustrates. The study of computer science leads by itself, for this reason, to the study of *partial* computability[23], and degrees on non-computability and non-machine 'emulability'. Marchal shows in a direct way that IF we are machines (whatever "we" might mean, as far as "we" have consciousness), then the physical laws cannot be computable or Turing emulable (Marchal, 1998). Despite this, it is also obvious that many biological phenomena are mechanical in their nature, for instance the reproduction process, self-regeneration and embryogenesis. The conceptual problems of reproduction and self-regeneration were not solved either by Descartes, despite his many attempts, nor by the embryologist Driesch who concluded on the presence of some unknown vitalist force. But those problems have been solved in the humble opinion of the present authors both in theory and practice (Case, 1971; Marchal, 1992). The basic idea is very simple, and has many very deep consequences, including eventually the possible refutability of mechanism or of the Aristotelian conception of reality. In a nutshell, the solution for self-duplication or for any more general formal self-transformation T is given by the idea to apply a duplicator operator of 'itself'. If Dx gives xx (or T(xx)), that is if DA gives AA (or T(AA)) and DB gives BB (or T(BB)), then what is it that will give DD? Obviously DD will give DD. And this solves the problem of self-reproduction. Or it will give in the general case T(DD), which gives in turn a general solution for arbitrary computable self-transformations. This technique has been used to implement "amoeba" (a self-reproducing program) and "planarian", a program that can be cut in pieces such that each piece regenerates the missing parts. It presupposes the existence of discretely standardized cellular components.

The same kind of "diagonalization" (going from x to xx, and applying the result to itself) is the basis of a whole field of self-reference theory, and it has been shown that machines are able to introspect and even to discover what the laws of physics have to

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[23] For a recent discussion of incomputability in biology and physics please refer to (Longo, 2010).

be, in case that the mechanistic hypothesis is correct. This leads to a total reversal of the Aristotelian paradigm and shows that the Platonist conception of reality is closer to the mechanist consequences than the Aristotelian.

Somehow the physical reality is no longer primary but appears to be the border of a Universal Mind, which can be seen as the mathematical structure describing the highly structured potentiality of a universal machine.

This insight is helpful to (re-)formulate the classic old "mind-body" problem in a mathematical way, and many promising results have already been obtained here. It shows, notably, that being a machine necessarily entails that physics cannot be entirely computational. And this in turn can be extended to life processes – despite the mechanist initial assumptions.

Paradoxically, this makes mechanism a very general vaccine *against* reductionist thought in general. Thus, Universal Machines already defeat all reductionist theories concerning their *behaviour* and *thought processes.*

The "physics of machines" is thus offered in two parts: a provable part and an unprovable part of the machine. And this motivates a theory of qualia as an implicit addition as it were extending the theory of quanta (or talia in Latin), which is the one we use to test mechanism, and also to measure our degree of non-Turing emulability in case that mechanism has been shown to be wrong.

All of this exemplifies also that the difference between natural and artificial is an artificial one, and thus is natural for any creature developing a self-centered conception of its surroundings. Just as Jacques Lafitte already foresaw in 1911 and published in 1932, that machines are natural collateral extensions of life, and biology cannot really be separated from engineering and computer science studies (Lafitte, 1932).

We have by now isolated and implemented eight modal logics which are variants of the Gödelian type of self-reference, which makes it possible to handle the two notions of first person and third person point of view for machines with or without oracles[24] (Marchal, 1998; Chaitin, 2011). Further research here would consist in developing a flexible categorical semantics, based on linear logic and sketches theory, allowing some "fuzzification" of those logics, and allowing the ideal case of correct self-referencing logics to be extended to machines capable of self-revision and self-updating. We thus have found an interesting link between the logic of first person knowledge and time-duration, which makes such an extension naturally embeddable into the Integral Biomathics of the INBIOSA project. We anticipate fruitful

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[24] An oracle is a machine that computes a single arbitrary (non-recursive) function from naturals to naturals (Turing, 1939). In other words, it is just another name for non-trivial meta-level heuristics that lies outside an object-level theory. In Integral Biomathics, we regard "oracles" truly lying beyond the object-level (scientific and/or mathematical) theories such as group theory and QM. In other words, an oracle is anything that *is* or *can lead to* a true statement that cannot be reached within a formalized (syntactic) system of the said theory. Oracles are part of all human knowledge that cannot be proven within any of the *currently known* formal systems; i.e. they contain “true” statements that cannot be proven in the Gödelian sense. All our theories will remain incomplete, but as they become richer, what once lied outside a given theory will become part of the (still incomplete) new theory.

consequences for anchoring Integral Biomathics as a major bridge across engineering, biology, computer science, mathematical logic and category theory.

We expect also some deep clarification on more philosophical issues related to Fredkin's Digital Philosophy[25] (Fredkin 1990; Fredkin 1992), Chaitin's Omega Theory (Chaitin, 2006) and a possible shift from an Aristotelian towards a more Platonist or Neoplatonist conception of reality, which would lead to a very important new emphasis on fundamental biology on the part of physics.

7.4.3 Back to Kant?

Although the critical thought of Kant was intended as a restoration of Newtonian paradigm of certainty questioned by Hume and in consequence led to conclusions limiting our access to knowledge of the world as it is – which may go beyond interests of this study – his greatest and most universal achievement was the *recognition of conditions for the acquisition of knowledge*. The pessimistic conclusions of Kant have been based on the assumption that the necessity of the intervention of the Twelve Categories of Understanding shaping or forming Sensibilities (or we could say perceptions) obstruct the access to things as they are. However, it may be reinterpreted simply as self-referential character of knowing. To know something, we have to employ our knowledge, considered by Kant as a priori to avoid problem of circularity. For us, it should not be a surprise, as it is yet another expression of autopoiesis, a characteristic of all living systems. We can attempt to change our perspective and instead of escaping, engage in resolving the issue of self-reference, for instance by investigating the mechanisms in the brain responsible for these categories, but in terms transcending classical conceptual framework. Such a framework can be found in the study of information, which gives a more general view of living systems, but includes cognition as one of many functions of the higher organized forms.

Kant believed that the statements of Euclidean geometry are synthetic, but a priori, and that they condition in a necessary way our understanding of the spatial relations. Non-Euclidean geometries have shown that we can go beyond these. It is true that our scientific analysis in science is guided by Boolean form of logic, which seemed necessary, but quantum mechanics shows that logic of events in the micro-world is non-Boolean, which does not preclude their comprehension. Thus, if we can go beyond the limits of the categories of understanding, there is no reason to believe that we cannot reach the level of perspective in which we can understand understanding. Moreover, we can expect that in an autopoietic process this may allow us to make our understanding essentially deeper. Conditions for transcending limits of the mechanisms of understanding consist in formulation of a conceptual framework in which living systems are both subjects and objects of inquiry. The concept of information is present in the study of such systems at every level of organization, and therefore it is a natural candidate for this conceptual framework. Schroeder (2009) considered also a secondary concept of

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[25] Fredkin's Finite Nature Hypothesis states that ultimately all quantities of physics, including space and time, are discrete and finite (Fredkin 1990; Fredkin 1992). It suggests that all measurable physical quantities arise from some Planck scale substrate for multiverse information processing. Also, the amount of information in any small volume of space-time continuum is supposed to be finite and equal to a small number of possibilities.

information integration, which allows the introduction of quantum logics into the study of consciousness, thus extending classical, Boolean logic without the necessity to involve quantum mechanical description of the system. The work includes a theoretical mechanism of processing information at this extended level.

This leads to another generalization, which allows the consideration of a wider class of theoretical processing devices corresponding to geometric, topological and other relations. This conceptual framework opens the way for studies of all varieties of categories of understanding in terms of theoretical brain mechanisms. However, understanding of the implementation of such theoretical mechanisms in the brain will probably be impossible without resolving the more fundamental problem of the description of a living system in terms of information and its processing, where the autopoietic essence of the mechanisms will have to be considered.

No matter what solutions are proposed, it is necessary to recognize the importance of the lesson from the great synthesis of Kant, and from its errors. Our comprehension of the world is conditioned and shaped by the fact that we are living systems, which are creating their (our) own tools for this comprehension and at the same time participating in the world. Thus, development of our knowledge is a subject of an autopoietic process.

What we know cannot be separated from how we know. From this point of view, biology has the potential to inform and guide other disciplines, in particular those considered more fundamental. Maybe better understanding of our understanding can bring solutions to the problems studied by physics and mathematics.

7.5 What Can We Do Now?

It is essential for this review that we recognize both perspectives taken on science, that of Plato and that of Aristotle. While empiricism has been dominating science ever since Galileo and Newton, the idealistic view was abandoned for a very long time. Now in the age of logic, computation, immersive reality and virtual worlds, Neoplatonism can have a renaissance. Instead of Plato vs. Aristotle, both viewpoints are suddenly legitimate and arguable under Kant. But we also recognize both their unity and antagonism with Hegel and Schelling. The issue of "assumed objectivity" becomes disputable again – and taboos such as the suggestion that the way of natural sciences is the only one that can be taken seriously are being questioned again (Fasching, 1996). We welcome the return of scientific disputes, for it is indeed dangerous to have a "thinking monoculture." After many years of research, we still do not know what reality is (Fasching, 2000; 2003). Therefore, there will be no taboo questions on the INBIOSA path. Note also that the position stated cautiously in section 7.4.2 above is only that, IF mechanism is true, THEN we are in a Platonist arithmetical video game. But it does NOT say that mechanism is true.

When questioning the foundations of biology, we are going to leave no stone unturned, including those on which we stand and will step on in future. Dogmas will not be accepted. We will also consider the implications of modern physics for this work. In particular, we realize the likely relevance of quantum theory (QT) to biology and the chance for a fruitful dialogue between physicists and biologists, specifically about quantum entanglement and quantum coherence which are considered by some to be the key to life and consciousness, despite the unsettled state of physics in this area. On the one hand, it could greatly benefit biology to take note of QT in accounting for living processes (Schrödinger, 1945; McFadden, 2002; Ho, 2008). On the other hand, biology could help explaining QT (Pattee, 1971; Josephson, 2012), an argument, which is relevant to Salthe's Hierarchy Theory (Salthe, 1985). Yet, it is Hierarchy Theory that erects the main problem to QM effects at above the microscopic scale[26]. If there are three levels separated by scale, such as [biological cell [macromolecule [atom]]] and there are occasional effects on atoms by QM fluctuons (in Conrad's terminology), this might have fleeting effects on several out of thousands of macromolecules. But the question is what would be the likelihood of significant effects on one cell? It is not easy to resolve this conflict between Hierarchy Theory and most QM interpretations.

