Biol Philos (2015) 30:629–652
DOI 10.1007/s10539-015-9496-9

Revisiting generality in biology: systems biology and the quest for design principles

Sara Green[1]

Received: 6 January 2015 / Accepted: 27 June 2015 / Published online: 25 July 2015

Abstract Due to the variation, contingency and complexity of living systems, biology is often taken to be a science without fundamental theories, laws or general principles. I revisit this question in light of the quest for design principles in systems biology and show that different views can be reconciled if we distinguish between different types of generality. The philosophical literature has primarily focused on (the lack of) generality of specific models or explanations, or on the heuristic role of abstraction. This paper takes a different approach in emphasizing a theory-constituting role of general principles. Design principles signify general dependency-relations between structures and functions, given a set of formally defined constraints. I contend that design principles increase our understanding of living systems by relating specific models to general types. The categorization of types is based on a delineation of the scope of biological possibilities, which serves to identify and define the *generic features* of classes of systems. To characterize the basis for general principles through generic abstraction and reasoning about possibility spaces, I coin the term *constraint-based generality*. I show that constraint-based generality is distinct from other types of generality in biology, and argue that general principles play a unifying role that does not entail theory reduction.

Keywords Design principles · Systems biology · Unification · Biological laws · Constraints · Generic abstraction

✉ Sara Green
saraehrenreichgreen@gmail.com

[1] Center for Philosophy of Science, University of Pittsburgh, Pittsburgh, PA 15260, USA

Is there room for generality in biology?

Could there be a role for laws and general principles in biology? For many philosophers and biologists the answer seems to be no. Burian, Richardson and Van der Steen (1996) observe that in biology we do not find fundamental laws or theories but loosely interconnected explanations and concepts that acquire meaning in local historical and scientific contexts.[1] Whereas their statement is based on observations of the prominent features of mainstream biology, some go further in stating principled arguments against the possibility of laws in biology. The strongest position takes biology to be *nomically inhibited* due to the contingency and variation of living systems. This position holds that no general law or principle could be universally applicable to the biological domain (Beatty 1995; Mayr 2005; Smart 1963).

Smart (1963) for instance argues that biological systems do not display the kind of regularity and uniformity that general theories and laws require. Similarly, Beatty (1995, 46–47) claims that "All generalizations about the living world: (a) are just mathematical, physical, or chemical generalizations (or deductive consequences of mathematical, physical, or chemical generalizations plus initial conditions) or (b) are distinctively biological, in which case they describe contingent outcomes of evolution". In Beatty's view, (a) presupposes an unacceptable form of reduction of biological structures to physical ones, whereas (b) is restricted by the high degree of nonhomogeneous outcomes of evolution. The apparent lack of generalization is not taken to diminish the scientific status of biology but rather to cement the autonomy of biology as a separate discipline. For instance, the fact that entities like genes lack an 'essence' has been used as an argument against reduction of biological explanations to physicochemical principles (Dupré 2007; Winther 2009).

Not everything in biology is equally contingent, though. Examples of general molecular features are the genetic code, protein-signaling cascades, and the universality of ATP as an energy source. Biologists often draw on rather general theories like cell theory or on law-like equations representing e.g. statistical regularities in population genetics, kinetic regularities in Michaelis–Menten rate laws, or formalized predator–prey relationships like the classical Lotka-Volterra model. Functional relations are sometimes described through abstract models. Examples are negative feedback control for homeostasis, amplifying control mechanisms, or the influential Hudgkin-Huxley model of action potentials in neurons that treat excitable cells like electrical components. Recently, tools from graph theory have been used in systems biology to investigate general organizational relations in regulatory networks. Such examples raise the question why some relations are generalizable across many specific cases in biology (see also Hamilton 2007).

[1] Darwin's theory of evolution through natural selection and principles of divergence may be an exception, since modeling of evolution resembles the attempt to treat biological processes as influenced by deeper laws (Depew and Weber 1995). Yet, there are major disagreements about the specific content and implications of the theory, e.g. the extent to which natural selection determines the direction of evolution, the dynamics and unit of natural selection, and the heuristic and explanatory value of adaptationism (Amundson 1994; Green 2014).