An interesting example in this respect is an unorthodox theory related to a key concept in quantum mechanics, – entanglement and the EPR paradox (Einstein, Podolski & Rosen, 1935). One interpretation of this entanglement is known as the "Everettian heresy", (Osnaghi et al., 2009). In 1957, Hugh Everett, III, proposed a new interpretation of quantum mechanics questioning the orthodox view of the Copenhagen school, proposing a "relative state" formulation (Everett, 1957a/b; Everett, 1973), denying the existence of a separate classical realm from the QM one and asserting a state vector for the whole Universe. According to this theory, known as the theory of universal wave function, the state vector never collapses, and hence reality as a whole is scale-free and rigorously deterministic. Everett's idea correlates to Hierarchy Theory because it is higher levels that govern the lower ones by imposing boundary conditions constraining them. This reality, which is described jointly by the dynamical variables and the state vector, is not the reality we customarily think of, but is a reality composed of many worlds[27] as a source of potential splitting to come in the development of time. By virtue of the temporal development of the dynamical variables the state vector decomposes naturally into orthogonal vectors, reflecting a continual splitting of the universe into a multitude of mutually unobservable but equally real worlds in retrospect, in each of which every good measurement has yielded a definite result with the aid of the environmental decoherence and in most of which the familiar statistical quantum laws hold[28]. Should we dare to question the foundations of modern

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[26] Any level constructs an interpretation of lower level effects (which do not penetrate as such to a higher level), while being governed by boundary conditions imposed by higher levels. The levels are screened off from each other dynamically; otherwise there would be no levels!

[27] The phrase "many-worlds" is due to Bryce DeWitt, who was responsible for the wider popularization of Everett's theory.

[28] Note that Everett's theory is only one of a number of alternative interpretations of quantum theory dealing with the measurement paradox. Roger Penrose listed six types of interpretation in his book "The Road to Reality" (Penrose, 2005, p.786), the last of which, calling for further theorizing about the nature of reality, has a number of variations. The list includes the many worlds interpretation of Everett-Wheeler, which Penrose lists as second. The only reason for selecting Everett in this example is that entanglement is connected with the observer as a living system and the state vector, which unifies the classical and the quantum world. A unifying theory is a clear objective of Integral Biomathics. But there might be better arguments than the option/choice of having multiple worlds that motivate this goal. We don't know yet.

science? Yes, because this makes it science. And it is our job to ask questions. Everett's theory is interesting for biologists because it has the potential to solve the riddle of entanglement in a rational (humanoid) manner without invoking laws except for those specific to QM, dispensing with the demarcation line separating the quantum and the classical. The "relative state" vector implies that the two measurements in the EPR experiment are each simultaneously connected (or even integrated!), by their very definition, with the observer, and hence automatically correlated**.** In other words, the fact that an observed object state (psi-object) is a function of BOTH the capital wave function of the whole universe (Psi-universe) AND the observer's own to himself unknown state (psi-obs) in the formalism of quantum mechanics was the solution (Rössler, 2011).

Perhaps the "many worlds" theory is only a (first person) subjective reality incompatible with (third person) objective physics? But isn't that another explanation for the information integration that Schroeder speaks about in his "quantum logic/coherence without quantum mechanics" (Schroeder, 2009), cf. sections 5.8 and 7.4.3? This question shows how we are going to attack the riddles of biology: by being open to and discussing any good idea. This holds particularly for the enigma of life, the genetic system, enabling the preservation of historical events.

The interpersonal (de)coherences in our INBIOSA discussion circle could be exemplified metaphorically by the following citation of one of our members about another one[29]:

> "Matsuno takes chemical reactions generally to be mediated by QM coherence with the end products falling into decoherence. This signals an escape from externalist 'statistical mechanics' into a QM 'internalist' mode of seeing the physical world. Matsuno argues that achieving QM coherence of chemical reactants can be seen as a process of mutual internal measurement – which we will note, would be a semiotic process – one which antedates the origin of life." (Salthe, 2008, p. 145)

In short, we have discovered an interesting theoretical co-relation between such ideas in biology as internalism (Matsuno, 1989, 1996, 2003; Rössler, 1998; Salthe, 2001), quantum coherence (Matsuno, 2000; Schroeder, 2009), emergence and self-organization (Salthe & Matsuno, 1995), development and evolution (Salthe, 1993; Salthe, 2010), perception/semiosis (Salthe, 2005b), cognition, consciousness, first person descriptions (Matsuno, 2003), information, information integration and the way we use it[30] when we actively participate in structuring the universe (Schroeder,

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[29] Everett's theory is contrasted with decoherence interpretations (listed third by Penrose, although he considers it a pragmatic, and now most common interpretation) that Matsuno is drawing upon. We often have disjoint and even rival views presented in INBIOSA (which is also the intention of the project). The important issue is, however, the consent that quantum entanglement is likely to be relevant in biology, and it could be that through biology it will be possible to get a clearer insight into which of these interpretations is best for living systems, or whether some new interpretation will emerge.

[30] Being 'mechanisms' of information integration in our brains, which create what we experience as *mind*.

2011), making science and so on: all this within the framework of Integral Biomathics. But isn't that a perpetual interaction and circulation of Plato, Aristotle, Kant, Hegel, Schelling and others?

Which are the major challenges on the three junctions described in the previous sections?

***Aristotle*:** A new challenge awaiting us will be: how to appreciate the class identity that can outlive the individual identities in our current practice of the empirical sciences? In physics, it has been common practice to conceive of the class identity of the atoms or molecules of the same kind only in terms of their individual indistinguishability. However, once we enter the biological realm, the situation becomes drastically changed. Even if the physicist cannot distinguish this from the outside, there arises the not unlikely possibility that a material body may maintain its identity through a constant exchange of its constituent material subunits.

A partial list of challenging questions, which can be addressed, reads as follows:

1. Does the exchange of materials assume an irreducibly fundamental significance, even without prior participation of possible cellular structures? (This question is related to another basic question seen e.g. by Putnam of whether the exchange of materials could be as fundamental a property as (in the context of the material body referred to in isolation) its inertia.)

2. What could the principal characteristic of a material body, whose class identity can outlive the individual identities of the constituent material subunits, be?

3. How does the flow of time unique to cyanobacteria differ from a similar flow of time so obvious to the physicist (except for Boltzmann)? (The question is how cyanobacteria experience what the physicist calls time, rather than how the physicist reads time into what cyanobacteria are doing.)

4. How influential could the likely existing network of the various biological clocks be on the distinction between the class identity and the individual identities? (Even in cynanobacteria, the clockwork of the KaiC protein requires ATP as the phosphate source, and this again requires a different kind of clocks for its own synthesis. The activity of signs also requires an attribute of time, e.g. an activity through some sort of medium. The same applies to action, reaction, synchronization and the like. The question is: from where can we recruit what is eventually called time that could apply to whatever material agencies?)

5. How can we describe[31] the synchronization of various clocks of material origin without relying upon the equation of motion? (If we employ a form of the equation of motion for describing the possible scheme of synchronization, this would turn out to

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[31] Note: Here is a deep confusion that is inevitable for all of us who can speak. All of us are inclined to think that time is irreducibly fundamental unless asked otherwise. However, this strange stipulation simply does not apply to biological organisms other than our human beings. Time for us is a representation of something enigmatic. All of the other biological organisms experience that "something" directly without using the tag "time" as we do. The underlying question is: how can we distinguish time as a representation from the original object to be represented eventually as time by us.

be self-defeating in the sense that it has already assumed the flow of time equated to the displacements of the state variables – unless time does not flow in physics as Boltzmann claimed.)

6. How can we estimate the robustness of a complex network of various clocks operating upon the distinction between the class identities and the individual identities[32]? (An answer to this question may be relevant to how and to what extent each biological species including ours can remain robust in the whole network. Addressing this kind of problem is possible in the framework of the present methodology since the flow of time is here tentatively attributed to each material body's capability of making a distinction between the class identity and the individual identities.)

Plato: From a logician's perspective, Everett's "interpretation" is the literal (technically, the free or Herbrand model) of quantum mechanics without collapse (Everett, 1957a/b, 1973). Everett only applies the wave equation to the couple made of the physicists and the observed particle. The work of Marchal (2001; 2004; 2005) is very similar, in the context of digital mechanics. Starting from a well defined distinction between first person and third person in the mechanist frame, Marchal discovers that physics becomes reduced to an internal many worlds, or probably better "many dreams" statistics on semi-decidable arithmetical relations (computations), where a dream is defined by a computation seen in some precisely defined first person perspective. These works accomplish a reduction of physics to the biology (or psychology, or theology[33]) of numbers (or digital machines).

It shows that Everett's way of embedding the subject (physicists) in the object (the quantum wave) *necessarily* has to be extended into an embedding of the subject

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[32] For instance, individual dogs are always "dog-like", even if the internal clocks vary from one dog to another. A dog is "dog-like" in the human frame of mind, not in the dog's mind. In a sense dog-like-ness is a timeless abstraction. But, *individual* dogs are different (Elsasser, 1981). How different? In particular, their bodies are constantly exchanging their constituent material elements. The individual identity of each carbon atom entering their bodies is traceable only over half a year at most. When we say that the major ingredients of dogs bodies are carbon atoms, what we refer to by the tag "carbon atoms" are not the carbon atoms to be distinguished individually, but the class property of the carbon atoms that can be maintained in their bodies even if each one of them is replaced by another one of the same kind (as implied in physics). Metabolism in biology makes any organism as a material manifestation of the class identity when viewed from the perspective of the participating atoms. Each atom in the material world has both the individual and the class identity. The question is about how can we distinguish between these two?

[33] Marchal defines the theology of a machine by the arithmetical truth *about* it, or involving it (in third and/or first person views) minus what the machine can prove about itself. He sums it up often by saying that theology is Tarski's truth minus Gödel's provability. This gives a "toy" theology of the ideally self-referentially correct machine. It provides a theology close to early Platonist theologies, which include physics as a sub-branch. Indeed, he proposed a complete and testable arithmetical interpretation of Plotinus's neoplatonist theology (Marchal, 2007), including his "two matters" theory (sensible and intelligible matter).

(mathematician, biologist, theologian) into arithmetic, and that this leads directly to an arithmetical quantum logic justifying why, from the points of view of 'number', physics seems linear, symmetrical and having many branches interfering statistically. It is the only precise theory, which provides a *testable* explanation of where the laws of physics come from, and which exploits the incompleteness phenomenon to distinguish a mathematically precise theory of quanta from a more general theory of qualia. The quanta appear to be first person plural sharable qualia. Marchal argues that the gap between proof and truth that machines can infer when introspecting themselves (a possibility already seen by Gödel), justifies the use of the term "number's theology" instead of biology or psychology. It shows also that Rössler's endophysics (1987; 1990; 1998) is naturally extended into an endoarithmetic once we assume digital mechanism.

A key question to answer on the way is: how could we save the best of the Platonic world in the wild if the phenomenon called time is not an illusion?

Kant: Kant (2003) based his synthesis on the distinction and opposition of the understanding, structured by categories and the sensibilities reflecting external structural characteristics of reality. The former basically defined the idea of an object (thing) in general; the latter identified its instances. They were related by means of schemata such as time or space without which there could be no explanation about how categories can function to organize sensibilities. It is clear that Kant's idea of schemata, although extremely obscure, served as the uniting element of his philosophy of knowing. The choice of time and space as schemata can be interpreted as a reflection of the mechanistic view of the reality influenced by the success of Newtonian paradigm. It implies that objects are assembled by schemata into an organized whole, which can be studied in a mechanistic way.

Our task is to review both the categories of understanding and the idea of schemata, to prevent the bias of the mechanistic view of the world. To some extent the initial steps in this direction have been taken by Humberto Maturana and Francisco Varela (1980), who focused their study of the foundations for the comprehension of living systems on the relationship between concepts of structure and function, with the autopoietic process as a uniting element. However, this framework is too narrow to provide a comprehensive vision of reality. Also, their explanation of the concept of autopoietic machine includes references to the spatial separation from the world outside and to the temporal aspects of perpetuation. Therefore, although autopoiesis remains an important concept characterizing living systems, it lacks generality and independence from more fundamental referents, which are necessary to initiate building of a new synthesis. For instance, the transition from the traditional focus on substantial aspects to organizational (relational) ones is, in the case of living systems necessary, but it is not obvious and very doubtful that the category of substance can be left without any counterpart.

The work on such tasks should proceed from beginnings in Aristotelian categories through Kant's more elaborate, but much less clear system of categories, sensibilities and schemata, to a system all of whose elements are clearly justified. In addition, it is important to analyze the mutual relations of these elements, in particular relationships between the categories, or whatever would take their place. If we want to retain the framework of Kant's synthesis, one key question we have to answer on the way is: how could we naturalize the Kantian schemata for space and time in the face of the latest version(s) of quantum mechanics at the turn of the 21st century? In other words, do we need to revise Kant’s synthesis?

Conclusion: Everett's interpretation is not the only choice among all other alternative theories of QM. In particular, it is based on concepts of the old, original wave function formalism which does not require mathematical elaboration and remains very useful in practical applications, but, because of the involvement of accidental, only historically justified elements and the lack of generality is of less value for understanding QM[34]. However, theories such as Everett's also have some merits: in provoking the established methodology of thinking, in the virtue of Aristotle's potentiality principle, in the conception of gedanken-experiments and in the scientific discussions that precede adequate choice and (if necessary) development of the mathematical apparatus. This is what really counts, but is usually neglected, when planning and doing science. Most of the time is used for thinking, which cannot be measured in physical, let alone, monetary units. Therefore, the Integral Biomathics approach aims to minimize presuppositions and consider all possible interpretations of physical theories for assessing their value in explaining life. It is interesting to note that very different approaches as those of Everett's, Marchal's and Schroeder's lead to some similar conclusions by involving the observer in the equation. This correlation must mean something. To answer what we need to do is more research. Nevertheless, theoretical advances in QM and its impact on biology are one issue, and their empirical evidence is a different one. Theoretically, QM effects might affect a macromolecule[35], but such events would be individual. The question is: how do they accumulate in order to have an effect on the cell? There are differing opinions:

> "Neurobiologists and most physicists believe that on the cellular level, the interaction of neurons is governed by classical physics. A small minority, however, maintains that quantum mechanics is important for understanding higher brain functions, e.g. for the generation of voluntary movements (free will), for high-level perception and for consciousness. Arguments from biophysics and computational neuroscience make this unlikely." (Koch & Hepp, 2007)

The quest continues, e.g. (Georgiev, 2011).

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[34] In particular, this formalism cannot accommodate superselection rules, which show that actual physical systems considered as quantum ones are partially quantum and partially classical.

[35] Salthe places them in the chemical realm on the basis of scale compared with the size of the cell (Salthe, 1985).

7.6 A Unifying Formal Framework

In biology, classical models (mostly based on non-linear differential equations, dynamic systems, graph theory, stochastic processes or information theory) are well adapted to study local problems, but it is impossible to extrapolate global properties of a system from its local features. For example, in a cellular system, the molecules that make up the cells follow different laws from those at the level of cells, even though both molecules and cells are part of the same whole. Moreover, each part operates on its own time scale, and these temporal variations play an essential part in the evolution of a system. So we need to develop another frame in which both local and global problems can be analyzed. Category Theory is a good candidate for providing the unifying formal framework for **Integral Biomathics,** in particular to propose solutions to some of the problems indicated in the preceding sections.

7.6.1 Why Categories?

Category Theory (CT) is strongly related to graph theory. A category is a (directed hyper) graph[36] plus an internal composition of directed edges. Conversely, a graph generates the category of its paths, obtained just by adding its paths as new edges (with convolution as composition). Eilenberg and MacLane introduced Category Theory in the early 1940's; it has a unique status, at the border between mathematics, logic, and meta-mathematics. It was introduced to relate algebraic and topological constructs, and later its foundational role in mathematics and logic was emphasized by several authors, for example, in the theory of *topos* developed by Lawvere and Tierney, and in the *sketch theory* developed by Ehresmann. In particular it provides a single setting unifying many domains of mathematics and makes a general concept of structure possible. Categorical logic is now a well-defined field based on type theory for intuitionistic logics, with applications in functional programming and domain theory, where a Cartesian closed category is taken as a non-syntactic description of a lambda calculus (Church, 1940; Lambek, 1986).

Category Theory, seen as an analysis of the main operations of the "working mathematician", reflects some of the prototypical operations that man does for making sense of his world.

Among these operations are formation, dissolution, comparison, and combination of relations between objects (morphisms and their composition in a category); synthesis of complex objects from more elementary ones ("colimit" operation); analysis (decomposition of complex objects); optimization processes (universal constructions); formation of hierarchies of objects ("complexification"); classification of objects into invariance classes (formation of concepts as projective limits).

As these operations are at the basis of science, it explains the interest of applying Category Theory in other scientific domains. For instance, categories propose new perspectives on the foundations of physics (e.g., using higher order categories and "higher symmetries") for studying quantum field theories, quantum gravitation, string

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[36] Here we restrict ourselves to 'small' categories whose objects form a set. In general, 'large' categories are also accepted. Lawvere has shown how Category Theory can serve as an alternative to axiomatic set theory (Lawvere, 1966).

and D-branes theory (cf. Baez, Coecke, etc.). In the late fifties, Robert Rosen introduced categories to develop a relational biology.

A 'dynamic' Category Theory (incorporating time and durations) is at the basis of the Memory Evolutive Systems (Ehresmann & Vanbremeersch, 1987, 2007), which give a frame for hierarchical natural systems with a multi-agent, multi-temporal self-organization, such as biological systems, cognitive systems or social systems. MES simultaneously cover the local, global, evolutionary and temporal aspects, in particular analyzing how the interplay among the possibly conflicting local logics of the co-regulator agents can lead to a 'less disruptive' global logic merging most of them into a higher synthesis. Among the categorical tools used in MES figure the (co)limit operation to model the hierarchy. Goguen, a well-known computer scientist (who died in 2006), one of the first to use categories, had proposed to use this operation already to this end in 1970 (Goguen 1970). However even in his later works (e.g., Goguen, 1992), he does not contemplate the main problems studied in MES. For instance in their first 1987 paper on hierarchical evolutive systems, Andrée Ehresmann & J.-P. Vanbremeersch already apply colimits in a more elaborate manner to develop a theory of emergence and complexity and to construct the "complexification process" (which relies on previous works of Andrée and Charles Ehresmann (A. Bastiani-Ehresmann & C. Ehresmann, 1972). And there is nothing in Goguen's work (e.g. Goguen, 1992, based on sheaf theory) that relates to the 'dynamic' aspect of MES with its multi-temporal self-organization as developed in (Ehresmann & Vanbremeersch, 1990, 2007).

7.6.2 The Memory Evolutive Systems (MES)

The Memory Evolutive Systems (MES) provide a mathematical model for autonomous evolutionary systems of higher complexity, such as biological, neuro-cognitive or social systems. Such systems have a tangled hierarchy of interconnected components varying over time; their self-organization is directed by a net of mutually entailed functional regulatory subsystems, the "Co-Regulators" (CRs), each operating with its local logic at its own complexity level, with a specific timescale and a differential access to a central flexible *memory*; where successive experiences can be stored and later retrieved for better adaptation. The model developed by A. Ehresmann and J.-P. Vanbremeersch since 1987 (Ehresmann & Vanbremeersch, 2007; for a summary, cf. the paper by Ehresmann and Simeonov in this volume) is based on a 'dynamical' theory of categories which provides a frame for studying the following problems:

1. The *Binding Problem*: how do simple objects bind together to form a complex object forming "a whole that is greater than the sum of its parts"? (The "whole" C is represented by the 'colimit' (Kan, 1958) of the pattern P formed by the interconnected simple "parts", explaining how the class identity (or complex identity of C) can be preserved while the "individual identity" of the components of P varies. And what are the simple and complex interactions arising between complex objects? The simple links just bind clusters of links between lower level components. However it is proven that "complex links" can emerge when the system satisfies the "Multiplicity Principle" (MP), a kind of "degeneracy" (in Edelman's sense, 1987), ensuring the existence of 'multiform' objects admitting functionally equivalent, but non-connected, lower order realizations. These complex links compose simple links binding non-adjacent clusters, and they reflect global properties of the lower levels not observable locally at these lower levels.

2. The *Emergence Problem*: how to measure the 'real' complexity order of an object and to characterize the property allowing for the formation of objects and processes of increasing complexity orders through successive "complexification processes" over time? The complexification process explains how new categories can 'emerge' and gives an explicit description of them. A major result proves that MP is the necessary condition for the emergence of objects and processes of increasing complexity order through iterated complexifications; for instance the emergence of complex organisms, or of higher cognitive processes (as explained in MENS, cf. Section 8.1.3). And MP clarifies the difference between "mechanisms" and "organisms" (in Rosen's terminology).

3. *Multi-scale self-organization*: how is the dynamic of the system generated internally, through the competition/cooperation between its net of coregulators, each operating as a hybrid system, at its own rhythm and with its own logic? Each coregulator selects a procedure on its "landscape", but their various procedures may conflict, requiring a global equilibration process, the interplay among coregulators, a kind of selection process among them, to which the Multiplicity Principle provides more flexibility. This process must respect the temporal constraints expressed by the "synchronicity laws". It leads to the global logic which will be implemented, possibly causing loops of dysfunction/repairs between the coregulators.

The MES model leads to several applications, for instance:

(i) Efficient *methods for ubiquitous complex events processing*, in particular leading to a *Theory of aging* for an organism (cf. Section 8.4).

(ii) Model *MENS* for a neuro-cognitive system (cf. Section 8.3). It is a MES obtained by successive complexifications of the evolutive system modeling the neural system of an animal.

MES allow incorporating typical biological properties, and also physical ones, for the first time in a formal mathematical framework. However they do not tell the whole story of living systems.

7.6.3 Open Problems

Up to now, the MES theory comprises the following characteristics:

> **Advantages:** The MES theory offers a model, which simultaneously takes account of the hierarchy, complexity and dynamic multi-agent multi-temporal self-organization (beyond autopoiesis). Its main result is the singling out of the Multiplicity Principle (MP) at the basis of emergence of higher structures and processes, providing the only explanation of emergence we know at this moment.