This paper challenges the view that there could be no role for laws and general principles in biology. Yet, I argue that we need not assume any connection between general principles and a form of reductionism that threatens the autonomy of biology. These views can be reconciled if we distinguish between different types of generality and clarify the purposes for which biologists generalize. Rather than focusing on possible discrepancies between necessary and sufficient conditions for laws and biological cases, my aim is to explore why some life scientists seek general principles. I first distinguish between different types of generality and focus in particular on what I shall call *constraint-based generality* ("Different types of generality" section). This type of generality will be illustrated through examples of *design principles*[2] from systems biology ("Systems biology and the quest for general principles" section), and reflections on constraint-based generality in evolution ("Constraint-based generality in evolution" section). Finally, I argue that principles based on constraint-based generality play a regulative and unifying role that is distinct from theory reduction.

Different types of generality

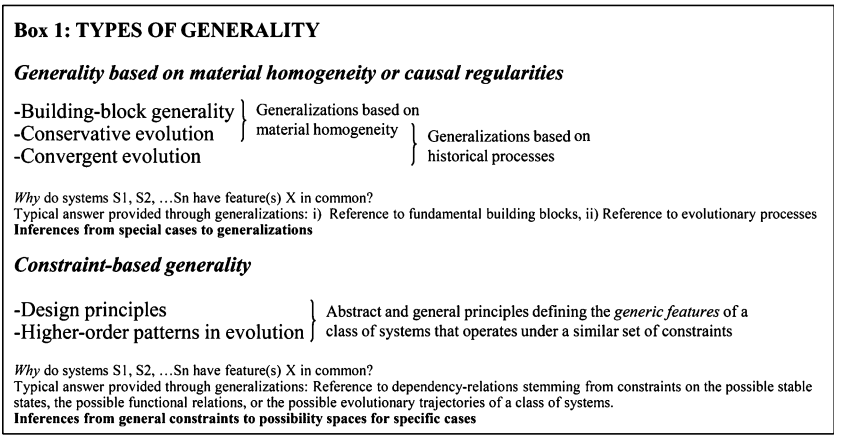
As a framework for discussing the role(s) of general principles in systems biology I distinguish between different (orthogonal but non-exclusive) types of generality. These are classified into two main classes based on the distinctive roles they play in the reasoning practices and on the sources of the generalizations (Box 1).

The first class contains generalizations based on *material homogeneity* or *causal regularities.* These are inferred through observations of similar causal patterns in concrete causal interactions. What I call *Building-block generality* stems from the material homogeneity and causal regularities of a physical system. This type of generality is typically taken to be limited in biology because biological systems form diverse and complex macrostructures organized in a variety of ways. Still, we may expect some regularity in biological traits due to *conservative evolution* because new organisms evolve from their predecessor through inherited material (DNA, membranes etc.). The universality of the genetic code, for instance, is typically explained with reference to common descent of all life forms. Other generalizations focus on functions rather than material similarities. Common traits observed across lineages may be the effects of *convergent evolution*. That is, natural selection promotes and preserves traits that are particularly well-adapted to particular types of environments in different species, such as wings for flying in bats and birds.

As mentioned, the scope of generality has been taken to be highly restricted in biology due to the contingency of evolution and the variation of organisms. This claim is, however, tied to a focus on the generality of specific features whereas I claim that there are more dimensions to generality. First, generality in the practice of biological research does not necessarily rely on complete uniformity of causal

[2] The quest for design principles does not assume an 'intelligent' designer, nor does it necessarily entail adaptationism (see Green et al. 2015b).

Box 1 Types of generality



relations. Generalizations may be based on a subset of causal similarities, e.g. when a regulatory circuit in a model organism represents similar interactions in other target systems, or when biologists discuss general adaptive strategies. Second, rejecting generality based on causal regularities should not lead to the dismissal of generality in biology altogether. I shall argue that a different type of generalization goes beyond similarities of cause and effect in serving to abstractly delineate a possibility space for any system of a particular type.