> **Weaknesses:** Theoretically, MES cannot solve the difficult problem of interplay among CRs; we point to the temporal constraints given by the synchronicity laws, but there are many other constraints, which should be taken into account. Besides, we need to answer the question of how to deduce a global logic from more or less conflicting local logics, each with multiple instantiations. Practically, the above issues are not easily amenable to computations of any kind to this moment. A possible approach for a more dynamic computing/communications approach to these problems could be through the *Wandering Logic Intelligence* (Simeonov, 2002a/c). This is what Ehresmann and Simeonov propose in their paper in this volume, (Ehresmann & Simeonov, 2012).

Another problem is to take account of the fact that living systems exhibit supplementary structures. To account for them, (the configuration categories of) a MES can be "enriched" with these structures. It is easy with topologies or higher categories. It is more difficult to introduce the kind of randomness natural phenomena exhibit (for instance the firing of a neuron when the depolarisation is above threshold generally occurs only with some probability). An important step in this respect would be to introduce a notion of "stochastic" category in which the composite only exists with some probability.

7.7 Conclusions and Outlook

The new paradigm of **Integral Biomathics** distinguishes physical structures from functional structures, the former being defined in physical terms while the latter are defined in terms of their behaviour. In physics there is little difference between the two in that structure or constitution tends to determine behaviour while given some observed behaviour one is often able to determine the structure that is responsible. In biology, on the other hand, there may be no specific structure associated with a given function; instead there are many ways to achieve a given goal: the functionality acts a filter determining which structures are possible.

Functionality is not entirely straightforward either, as it is typically achieved through a number of components working together. Thus, an important aspect of functionality consists in components *learning to play their part* in a larger system, consisting of two or more components. In some cases this involves systems learning to recognize *signs* and responding appropriately. In other cases a function is developed by a less constrained process, which can be characterized as play. These processes all go towards making a biosystem behave as a unitary whole, with a particular perspective of its own.

This tendency to create "wholes" extends to the environment of a biosystem, as each particular unit finds *niches* in which it can function effectively. In an even subtler mode, *signs* may find niches where they are effective, as in our use of language.

Another unique aspect of biological systems is that as they evolve, they create new *signs* and new niches. Niche creation is a relatively new and rapidly growing field of study, mainly in ecology (Ulanowicz, 1986; 1997), but it is a concept that applies to all levels of organization. One of the most intriguing aspects of niche creation is that it is often the excreta of one organism that creates the niche for another (classic examples being oxygen, which poisons anaerobes but created a new niche for aerobic organisms, and dung and the evolution of dung beetles).

Furthermore, the concepts of selective retention of some components and the selective elimination of others also seem to be unique to biology. A further twist is provided by the idea of complementarity (see section 5.1). Complementarity relates to the ambiguity of reality in our perception of it. The fact that we may view, for example a situation or thing as one entity or alternatively as another entity, or even choose between the two to fit our purposes, reveals Nature, as it were, offering us options.

The usual ways of characterizing Nature loses these subtleties, treating Nature in objective terms, assuming we can master it cognitively and say definitely what is there. With the concepts discussed above we can start to consider the question 'what is really going on', in the new light of **Integral Biomathics**.

8 Initial GTLS Application Domains

This section describes the efforts to apply this general theory in many domains, with special emphasis on cross-disciplinary problems and multiple domains spanning both "hard" and "soft" sciences. The result will be a coherent collection of computationally hostable analytical techniques.

The following sections present a non-exclusive list of applications in Brain/Mind Science using Category Theory as major tool.

8.1 Fusing the Different Levels of Brain/Mind Modeling

At the synaptic and neuronal level, since Hodgkin-Huxley's seminal work in the early 50's, we have accurate biophysical models of single neuronal dynamics. Sophisticated computational models have been produced since then, but neuroscience itself has remained fragmented at the different levels of organization in the brain. These are the microscopic level of neurons, the mesoscopic level of networks of neurons, and finally the macroscopic level of whole brain areas in which cognitive function arises. Thus, we have a whole host of mathematical structures and frameworks to fuse together. Each one of them has to be evaluated regarding its effectiveness in order to decide how it could be developed further into a larger framework for which we are searching.

The use of mathematical tools, such as Category Theory combined with stochastic continuum neural field theory and related dynamical systems analyses, will give a common underlying framework to obtain variables relating the different levels of description (micro, meso, macro) for studying these mechanisms, and for explaining how they may lead to the emergence of higher cognitive processes. Computational models of the hippocampus (Burgess, 1994; Arleo, 2000) state that the sum of a set of elements (grid cells) directly produces another element, a place cell. In doing so, these models take for granted that the properties of the sum are directly reducible to those of its components. This strict form of reductionism is at odds with the nature of complex systems. Gomez-Ramirez (2010) has used Category Theory for modeling the formation of place cells from grid cells in the hippocampus in a non-reductionist way. The cooperation of the grid fields gives rise to a colimit, which is a place field.

8.2 Scale-Free Dynamics

An object that presents invariance over changes of scale of observation is scale invariant. This is a symmetric property of paramount importance in mathematics and natural science. Simply stated, scale invariance means that the object reproduces itself on different time or spatial scales[37]. For example, it presents self-similarity in a geometrical context. Scale free dynamics refers here to the invariance of the equations that describe the dynamics of the system. Thus, given an observable O i.e. an equation, which depends on the parameter x, we say that it is scale invariant under the change of x by αx, if exists a number, $\phi(\alpha)$, such that $O(x) = \phi(O(\alpha x))$. For a more in depth characterization of scale invariance, and other related phenomena like self-organized criticality or fractality, see for example (Sornette, 2000; Embrechts 2002).

Studies on scale invariance in the brain are being spurred thanks to the progressive increase in spatial and temporal resolution of recording techniques. It has been recently demonstrated (Expert et al., 2010) that even fMRI data when appropriately analyzed, exhibits self-similarity and hierarchical structure at all length scales. Indeed, the apparent heterogeneity of various parts of the brain hides some general mechanisms at the basis of its functioning. In particular, it is well known that mental operations depend on the activation of synchronous neuronal groups, different such neural groups having the same role. We explore the concept of meaningful patterns, which is similar to the term "cognit" coined by the neurobiologist J. Fuster (Fuster, 2005) and with the concept of "neurocognitive networks" conceived by S. Bressler (Bressler, 2007). The neural populations at the mesoscopic level in the olfactory bulb studied by W. Freeman (Freeman, 2000) are also similar to our meaningful patterns.

However, the identification of meaningful networks or patterns that express those cognitive functions, which are what this theory promises, is, as is recognized by its own proponents, simply daunting. Indeed, when dealing with broadly distributed connections of a large number of components, highly coupled with non linear dynamics, the resulting behaviour of the neurocognitive networks are, in many cases, impossible to control and predict.

The problem is as follows: assuming that we know how to describe the dynamics that neurons would exhibit in isolation, and assuming that the dynamics of the temporal patterns of those isolated neurons have a well-known long-term behaviour, like for example stable fixed points or chaotic attractors; if we couple those systems together the global behaviour is still missing.

This is the essence of Complexity Science: understand the global dynamics of complex systems, consisting of a number of elements, strongly coupled and with highly non-linear dynamics. We believe that i) by acknowledging scale free dynamics

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[37] In a topological context, it is interesting to note that a scale-free network is one that does not have a specific scale of the size of connection e.g. power law distribution is scale-free (Barabási, 1999)

hypothesis, and ii) by using mathematics like Category Theory combined with other methodologies of complexity sciences such as Network Theory, a more effective and fruitful approach in the unveiling of meaningful patterns in the brain will be possible.

Scale-free dynamics of neocortex are characterized by hierarchical self-similarities of patterns of synaptic connectivity and spatiotemporal neural activity (Freeman, 2007). We are going to develop a novel framework to investigate the structure of complex brain networks, based on Category Theory, combined with statistical mechanics to model high-dimensional complex data.

8.3 The Model MENS

MENS (Ehresmann & Vanbremeersch, 1990, 2007, 2009) is an application of MES (cf. Section 7.6) to a neuro-cognitive system. This hierarchical model has the neural system at its base with its neurons and synaptic paths between them. The components of higher levels, called category-neurons, represent increasingly complex mental objects or processes obtained as the colimit of each synchronous neural (hyper-)assembly which they activate. Such category-neurons are obtained from the neural level by iterated complexification processes, and they have multiple physical realizabilities into neural 'pyramids'. The model accounts for the formation of a flexible internal model of the Self, the Archetypal Core, and explains how it is at the root of the emergence of higher mental or cognitive processes, up to consciousness (Ehresmann & Vanbremeersch, 2002, 2009). For a more precise discussion, please refer to (Ehresmann, 2012) in this volume.

8.4 Application to Complex Event Processing: A Theory of Aging

Organisms such as living systems have a multi-agent multi-temporal self-organization. In MES the agents are the coregulators (CRs). Each CR operates locally stepwise with its own rhythm, logic and partial information. However, their commands to effectors must be coordinated through 'interplay' among CRs, which, as said in Section 7.6.2, causes dysfunctions (fracture, dyschrony or even the need for re-synchronisation) to the CRs whose commands cannot be realized. In particular the temporal constrains of each CR must be respected, and hence the synchronicity laws relating the period of a CR to the stability span of the intervening components and the transmission delays between them; these laws are indicated by (Ehresmann & Simeonov, 2012) in this volume.

Failure to respect these laws may lead to loops

fracture → repair → fracture…

between CRs of different levels, possibly leading to a re-synchronisation of some CRs.

One application is an Aging Theory for an organism, through a cascade of re-synchronisations for physiological co-regulators of increasing levels (Ehresmann & Vanbremeersch, 1993). This theory agrees and unifies most known physiological theories. On the other hand, Zlotin's work (Zlotin, 1972) forms the physical basis of a theory of aging, which applies to all dissipative systems (Salthe, 1993).

Other applications of this process have been developed for complex event processing for various organisms (Ehresmann & Vanbremeersch, 2011), leading to a methodology for anticipation using complex switches between different realizations of multiform objects to generate complex scenarios.

9 The GTLS Test Cases

This section describes the theory’s test cases. These are designed to demonstrate, prove and communicate the results. The problem is one that spans physics, chemistry, biology, societies and societal dynamics. It requires integrated measurable results at many levels, and it is in a general area known to present "grand challenges" to existing methods.

A key aspect of understanding the brain and other complex systems is to appreciate the logic in relatively small and simple sets of information. The goal should not be complexity per se, but design systems that provide complex functions, without structural complexity. Thus the goal is to eliminate complexity from the design side. If we can do that we can understand complexity in biological systems. This can only be done by grasping the underlying principles, such as robustness, stability etc. We need to go small for doing that, e.g. to start with small complex systems like the E. coli. In the following we propose three projects as test cases.

9.1 WLIMES

Living systems are systems with a tangled hierarchy of interconnected components varying over time, with a multi-scale self-organization. As explained in section 7.6, the *Memory Evolutive Systems, MES* (Ehresmann, A. C., Vanbremeersch, 2007) provide a mathematical model based on a 'dynamic' category theory for such multi-scale complex systems. However MES are not yet amenable to some kind of "computation".