Researchers sometimes abstract from causal processes of specific systems to investigate why a causally diverse set of systems displays a similar behavior. What I call *constraint-based generality* refers to abstract principles that define the *generic features* of a class of systems that operates under a similar set of constraints. Key to this type of generality is that common patterns may not be observed due to causal uniformity, or a drive towards specific optimal traits, but due to constraints on the possibilities for the systems to instantiate other configurations or behaviors. The question of why a set of systems shares certain features is in this context not answered through reference to material homogeneity or evolutionary processes but through formalized dependency-relations. Such relations stem from constraints on the possible stable states, the possible functional relations, or the possible evolutionary trajectories of a class of systems. Thus, the inference made is from general constraints to possibility spaces and dependency-relations that, as a result, must hold for specific cases.

The different types of generality are not exclusive, but I am distinguishing them because of the distinctive role they play in the reasoning practices of the scientists. Even if in particular cases of constraint-based generalities are products of conservative processes or natural selection, researchers may analyze these systems with different questions in mind. Importantly, the consideration of what relations are possible for a given type of system is distinct from questions about the causal operations in, or origin of, a specific system. In informing about possibility spaces, constraint-based generality goes beyond generalization from specific features to

general cases. To make this type of generality clearer, the following section elaborates on the notions of constraint and generic abstraction.

Constraints in biology and generic abstraction

Constraints refer to conditions that at the same time limit and afford a certain scope of possible structures and functions that can be instantiated in a system of a particular type. Constraints do not explain how a phenomenon is produced by a mechanism in virtue of the interactions between component parts but rather denote the boundaries of such processes through reasoning about spaces of possibilities. Biological systems operate within different types of constraints, such as physical (mechanical and thermodynamic), structural (or organizational), functional, and developmental.[3] To understand how the interplay of constraints both limits and affords a certain scope of possibilities, consider the implications of the rigid skeleton of vertebrates. Having a rigid skeleton *limits* the functional flexibility of body parts but also *enables* upright movement on land. The significance of such forms is greatly influenced by the physical constraints of the environment. For instance, a rigid skeleton has different significance in aquatic environments due to the density of the medium. In this interplay of constraints, the size of the organism matters too. Gravity is a major constraint for large organisms but only a weak force in the world of insects and microorganisms (Gould 1977/2006). For animals with a high surface-to-volume ratio, the world is instead dominated by surface forces that define a different space of possibilities.

Reasoning about constraints not only plays an important role by imposing boundary conditions for research on specific functions but also helps biologists understand why certain functional or organizational patterns are common or absent in nature. The diversity of biology reflects a variety of evolutionary strategies for dealing with specific constraints while adapting to new environments. Yet, considering similarities of life forms from a more abstract perspective, there are general relations that become comprehensible through reasoning about constraints. Consider for instance the general relation between size and shape. As organisms grow larger, the relations between volume, surface area and weight grow disproportionally. Already Galilei (*Discorsi*, 1638) provided a mathematical scaling argument for the disproportionate relation between the thickness of bone structures and animal size: the strength of a given material depends upon the area of its cross-section, but the weight of the animal increases with the cube of its length. This general relation places restrictions on the possible "designs" in biology and beyond. Gould (Gould 1977/2006) exemplifies how medieval churches cannot be up-scaled without adding intermediate support to the ceiling or narrowing the building. Reasoning about constraints is therefore of practical relevance for design in engineering and synthetic biology, and of theoretic relevance for biologists when identifying possibilities for biological variation.

[3] Developmental constraints refer to features that set the boundaries for possible processes in embryonic stages. For instance, developmental constraints are taken to explain the lack of variation in the number of cervical vertebrae or five-digit limbs among vertebrate species because the embryonic stages in the production of these cannot be altered without affecting other developmental processes. For an analysis of the historical role of developmental constraints in biology, see (Brigandt 2015).

Constraints are often taken to play a purely negative role in biology. In the naïve adaptationist framework, traits develop towards optimal solutions via natural selection promoting beneficial functional variants while physical and developmental constraints only play a limiting role on the variation that selection can act on. In contrast, developmental biologists have brought attention to how constraints also afford the production of stable phenotypes by dampening the effects of environmental or genetic perturbations (Amundson 1994; Collins et al. 2007). For instance, the gap gene system responsible for segment development in *Drosophila melanogaster* has a regulatory structure (a double negative feedback loop) where two important genes repress each other's transcription. The configuration, called a bi-stable toggle switch (Tyson et al. 2003), supports the stability of two mutually exclusive gene-expression patterns over a variety of initial conditions (Jaeger and Crombach 2012). Thus, the regulatory structure at the same time limits and affords the space of stable states. Moreover, the abstract formulation of the double negative feedback loop allows biologists to relate specific regulatory circuits with this configuration to a broader functional class of 'toggle switches' ("Systems biology and the quest for general principles" section).

The investigation of the stabilizing aspect of constraints in biology was pioneered by theoretical biologists such as Stuart Kauffman and Brian Goodwin. Kauffman (1969; 1993) modeled random Boolean networks to investigate how the structure of gene regulatory networks constrains the possible network states. The nodes in Kauffman's networks represent N genes in different states (ON/OFF), determined by inputs from other genes. The state of the network is modeled as an ensemble of Boolean functions, based on K inputs, over time. Kauffman shows that despite the complexity of such networks, the number of sequences (or cycles) of states are rather low and the system converges to a limited number of stable states (attractors).[4] Kauffman argues that constraints on the degrees of freedom for possible system states provide 'order for free' in the sense that the production of stable patterns is independent of selection mechanisms. Yet, self-organizing processes complement selection by affording stable variants on which selection may act (Goodwin 2009; Jaeger and Crombach 2012; Kauffman 1993). Theoretical approaches of this kind have so far had limited uptake in mainstream biology but this may change as systems biology can combine theoretical models and new biological data ("Constraint-based generality in evolution" section). Moreover, constraints play an important role in biological reasoning that deserves more attention from philosophers.

Biological reasoning often involves relating particular cases to general types. Some biologists may foremost be interested in explaining, for example, how a specific bat species echolocates. Yet, this investigation is informed by how the specific acoustic strategy relates to other, more general strategies, and how the specific strategies are influenced by physical and functional constraints. For instance, all strategies for sound emission in echolocating animals must operate within constraints pertaining to the relations between the directionality and

[4] The model only includes internal inputs and is therefore deterministic with a finite number of network states.

frequency of sound beams and emitter size (Jakobsen 2010). Whereas generalizations about how such designs evolved, or how these are causally instantiated, depend on the specific historical and causal processes, the general relations are independent of such contingencies. For *any* sound emitter, the sound beam gets broader the lower the frequency is. At the most abstract level, the class of sound emitting systems may also involve engineered systems, which explains why the same formalized acoustic model can be applicable in both contexts. Because explanations of concrete systems are often taken to be *the* research aim in biology, the theoretical importance of reasoning about constraints in biology often remains unarticulated and unanalyzed. But many aspects of biological practice cannot be understood without considering these aspects. This holds in particular for research practices in systems biology that aim to identify generic features of system organization and formalize these as general 'design principles' ("Systems biology and the quest for general principles" section).

Constraint-based generality makes possible the identification of general principles underpinning a class of systems exhibiting similar structural or dynamic patterns. I shall argue that general principles can play a unifying role in biological theorizing without entailing a reduction of the specific to the general. What is at stake is a *type-classification* via *generic abstraction*. I here draw on Nersessian's (2008) analysis of how reasoning via generic abstraction was important for the work of Maxwell and Faraday. Generic abstraction involves "selectively suppressing information instantiated in a representation, so as to make inferences that pertain only to the generic case" (Nersessian 2008, p. 193). Thus, rather than focusing on causal similarities, generic abstraction distills what all sound emitters, triangles, harmonic oscillators, electromagnetic fields etc. have in common. The notion of *generic features* thus refers to relational properties that hold for a class of systems, regardless of their causal differences.

Consider for instance the class of systems instantiating so-called Belousov-Zhabotinsky reactions. In Belousov-Zhabotinsky reactions, concentric ring patterns of oscillating color are produced from a center through waves of oxidation propagating through a reduced medium. Such ring patterns are observed in chemical reactions where metal ions catalyze waves of oxidation of reductants by bromic acid. Similar structural patterns are also observed in some biological systems, e.g. in media for cAMP excreting slime mold amoebae under stress conditions (Goodwin 1994). Although the systems and substrates differ, the Belousov-Zhabotinsky reaction serves as a functional model in biology as well as in chemistry. It denotes a common non-equilibrium dynamic behavior of spatial and temporal symmetry breaking for the same *type of excitable medium* under the influence of stimuli (Shanks 2001). Regardless of the specific chemical components of the system, what is common is that an oxidative agent diffuses ahead of the wave front while reactions occur which inhibit the production of this chemical. This leaves a reduced medium in a refractory state behind the rings of wave fronts, and results in colored ring patters.