The Wandering Logic Intelligence, WLI (Simeonov, 1999-2002a/c), is an open, hierarchical and dynamically structured model for communication systems. It enables the design of a special class of ad-hoc mobile active networks, Wandering Networks (WN), defined by the following characteristics:

a) flexible, multi-modal specialization of network nodes as virtual subnetworks;
b) mobility and virtualization of the net functions as hardware and software;
c) self-organization as multi-feedback-based topology-on-demand.

Network elements can contain several exchangeable modules capable of executing diverse network functions in parallel. They can be invoked, transported to or generated in the nodes upon delivery of mobile code about the node’s behaviour. For this purpose, both the processing nodes (ships/netbots) and the information packets (shuttles) are active (i.e. executable), exchangeable, re-configurable and programmable. The WN elements are of temporal character; they can be created, configured and removed. Functions can change their hosts, wander and settle down in other hosts.

WLI is a technical concept taken from the domain of biology, i.e. a "bio-inspired" mechanism with the goal of solving problems of growing complexity in communication networks. It combines the issues of information processing, exchange, storage and virtualization into a robust operational engineering framework.

The solutions are distributed "human-designed" self-organization algorithms such as WARAAN (Simeonov, 2002b) and HiPeer (Wepiwé & Simeonov, 2006) implemented as conventional Turing Machine computation. They are artificial constructs and run essentially as any other communication protocol or resource discovery scheme. The only distinction is their inherent growing behavioural complexity achieved by "memorizing" and distributing navigation and structural information about the evolving environment "locally" in the genetic code of the shuttles when traversing the netbots.

Now, WLI as an extracted-from-Nature model can be applied back to biological systems in a series of iterations to ensure its verification. The most characteristic concept is the one of fractal virtualization of resources and its continuous multiplication in terms of "software chunks" over time, which does not really have analogs in biology and physiology.

Therefore, one of the intended projects is to combine the two approaches WLI and MES into a novel theoretical model framework, WLIMES, the Wandering LIMES, the suitability of which has to be verified against real world biological systems. In particular this frame could approach the computational problems raised by MES. The idea is that the CRs of MES and the *netbots* of WLI play similar roles. What of the shuttles? In MES a link is 'active' at t if some information passes through it. This information of various kinds (physical, chemical, code, etc.) could be carried by *shuttles,* which activate several consecutive links on their way.

One of the main problems for making MES amenable to computation is the 'interplay' among the CRs. Indeed the commands sent to effectors by the various CRs at a given time can be conflicting. In terms of WLI it means that there are competitive shuttles. Can WLI methods be extended to solve this problem? We will try to answer this question.

9.2 Hyper-B

The importance of scale to biological systems makes it imperative that one of our test cases should face this issue head on. Our second project addresses the properties and operation of a multiscale complex computational hierarchy, as briefly described earlier.

Following the description of Section 5.2 of this document (‘Scale and Hyperscale’) such a computational hierarchy will consist of alternating levels of logical ‘normality’ and logical ‘complexity’. The former will be provided by *InfoMax*, a currently successful cortical processing model, (Cottam et al., 2000), while the latter will be modeled using Schroeder’s (2009) informational integration ‘quantum logic without quantum systems'. In many ways this project is parallel to WLIMES, but its grounding philosophy and integrated mechanisms are very different. This follows from the Integral Biomathics approach of testing different approaches to the same target – that of modeling biosystems.

Hyper-B will start by establishing a single computational scaling model – where data at one level becomes contextualized to information at another. The following phase will be to couple more than one of these computational schemes together to represent the multiscale nature of biology. In doing so, the information created at one level becomes the data for the next, as the context itself will be scaled. As indicated in Section 5.2, inter-level transit appears to resemble quantum error-correction techniques, and this will be simulated by the collection of contextual ecosystemic information at one level to facilitate transit to a higher one.

This kind of scheme is neither bottom-up, nor top-down in character: propagation in both of these directions is necessary to instill the required cross-scalar correlations, which will lead to the generation of a global systemic identity.

We envisage two different ways in which the resulting computational assembly will be accessed by considering applications. The first corresponds to a scheme, which was put forward in 1991 (Cottam et al.) to provide computational responses to threats within a limited time-window. This kind of *survival computation* envisages access to a hierarchical assembly by propagating a (threatening) stimulus internally from the highest hierarchical level towards the lowest. Each successive level takes more and more processing time, but results in progressively greater accuracy of response. Waiting as long as possible during the available window of time then yields the 'best' response possible.

The second way in which we envisage access is through a separately computed *hyperscale* representation of the multiple scales. This hyperscale representation will be created in a manner similar to that integrating the multiple scales themselves – by a combination of *quantum logic without quantum systems* and *InfoMax*. In this case, all of the scales will be simultaneously accessible, but only with a reduced precision (as the scales themselves are partially enclosed when viewed from outside). The net result here will be a systemic identity which takes account of the degrees to which individual scales are enclosed (and therefore partially inaccessible), and which delivers a systemic image which is biased towards the naturally most open, and therefore most representative scales.

9.3 Morphogenesis

A third test case could be the realization of a computational framework dedicated to the generation of multi-scale models of living tissues and organs. The framework would be founded upon the self-organizing principles of morphogenesis. One of the most spectacular and fascinating manifestations of self-organization in living systems is embryogenesis and the morphogenesis of organs during the developmental phase of the embryo. It is during this phase that the exceedingly complex and interwoven structures of tissues and organs are grown out of a "disordered" mesenchyme. Only morphogenetic-based methods will be able to produce realistic multi-scale 3D models of tissues and cells. Manual modeling can only produce a stereotyped organization by concatenating parametric "template" elements. Today's modern imaging systems (RMI, scanners) can provide gross anatomical features but are a far cry from "showing" the intricate capillary and lymphatic networks and nerve structures around, say, a small group of cells. Yet, if building models of living tissues and organs is the goal, we need to model all the dynamics that occurs around and within its most important unit: the single living cell. The structures involved are individually complex, interwoven, and anisotropic in their physico-chemical properties.

The challenge then is to devise self-constructing models that can simulate the self-organizing processes that underlie embryogenesis, growth and adult-life adaptation.

Living tissues are highly complex and intertwined. They perform functions like mass transport. And any attempt to model such functions requires shape information at all levels of detail before setting the boundary conditions across each interface (e.g. flux, partial-flux or no-flux across boundaries for a given chemical species). Thus an important part of modeling life-like tissues lies in producing realistic multi-scale 3D morphologies, boundary conditions and incorporating the anisotropic properties of the system under study. This is particularly true when modeling living organisms.

Understanding the morphogenesis of tissues and organs from a single cell will open the window to Nature's secret of generating forms of tremendous complexity from the initial egg structure. Despite this complexity, fundamental research in developmental biology seem to confirm that morphogenesis results from coordinated cell behaviour such as signaling motion and aggregation, division, differentiation and apoptosis (Dressler, 2006). The process is initiated by inductor cells and coordination is mediated by short-range direct cell-cell and cell-extra-cellular matrix interactions as well as medium to long-range interactions mediated by chemical and electrical morphogenetic fields. It is the spatiotemporal organization of these interactions that determine the final structure.

This test case addresses many issues of the INBIOSA research program. Indeed, the following points could be studied:

a) multi-scale structural generation;
b) multi-modal, short, medium and long range interactions;
c) simultaneous co-dependencies between these interactions and the global form/geometry of the structure being generated;
d) combination of discrete structures (e.g. cells) with "continuous" quantities such as morphogenetic chemical and electric fields.

In addition, descriptive knowledge (predicates) could also be included in the framework in order to inform the latter about the agents and entities involved in morphogenesis.

This would open the door to other INBIOSA issues, such as:

i) addressing entailment and relational biology,
ii) incorporating Category Theory / MES,
iii) developing introspectively articulated systems.

10 Call to Action

In the following sections we summarize the major conclusions of this report.

10.1 The Case for Transformative Research in Biology

This section summarizes the argument in this paper seeking FET support for a continuance into Phase 2 of the transformative, i.e. high risk, high payoff research proposed by the INBIOSA group of researchers. The proposals are organized around the broader theme of the sciences of complexity rather being narrowly focused on biology as a complex science *per se*. However there is a central focus on biology because of the many advances contributing to the new sciences of complexity achieved from the massive societal investment in health and related sciences research over the past 50 years.

Our proposals are organized around two fundamental themes that we believe are essential to the transformation of modern science:

a) the need for convergent theoretical syntheses which will crystallize the theoretical challenges, and
b) the need for innovative mathematical concepts to effectively articulate these new syntheses into a verifiable theoretical foundation for practical applications.

Lastly, we provide proposals for institutionalizing these transformations into future FET funded research.

We believe that our research proposals meet the criteria for qualification as scientific grand challenges and are worthy of further investment as the spearhead of a new renaissance in science. The proposals are critically relevant to scientific progress because they address the issue of systems (real and artificial) of increasing complexity; they are paradigmatically radical because they call for convergent theoretical synthesis of a magnitude not seen in biology since Darwin; and they will have a radical impact on all sciences of complexity because they will offer new metaphors and mathematical innovation. We recognize that such language may appear to be overly and insupportably ambitious. Indeed, we do not know if among the world scientific community, there exists the genius to address the problem statements we have put forward.

What we do know is that is has happened before – a methodological revolution in the physical sciences: the transformation of physics into a dual discipline of experimental and theoretical physics – that brought forth the modern world.

That revolution was founded on the discovery that the apparent complexity of the world could be addressed by rigorous experimental methods and the development of mathematical languages and grammars that stunned our own beliefs in the power of human thought (Wigner, 1960).

But now we face a new intellectual challenge, not of apparent complexity but of *genuine irreducible* complexity in our quest for a more fundamental understanding of living entities and the complex institutions and technologies enabled by our scientific culture. The rigor and fundamental paradigms of physics advanced all sciences across a very wide field of knowledge bringing new observational tools and computational capabilities to bear on the new quest. That quest is beleaguered by the intransigence of living systems to submit to the assumptions of simplification and computation of the physical sciences. The dynamic complexity of all living entities appears to be irreducible and totally confounding.

Our ability to describe the biological world in all its manifestations has reached the point where we can track neurons and chemical transactions in the brain simultaneously; at the higher levels of the organization of life we have terabytes of data describing our social, ecological, technological and economic systems. We have reached this condition of information overload in the sciences of living systems because our theoretical understanding greatly lags our observational capabilities. We are confounded with an excess of incommensurable observation and theory in much the same way that the astronomers of old were confounded with what appeared to be irresolvable inconsistencies in their observations of the stars and Ptolemaic theory until the Copernican Revolution. Because biology has proliferated too many theories and paradigms, all too narrowly focused, there is the need for convergent theoretical synthesis ultimately synthesizing a simpler theory (canon of parsimony) that encompasses the subordinate ones. The implicit response of mainstream science is to wait for the Copernicus of the modern era and for the generations of genius that will inevitably follow him. But we have reasons not to wait.