The general features in such examples are not the properties of specific components but the "relational order" among properties (Goodwin 1994). Thus, the generality of such principles does not result from a uniformity of molecular building

blocks and homogeneity of causal regularities in nature. Rather, dynamic patterns become visible through abstraction from the causal differences that do not matter for the pattern-forming relations. The following section further analyses this role through an examination of the quest for design principles in systems biology.

Systems biology and the quest for general principles

Systems biology comprises diverse approaches. Whereas some view systems biology as a successor of genomics and molecular biology, others have emphasized the relation to theoretical engineering disciplines, systems theory or classical physiology. These two viewpoints are sometimes captured as the *pragmatic* and the *systems-theoretic* approach, respectively (O'Malley and Dupré 2005). I focus on the systems theoretic approach which aims to identify general principles of biological organization. To justify the claim about the importance of such principles and clarify their role in biological theorizing, I have compiled a list of examples in Table 1. The principles are grouped according to the concepts used by scientists (higher order laws, design principles etc.) and the lines of research associated with these (General System Theory, systems biology etc.). I stress some important characteristics of these and analyze a few examples in further detail.

The quest for design principles has historical precursors in so-called *higher-order laws* in the framework of General System Theory, where Bertalanffy aimed to identify features that all systems of a particular type have in common (Bertalanffy 1969; Green and Wolkenhauer 2013). Bertalanffy wanted to understand why causally different systems can often be described via the same general models or equations. For instance, the logistic law of Verhulst can be used in physical chemistry to describe autocatalytic reactions, in population studies to capture population growth, or in sociology to characterize the growth and spread of technologies. The s-shaped sigmoid curve generated by the equation describes the generic features shared by the different processes: an initial exponential increase in elements that at a certain point becomes limited due to external constraints or limited resources. At the level of causal explanations we need to specify the causal make-up and operations of these systems which limits the generality of the explanations. But to answer Bertalanffy's question, one must abstract from these differences to identify the basic features underpinning general patterns. Other examples are allometric scaling relations (e.g. between metabolic rate and body mass), growth equations for different metabolic types, and formalizations with cross-disciplinary applicability such as equations describing flows of energy and heat, equilibrium models in chemical systems or populations etc.

Some approaches compare living systems to well-functioning engineered systems to identify so-called *optimality principles*. Examples are the discovery of the general 'optimal' branching angle in vascular systems inspired by the designs of pipe systems that minimize the flow of resistance (Rashevsky 1961; Rosen 1967), and Savageau's demand theory for optimal gene regulation (Savageau 1989). Engineering approaches have recently had a renaissance with the application of graph theoretical tools to biological datasets. In systems biology such principles are

Table 1 Examples of general principles in biology

Description and field	Examples of general principles	References
Higher Order Laws/ Isomorphic principles *General System Theory*	Allometric scaling relations Exponential equation (growth/decay) Logistic law Growth equations Principles of open systems	Bertalanffy (1967, 1969) Gould (1977/2006)
Optimality principles Design principles Evolutionary Design Principles *Cybernetics/Systems Theory (Evolutionary) Systems Biology*	Branching angle in vascular systems Demand Theory of gene regulation Network motifs Bi-stable switching Robustness, modularity Integral feedback control Principles underpinning common trajectories of evolutionary change, leading to design principles	Rashevsky (1961), Rosen (1967) Savageau (1989) Alon (2007) Tyson, Chen and Novak (2003) Csete and Doyle (2002), Velazquez (2009); Yi et al. (2000) Soyer, ed. (2012)
Organizing principles *Cybernetics/Mathematical General Systems Theory/ Systems Biology*	Feedback underlying regulation, control and adaptation of dynamical systems Bounded Autonomy of Levels Closure to efficient causation Coordination principle Principles of tissue organization	Wiener (1948), Mesarović et al. 2004 Mesarović and Takahara (1975) Rosen (1991), Letelier et al. (2001) Hofmeyr (2007) Wolkenhauer and Hofmeyr (2007) Wolkenhauer et al. (2011)

typically referred to as *design principles*. These need not focus on optimal performance but are organizational rules "that underlie what networks can achieve particular biological functions" (Ma et al. 2009, 260).