10.2 The Threat to the Certainities of Continuing Progress

The first reason why we cannot wait and why we must attempt to accelerate the progress of science is that the growing complexity of the modern world – the product of first scientific revolution – is becoming increasingly evident to all. We are many now. We are massive consumers of the earth's energy resources. Our information technologies support industries, economies, education and financial systems from the global to the individual level. Our medical and biochemical technologies enable bodily interventions of unparalleled complexities in an ever more costly effort to manage the diseases of modernity. Our industrial technologies demand equally intensive and complex interventions in all the natural ecologies that support life on this Earth. But all is not well. Despite the undeniable progress in human welfare the complexities of modernity are growing and threatening the certainties of our continuing progress as a society and species.

What makes these threats extremely problematic is that we have a world universally entrained in complex systems and interventions where we know scarcely anything of their potential interaction and failure rates and forms[38]. The risk is therefore of catastrophic failure because of this universal deployment and extreme dependence. In some areas, such as national security, where our security is based on engineered systems of complexity, we take steps to limit catastrophic failure by pursuing the development of systems of even higher complexity (e.g. countermeasures utilizing quantum computing as the shield against computer hacking or subversion).

However the availability of opportunities in most areas of natural complexity is very limited because we do not understand how Nature develops complexity in the first instance.

10.3 The Intellectual Challenge of the Complexity Sciences

There is a second reason not to wait. Frustration with the inadequacy of conventional scientific approaches in addressing societally supported research objectives and the unquenchable thirst for understanding that drives human existence invites intellectual risk-taking. Some of that risk-taking is paying off. We are painstakingly learning how to conduct the many sciences of complexity[39]. For science itself is a complex system of human creation[40].

We now understand science as a highly complex hierarchical system of thought, a noetic system in itself, whose careful reasoning and open-ended insight processes are irrepressibly capable of generating novel theories. We can have a new confidence in embarking on a journey of intentionally challenging ourselves to explore the complexity of living entities because we have begun to learn from the history of science how to advance science itself.

The lessons are twofold: first, there is a need for theoretical convergence of the many working theories and hypotheses that arise across the many narrow subdomains of complex fields; secondly that it is essential to develop mathematical formalisms

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[38] Notably, an earlier EC expert consultation has reported: "… that the number of digital systems and artifacts is increasingly exponentially, such that we are approaching a point where digital entities have ceased to be just technical systems and have become part of the socio-technical fabric of society. This plethora of semi-autonomous, 'cyberphysical systems' – which all rely on embedded ICT and are connected to the information ether – will constitute a new kind of physical intelligence…For our societies to function effectively, we have to learn to identify and give meaning to interactions within these highly complex, cooperative and dynamic systems. This poses severe challenges from both technological and societal perspectives." *FET Consultation on Collective Adaptive Systems,* November 2009.

[39] "Semiosis and self-organization are co-extensional - there are as many different basic types of semiotic processes as there are basic types of systemic self-organizing processes." (Hofkirchner, 2002)

[40] "Human language, culture, science, technology, systems of governance and economies are all examples of human symbolic systems that propagate their organization. They occupy a special place in the biosphere. They are products of human conceptual thought and represent emergent phenomena. They differ from the materially based information in biological systems in that they are abstract and symbolic and not materially instantiated as such with the exception of technology. In the case of technology it is the concepts and organization that goes into the creation of the physical tools that propagates." (Kauffman et al., 2008).

derived specifically from and for the fields in which complexity reigns. *If we adopt these overarching principles of scientific innovation we will have new tools to apply to the methodological challenges in biology and complex systems generally.*

10.4 Programmatical Advance in Theoretical Research

While history is replete with stories grand and (sometimes) failed of intentional efforts to develop technologies for extremely ambitious human undertakings (e.g., the Manhattan Project, the Man on the Moon Project, the (Japanese) Fifth Generation Computing Project, The Human Genome Project, The Blue Brain Project, etc.) there is no history of programmatic advance in theoretical science, the essential foundation for all scientific and technological advance. It took two thousand years for the world to be persuaded of the importance of theory to the establishment of heliocentrism, but only four hundred years more to await the discovery of the power of mathematical abstraction to advance theoretical science. Perhaps within a generation we will extend our grasp of the dynamics of living systems and their sister technologies. Let us assume that there may indeed be genius in our midst with the imagination required to unlock this most complex of mysteries. How should we accelerate engagement with this challenge among our best and brightest?

We have no answer to this question but offer three considerations:

1. The first is that the modern world is unique in history in that it is rapidly proliferating complex technologies of production and intervention on a global scale and it does so without full and responsible knowledge of the consequences of continued complexification of these technologies; that is a risk no one has measured or considered; the need to understand is great; never has the project of scientific advance worked under such conditions.
2. The second consideration is that of the possibilities of the complexity sciences enabling a second revolution in the re-shaping of the world towards human needs, security and sustainability. Advances in disease management, ecological stabilization, resource efficiencies, and social justice are potential outcomes of greater understanding of basic life processes and the cultural edifices and artifacts enabled by cumulative human creativity and collaboration.
3. The third, and even more encouraging consideration, is that we have a much greater potential in terms of human resources and its new-found connectivity to bring to bear the human intellect required to address the challenge – if we want; we lack only the institutional frameworks to do it. The challenge is to invent and create the necessary institutional settings required to foster specific methodologies for the advance of critical areas in science.

INBIOSA suggests consideration of a conceptual model for such an institutional framework based on the concept of emergent complex systems itself: in other words to mimic, in the larger world, the thought processes and structures that enable the emergence of new ideas in the human mind. The list in the next section is a reformulation of the previous table in section 6.4 listing potential fields of research addressing complexity issues. The reformulation as a (tentative) hierarchy of theoretical orientation is a first-cut schematic for implementing the central scientific challenge of performing the necessary convergent synthesis of theory underlying the complexity of living systems. The institutional challenge is to recreate that thought process at the scale of the total societal effort in the relevant sciences.

In other words, the co-ordination – but not the control – of the many modules of thought that could, but are not being brought together into a more coherent model of life itself. This would involve co-coordinating efforts through FET for academic and private interdisciplinary collaborators guided by the principle of synthesis. Implementing such co-ordination is the institutional challenge. The form of structure and communication that would most benefit the process is not yet known. What is known is that existing processes of collaboration and disciplinary integration and co-ordination do not support such synthesis and mathematical innovation. There is a great deal to explore ahead of us.

Despite revealing more detail, natural sciences have not provided a complete theory of reality yet. Modern culture and science constrain us (Pickering, 2011). For instance, mind and intelligence have been investigated in a very limited way in Artificial Intelligence (Ray, 2011). There are natural phenomena such as sentience (Clarck, 2000) and emotion (Damasio, 2005) that do not have measurable characteristics (quanta).

The nature of Nature is its incompleteness (Deacon, 2011). Integral Biomathics accepts that and tries to discover the missing links and fill the gaps by putting/developing mathematical theory and computation into/ out of biology. A part of the broad perspective that lies in the future of Biocomputing and **Integral Biomathics** is shown in (Seaman & Rössler, 2011) and (Josephson, 2012).

10.5 A New Framework for Mathematics and Computation

In what follows, we present a (non-exhaustive) list of key themes for research in Integral Biomathics. It is far from Hilbert's famous list of challenging problems in mathematics (Hilbert, 1902). We do not believe in reviving the idea of an axiomatic system of science. We consider INBIOSA, as a developing project, a permanent "building site" with concepts and ideas in permanent movement. "The future is easier to predict with hindsight". So, this list should be considered to be a preliminary one. We will continue working on it in a follow-up project.

The following two activity fields comprise our research framework.

Living Systems Modeling

i) Develop new realistic mathematical models tailored for living systems, obtained by integration and development of different domains of mathematics: algebraic topology and geometry, cohomological algebra, functional analysis and differential equations, differential geometry and fibred spaces, statistics and probability, different kinds of logic, and so on.

ii) Develop new simulation, visualization and creativity support techniques and tools for these novel mathematical models of the living.

Steps towards a "New Integral Science"

The essence of typical questions to be addressed is how to take account of the (possibly fuzzy) interactions between discrete and continuous phenomena, leading to the emergence of complexity.

1. Design an original general system of abstractions within the biological domain that can be relationally examined. It should support multiple complementary mathematical approaches to phenomena that can be brought into dialogical juxtaposition.
2. Define ways of identifying the biological properties that are as unique to such complex conglomerations as ‘temperature’ is to a set of molecules, or the 'flexible redundancy' property ubiquitous in biological systems, called degeneracy or multiplicity. What we seek to articulate is an evolutionary mathematics that deals with the emergence of organization from non-random selection among replicating variations within complex populations of processes.

We are looking here not only for space-time scale invariant properties of living organisms, but also for *cardinal* properties that may *differ* across the space-time scales, which are still inherently "biological". Our view of emergence includes both the emergence of more complex objects as aggregates of patterns of interacting lower level objects, and the emergence of complex interactions between them, which emerge at the higher level from the global structure of the lower levels but cannot be locally observable via lower level components. Also we understand emergence as a product of a system functioning over time falling in relation to the unfolding of its larger environment.

10.5.1 Approach: Constructivist Innovative Mathematical Cross-Disciplinary Models

The main activities that need to be addressed here are:

- Develop dynamic models of biochemical and biophysical systems accounting for multiple scales and time frames as they relate to new forms of dynamic modeling and physical mapping/scanning systems. Analyze how scales themselves can be of emergent character.
- Develop convergent theoretical syntheses of adequate mathematical concepts and methods, bringing them into dynamic relation with each other. Such a relational mathematics is expected to model both the dynamics of the system in a local neighborhood with its specific temporality, and at the global level of

the system emerging from the possibly conflicting relations between these local dynamics, through a kind of communication and negotiation between near and far neighborhoods.

- Construct models of "hybrid" systems presenting a combination/ juxtaposition of continuous as well as discrete time changes accounting for their relational, statistical and geometrical aspects as well. To analyze biological problems, the mathematical challenge is how to combine these different domains, which are generally studied separately in orthodox mathematics.

As Category Theory unifies many mathematical domains and is also at the frontier with logic and computer science, it should be used in models formally describing natural phenomena, as well as more orthodox domains such as partial differential equations and chaos theory, topology and cohomology, dynamical systems, geometry and field theory, fuzzy sets and probability, and so on.

Category Theory should itself be enriched and made more flexible by addition of more structure, for instance by introducing statistical categories. Categorical models are well equipped to analyze the problem of emergence, going further than Rosen's notion of entailment, up to the emergence of higher cognitive processes, perhaps allowing the incorporation of first person approaches (Topological Psychology). They can also provide multiple perspectives related to the problem of "class identity" and material space/time flow.

The working "algorithm" to realize this approach might be defined as follows:

1. Investigate phenomena in living systems by trying to describe them using the above (integrated) formal toolset to deliver an evolving model.
2. At the point where the model does not match the experimental results, develop new formal means to reflect and explain these peculiarities, thus advancing the model to a next stage.
3. Focus on both objects and processes and on their interactions.

This method should not be understood as strictly formal. In other words, the "match" with experimental results could be verified by means of computer programs, or only require pencil and paper. On the other hand, there are also *negative* mathematical proofs (limitation results), e.g. by logical deduction, predicate calculus, or even gedanken-experiments involving visualization tools (geometry, animation).

10.5.2 Focus and Implementation: Integral Biomathics

Integral Biomathics (Simeonov, 2010a/b) is a cross-disciplinary meta-theory, involving both internalist and externalist mathematical biology and biological mathematics based on advanced mathematics formalisms, such as e.g. the Memory Evolutive Systems (Ehresmann & Vanbremeersch, 2007), an evolutionary dynamic category theory aimed at integrating (halting)[41] oracle machines (Turing, 1939) and other related mathematical and computational theories and abstractions, as well as heuristics and a broad range of simulation, visualization and other creative support techniques capable of dealing with phenomena and data that cannot be handled by formalisms alone. It allows interrogation marks/interfaces between its constituents and builds bridges to other disciplines.

The operative framework of Integral Biomathics is defined as a multi-perspective approach to knowledge production: observation of new phenomena / incorporation of new forms of entailment-generating-technology (e.g. scanning methodologies) as well as modeling approaches → articulate convergent theoretical synthesis across divergent fields → integrate multiple mathematical formalisms under one relational umbrella → *develop integrated mathematical models accounting for multi-scale structures and multi-temporal dynamics* → study the dynamic relation between emergent phenomena and predictive phenomena → justify initial theoretical approaches via computational modeling → develop empirical demonstration and verification → articulate a falsifiable theoretical foundation for practical applications.

This gives us a panoramic view of the system with all its structures, dynamics and functionality:

- Enable the use of information from different areas of discourse to examine how low level processes "percolate up" and relate to higher levels, and how human scale behavioural processes may enable first and third person comparative relations.
- Define concrete approaches to discrete computational methodologies (functioning at different scales) to capture change over time from a series of different multi-modal observational perspectives. Define systems that can also present coherent integrated high-level processes that relate to the lower level processes. This is about the integration of the computational aspect and its material underpinning.

A first step towards realizing this goal is a follow-up project of the INBIOSA initiative that will devise a research framework combining object-level mechanisms with

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[41] The halting problem is indeed among the most famous ones in computer science. The question here is: should we restrict ourselves to *halting* oracles only? Indeed, any meta-heuristics that lies outside an (object-level) theory is an oracle *with respect to the object-level*. For instance, an agent (natural or artificial) that decides to include group theory as a means to tackle quantum mechanics takes an "oracle"-like decision with respect to both (object-level) group theory and QM. The questions/goals that arise then are: (i) how to model such an agent for biology? and (ii) can we later devise a more general theory that would substitute the oracle and where the decision would naturally fall *within* the theory? So, we pursue the replacement of oracles in general, but as a short and middle term goal we have to focus on the halting problem. Therefore, we decided to use the term "halting" in braces henceforth to capture both the short and long-term INBIOSA objectives.

Turing oracles[42] (Chaitin, 2011). This is going to be a step stone towards a "unified theory" of living systems, both "natural" and "artificial" ones. Therefore, our longer-range objective will be to step-wise replace the oracles by a more general theory of life. Our approach is mathematics-based and biology-driven.

Further, we are dealing with life that includes artifacts with self-reference (i.e. first person vs. third person) as key issues; the development of self-* software is the high-yield intellectual, practical and economical reward of this high-risk program. Following results stemming from Systems Biology, AI researchers may want to extrapolate and use the life metaphor to build systems capable of general intelligence and autonomy. But General AI, e.g. (Fogel, 66; Holland, 1975), in itself is *not* the concern of Systems Biology.

INBIOSA addresses life in general (both natural and artificial). Our program treats both subjects at the same time. Systems Biology and other related disciplines (Biological Computation, Computational Biology, etc.) address specific problems in biology, which are of considerable practical interest, but are not fundamental biology problems in the sense defined by the INBIOSA project[43]. The same holds for the recent efforts to apply Quantum Physics for explaining biological phenomena in the same style as for the emergence of classicality from the quantum. Each one of them is based on a certain interpretation of QM taken as a base, but not on a systematic review and analysis of the appropriate theoretical models (and perhaps the creation of new ones) from the viewpoint of biology. The INBIOSA focus is on looking for new ideas. In particular, contemporary biology and physics do *not* address the following questions/goals:

1. Are the currently existing scientific/mathematical/computational theories sufficient, such that meta-level Turing oracles could be replaced by models within these existing theories, and given that we have more data available?
2. Are the current theories insufficient in the sense that no amount of additional data is going to replace some of the oracles in our models?
3. Can we postulate/conjecture that even if (2) holds, a theory (or a set of compatible and/or complementary theories) able to replace oracles by models can be conceived/unveiled? In other words, can we imply that decision making and judgments lie *within* the theory?
4. What is missing on the way to creating a Unified Theory of Life and Consciousness?

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[42] We have to take oracles into account, because they are characteristic for biological phenomena. For instance, the evolutionary transition from dinosaurs to mammals can be modeled by halting oracles, although they do not entail local changes in the probability of histories. A reference paper about the role that oracles play in problem solving in the case of a random oracle is (Kurtz, 1983).

[43] Recently, some authors began speaking of "integrative" systems biology realizing that orthodox systems biology does not address fundamental issues (Auffray & Nottale, 2008; Nottale & Auffray, 2008).

5. How to create a "Tree of Life" (or perhaps a universe of multiple and simultaneous worlds), a living ontology of facts, axioms, propositions and theories, in biology, physics and science as a whole guiding the evolution of science?
6. Can biology be associated with the emergence of decoherence in quantum mechanics? How could the Turing's oracles be naturalized in the framework of quantum physics?

Integral Biomathics can be regarded as a new branch of Theoretical Biology. If the intended Theoretical Biology has an empirical relevance as it should do, it must be also anchored on solid material or physical grounds.

Therefore, we aim to devise a research program on a global scale in a follow-up project with the following foci:

1. development of a theoretical and computational framework that incorporates both oracles and mechanisms whereby real-life complexity can be captured to an extent that other contemporary approaches (e.g. systems biology) do not;
2. stepwise elimination of oracles by generalizing the theory (or theories) underlying the framework; i.e. the oracles will gradually be replaced by statements/models that lie within the mathematical and computational theories being generalized;
3. clear definition of milestones that include the following:
   a. conceptualization and elaboration of the computational framework that includes, but also separates meta-level oracles from mechanisms;
   b. construction of experimental and validation protocols to verify the legitimacy of the oracles (or classes thereof) and their interactions with the modeled mechanisms;
   c. search of statements/models within existing theories that will eventually replace a subset (if not all) of the oracles;
   d. discover/unveil new/neglected theories in an attempt to obtain a single "unified theory".
   e. physical or hardware implementations of oracles.

Life and mind have escaped all effective complete theories up to this moment. Therefore, we require that Integral Biomathics be an incomplete theoretical and computational framework. It uses oracle machines, but it remains always incomplete and extendible. Without (halting) oracles, theories can only be "more incomplete". With (halting) oracles we obtain a research program on hyper-computers or super-Turing machine (Siegelmann, 1995). **Current theories about life, such as systems biology and related computational frameworks (Wolfram's Science, DNA/cellular computing, etc.), do not use oracle machines to model living systems in their full complexity. By involving oracles in our Integral Biomathics research framework we create a methodology, which leads us stepwise closer to reality.**

We have recognized that quantum mechanics is now entering the second revolutionary stage particularly from the perspective of practicing biology. That is the resurrection of the time-honored issue of causality under a rejuvenated guise. The act of measurement comes to be internalized within quantum mechanics. In essence, our main focus will be in how to implement the role of the oracles within the proper framework of quantum mechanics.

10.5.3 Summary and Prospects

Every level of a living system is partially enclosed and partially in communication with its neighboring scales, and the entire system forms a 'self-correlating' whole of partially autonomous scaled 'sub-systems', each with its logic and temporality. The global logic and dynamics are modulated by their cooperative or conflicting interactions. **Scales of time and space emerge through this sort of communication. This is the real strength of the Integral Biomathics approach.**

The problem with both systems biology and molecular genetics is that they make use of standard reductionist approaches which visualise organisms as machines[44]. There are aspects of living systems that can be described in this way, and so we are trying to pass beyond this into uncharted territory. Biology is not simply about *such* automata.

We believe that phenomena in living systems can be explained using a robust mathematical theory.

There are a few options related to mathematical and/vs. computational approaches:

1. Extending an existing scientific theory that is mathematized, such as QM, GR, String Theory, etc. to life;
2. Using new mathematical specialties/tools *independent* of, although applied by, science; new advances within known mathematical domains or entirely new subdomains;
3. Developing a scientific theory of life that is mathematized *and* supported by computation (barring the non-computable parts);
4. developing new mathematical specialties/tools *independent* of, although applied by, science *and* supported by computation (barring the non-computable parts);
5. Developing a new theory in computer science;
6. Making a radical computational shift but without either a new scientific theory or new mathematics (e.g. Wolfram's Science (Wolfram, 2002), quantum computing, DNA/cellular computing, etc.);
7. All of the above?

We actually vote for the last option and wish to go even beyond it, assuming also other options, not listed above and reaching far into the fields of the arts and humanities. These are the new concepts related to mathematics and computation we often use

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[44] Pre-Gödelian (almost clockwork) notion of machine.

interchangeably throughout this White Paper, demonstrating the true essence of the adjective *Integral* before *Biomathics.*

The following actions are expected to take place on the way to realizing this goal.

Action 1

Define a mathematical ecology that can bring the following dynamic processes in relation to:

- a. autopoiesis (self-construction) and self-organization of biological systems;
- b. emergence of modules of hierarchy [and potential dynamic heterarchies/bifurcations] in all complex systems;
- c. variation of communication modalities within/between multiple hierarchical levels in living systems;
- d. transformations of information processes from scalar to vector/tensor quantities and vice versa (see discussion in section 4: the fourth major problem) ;
- e. integration of mathematical approaches that can link discrete, continuous, fuzzy/vague, probabilistic and geometrical information simultaneously; and
- f. formal treatment of heuristics[45], e.g. (Chaitin, 2011).

Action 2

1. Define an n-dimensional visualization that runs in dynamic parallel form.
2. Articulate relational definitions of biological functions and their boundary conditions.
3. Articulate a set of theories that cross boundaries between traditionally distinct domains:
   - a. time scales, spatial scales, adjacencies/material proximities related to neighborhoods;
   - b. new mathematical analysis of emergence;
   - c. mathematics of vague/fuzzy spatial-temporal boundaries;
   - d. contextual boundaries: boundaries between processes functioning at different scales of time and space; boundaries that describe the relationship between, and nature of fragmentation of, the entities they separate;
   - e. subject ←→ object relation; this is about first vs. third person issues: how they are separate, yet also unified.

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[45] To our knowledge, there is no current theory, computational framework, or applied field such as systems biology where oracles or meta-level decision rules are used to model living systems in their full complexity.

4. Define form and function — model the following form-function interactions:
    a. exploring mathematical viability for biology and biological process suitability for mathematics;
    b. developing of new *biology-driven* mathematical branches;
    c. maturing **Integral Biomathics**: integration of mathematical theories under a common umbrella for *biology-driven* mathematics and computation which goes far beyond what we know today as Computational Biology (Russe, 2009) and Biological Computation (Lamm & Unger, 2011).

The central questions to explore within this action plan for Integral Biomathics are:

i) *What* is computation within the biological context?

This question is about the relationship between the Church-Turing thesis and Turing's oracle machine. In short, the role of the (halting) oracle machine in the naturalized empirical setting is first on the agenda of the INBIOSA initiative.

ii) *How useful* is computation for living systems, where usefulness is considered from the viewpoint of the entity performing the computation?

This question is about the possibility for naturalizing the oracle machine. *How*? The strength of INBIOSA is in raising such a question.

iii) *To what extent* can a computation be carried out in an organism or an ecosystem with the available resources?

The computation cannot be separated from the matter of resource intake. This is another strong point of INBIOSA.

Finally, we have to articulate a program that can be managed and measured as it progresses.

Acknowledgement. This is all what we were able to write within this small and short project. If we had more time and money, we could do better. We believe that if the decision makers in the EC follow our recommendations on how we might better understand complexity, they would be better able to solve some of the most urgent problems in future.

We wish to thank all INBIOSA colleagues for the exciting discussions and valuable contributions and comments during this project that led to this White Paper. The members of INBIOSA also gratefully acknowledge the vision and support provided to this activity by the EC FET program and its staff. This report does not address itself to the considerable resistance to the transformation of science created by the institutional structures and prejudices of the academy and in the research funding priorities of most public agencies.

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Epilogue

By Arran Gare

Self-assembling, self-organizing, self-maintaining and self-replicating anticipatory systems with multiple levels of organization, adaptive dynamics, purposeful behavior and emergence and the complex forms of computation associated with these, the phenomena on which Integral Biomathics, or INBIOSA, is focused, are not abstruse theoretical constructs. They are characterizations of what we see all around us as life. That these concepts should appear abstruse reveals both the major obstacle standing in the way of this research project, and its importance. Integral Biomathics represents a new phase in the effort to comprehend what we see, as Robert Rosen put it, to comprehend *Life Itself.* The practical returns of such comprehension are likely to be new forms of computation, robotics and cognitive systems vastly superior to those that now exist, providing the means to reshape the world towards human needs; but this is only the beginning. The project will involve overcoming entrenched ways of conceptualizing the world that, in denying the reality of life, are blocking the advance of science and thereby foisting on societies fundamentally defective models of reality. When acted on, these defective models generate one problem after another while making it virtually impossible to deal with them effectively. Such problems now have a name, ‘wicked problems’, which understates their seriousness. They include the global ecological crisis that could lead to the destruction of most terrestrial life forms, including civilization. The new forms of mathematics and computing that Integral Biomathics is striving to develop are not merely better and faster versions of what we already have. The nature of mathematics and computation are being reconceived as part of an overhaul and transformation of the concepts that presently dominate science and society. These new concepts and the new computational technologies they make possible should enable us not only to better comprehend life, the physical world and society, but reveal how to address what previously appeared to be insurmountable problems of society and civilization.

The modes of thought that this project is struggling to overcome have never before been so completely entrenched. In the past, science based on Newtonian assumptions was so obviously limited that it had to be complemented by different ways of thinking. Kant and those influenced by him defended this. They accepted that true science had to be based on Newtonian assumptions, but allowed that life processes could be assumed to be teleological and gave a place to practical philosophy assuming free agency. With the advance of reductionist science, however, descriptive accounts of life ceased to be taken seriously and the humanities, based on the assumption of the capacity of humans to be free, began to self-destruct. The development of technology based on Newtonian science, culminating in digital computers and other forms of information technology, has consolidated this tendency. People are now enclosed in constructed worlds that channel how they live, perceive and think, blinkering them to the reality of anything that cannot be comprehended from this physically embodied perspective. Illustrating how such entrenchment is advancing, in a short piece on ‘Cells as Computation’ published in 2002 in *Nature*, Aviv Regev and Ehud Shapiro argued that current computer science now can provide the abstractions required for a scientific understanding of life. The ‘abstractions, tools and methods used to study computer systems’,[1] systems that are built on and embody Newtonian assumptions, are claimed to provide the basis for integrating all our knowledge of biomolecular systems. The acceptance of this argument would virtually rule out challenges to these assumptions, only allowing those aspects of life that could be comprehended through digital computers to be acknowledged as real. Such entrenchment has distorted our understanding of science itself and stultified its development. Science is now commonly seen as a linear accumulation of knowledge advanced through increasing specialization, while ways of thinking and ideas that are inconsistent with this body of accumulated knowledge are held to be unscientific. Conceived in such a way, scientific research is assumed to be manageable through bureaucratic structures controlling inputs and measuring outputs, collected, stored and analyzed by digital computers. This has reproduced the blinkered outlook of medieval scholastics who refused to acknowledge any experience that did not fit their received view of the world.

It would be unfortunate for science and technology if such self-enclosed ways of thinking were to continue to dominate. However, the implications of this mindset go much further than the practice of science. As Robert Rosen argued, organisms grow and act on the basis of models of reality, and this is no less true of human societies than other organisms.[2] The entrenchment and locking in of Newtonian assumptions has resulted in the failure to comprehend some of the most important aspects of reality, resulting in failure to identify and effectively respond to problems, and an inability to comprehend the reasons for this failure. The nature of such ‘wicked’ problems has been brought home most fully in efforts to deal with ecological destruction. Over and over again, efforts to manage ecosystems have failed, with proposed remedies based on resource management science with its emphasis on centralized institutions and command-and-control resource management has exacerbated the problems. As the ecologist Fikret Berkes and his colleagues noted, ‘A gap has developed between environmental problems and our lagging ability to solve them.’ The models of reality based on concepts adequate only to isolated systems or specially engineered experimental situations designed to exclude real complexity have themselves become an ecological problem. Recognizing the complexity of relations between natural and social systems which ‘cannot be understood, let alone managed or controlled, through scientific activity organized on traditional disciplinary boundaries’, these ecologists are calling for radically new ways of operating.[3] This situation in itself is a wicked problem as the same reductionist mindset that is responsible for defective management of ecosystems is also responsible for command-and-control efforts to manage

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[1] *Nature*, 419, 26th Sept, 2002: 343.

[2] *Anticipatory Systems,* Oxford: Pergamon Press, 1985, p.6f.

[3] Fikret Berkes, Johan Colding, & Carl Folke, ‘Introduction’, *Navigating Social-Ecological Systems,* Cambridge: Cambridge University Press, 2003, p.1&3.

science through centralized institutions. Genuine research, research in which the behavior and outcomes of researchers cannot be predicted, where if asked about their research they are likely to respond as Einstein responded to such questioning: ‘If we knew what it was we were doing, it would not be called research, would it?’, is now scarcely tolerated. This is particularly true of research opposing reductionist thinking. Rosen in his short *Autobiographical Reminiscences* described the difficulties brilliant thinkers such as Nicolas Rashevsky, James Danielli, Ludwig von Bertalanffy and he himself had with administrators; similar thinkers now face a much more hostile environment, crippling the advances in science required to address wicked problems.[4]

By working towards concepts and a form of mathematics that does justice to experience rather than forcing experience into the procrustean bed of defective concepts, Integral Biomathics and the INBIOSA project are reviving the openness to the world and the creative imagination that gave birth to modern science. In doing so it is not completely breaking with past science, or mathematics, however. While Newtonian assumptions are deep-rooted and have had a pervasive influence, there is a long tradition of opposition to them. Much of this has been inspired by those who could see the incompatibility of Newtonian cosmology and the reality of life. While the life sciences along with the humanities are frequently denigrated as ‘soft’ by adherents to the Newtonian paradigm, Rosen pointed out in a Festschrift for the theoretical physicist David Bohm that: ‘In every direct confrontation between universal physics and special biology, it is physics which has had to give ground.’[5] At the end of the Eighteenth Century Friedrich Schelling responded to Kant’s characterization of life by embracing it and rejecting the subordinate place allotted to it by Kant, and developing a speculative physics that challenged Newtonian assumptions, offering a conception of physical existence consistent with the emergence of life. Newtonians were interpreted as only having grasped superficial aspects of reality. We now know that Schelling’s speculations were a major contribution to the development of field theory and inspired the formulation of the first law of thermodynamics, developments in science which have in fact transcended Newtonian physics.[6] To further this conception of physical existence, Schelling also called for a new constructivist approach to mathematics. This inspired the work of Hermann Grassmann whose theory of extensive magnitudes, linear algebra and vector spaces not only had a major influence on mathematics but is now central to modern physics.[7] In conceiving the universe as self-organizing, Schelling was also a precursor to systems theory and complexity theory, including hierarchy theory.[8] Far from science being a linear accumulation of knowledge, Schelling’s contributions to science show that the most important

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[4] Judith Rosen, ‘Autobiographical Reminiscences of Robert Rosen’, *Axiomathes* (2006) 16: 13ff.

[5] ‘Some epistemological issues in physics and biology’, *Quantum Implications: Essays in Honour of David Bohm,* ed. B.J. Hiley and F. David Bohm, London: Routledge, 1987, p.315.

[6] L. Pearce Williams, *The Origins of Field Theory,* Lanham: University Press of America, 1980, ch.2, and Thomas Kuhn, *The Essential Tension,* Chicago: Chicago University Press, 1977, p.97ff..

[7] H.-J. Petsche et.al. eds, *From Past to Future: Grassmann’s Work in Context,* Basel: Springer, 2011.

[8] As Marie-Luise Heuser-Kessler argued in *Die Produktivität der Natur: Schellings Naturphilosophie und das neue Paradigma der Selbsorganization in den Naturwissenschaften,* Berlin: Duncker & Humblot, 1986.

achievements of modern physical science have been made possible by bold speculative efforts to comprehend life. This supports Rosen's further contention that 'it is physics, and not biology, which is special; that, far from contemporary physics swallowing biology as the reductionists believe, biology forces physics to transform itself perhaps ultimately out of all present recognition.'[9] This is the horizon that Integral Biomathics and the INBIOSA project could reopen.

The development of new forms of computation and their technological implementation is particularly important to this project. Not only could such advances facilitate the advance of science to a deeper understanding of life and physical existence and assist the kind of management required to deal with complex 'wicked' problems, it would physically instantiate a different way of conceptualizing the world and our place within it. Such technology would foster a different way of understanding nature, society and people. In place of the quest to occupy the transcendent position of cosmic tyrants reducing the entire world and everything in it to a predictable instrument, such technology would foster an appreciation by people of the autonomous dynamics of the world in which they are creative participants.

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[9] 'Some epistemological issues in physics and biology', p. 315 (s. footnote 5).

ming k’o ming, fei ch’ang ming.

The names that can be named are not unvarying names.

Lao Tzu, *Tao Te Ching*, 4th century BC

Author Index

Index