Examples of design principles are the previously mentioned bi-stable toggle switch (Tyson et al. 2003) and Alon's (2007) discovery of a set of *network motifs*, i.e. frequently occurring circuits in transcriptional regulatory networks (Fig. 1). The organizational structure of the circuits are taken to constrain (in an enabling and limiting sense) the possible regulatory functions performed by the circuit. For instance, regulatory systems with the Feedforward loop (FFL) structure are understood as persistence detectors for noisy input signals. This function was demonstrated mathematically for the general case (note the lack of details about the nodes in Fig. 1), and the motif was experimentally confirmed to perform this function in metabolic regulation in *E. coli* (Alon 2007).

Design principles signify the hope that functions in biology, as in engineering, are supported by general design principles that are independent of specific contexts of implementation. The formalization of such principles serves an important role in identifying organizational features that *in general* will support behaviors such as sustained oscillations, amplified signals, homeostasis etc. Accordingly, the same cybernetic model can facilitate reasoning in several contexts. For instance, negative feedback control is a central principle in mechanical and electronic engineering to maintain stable states, minimize fluctuations and create oscillatory behaviors, and is also widespread in biological systems. The same formalization—defining negative

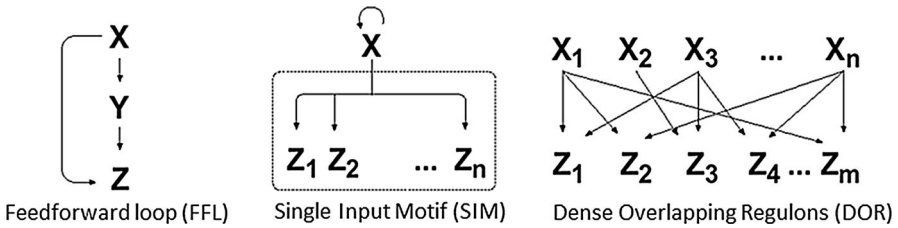


Fig. 1 Examples of Alon's network motifs (see text)

feedback as inhibition of a reaction as a result of accumulation of the product of the same reaction—can be applied in both domains (Wiener 1948).

Further down the list in Table 1 we find the notion of *evolutionary design principles*. Some systems biologists refer to natural selection when reflecting on the origin of design principles such as network motifs (e.g., Alon 2007).[5] Yet, evolutionary design principles typically refer more broadly to generic features (adaptive or non-adaptive) underpinning evolutionary trajectories that lead to common patterns of network organization or morphology (Soyer 2012, see "Constraint-based generality in evolution" section). In Table 1, I have listed *organizing principles* as a category separate from design principles because this notion is preferred by some systems biologists to emphasize what is characteristic for living systems only (Mesarović and Takahara 1970, 1975; Wolkenhauer and Hofmeyr 2007).[6] I shall focus mainly on design principles in this paper but the lessons drawn holds for all of the abovementioned types of general principles.

General principles provide an understanding of the generic features that enable causally different systems to produce a similar pattern under a range of implementations. General principles do not stand in a direct representational relationship to specific causal systems, but rather abstract from causal differences to identify common relational properties among members of a given class of systems. In the words of the systems biologists Ma et al. (2009, 760), the hope is that "Despite the diversity of possible biochemical networks, it may be common to find that only a finite set of core topologies can execute a particular function. These design rules provide a framework for *functionally classifying complex natural networks* and a manual for engineering networks" (my emphasis). Similarly, Wolkenhauer et al. (2012, 59–60) state that: "An organizing principle in this context specifies a category of systems to which a model belongs to; it describes an essential characteristic feature, *a rule or law of which the function identified is an instantiation*" (my emphasis). The general categories can be identified through discoveries of common organizational patterns (as in Alon's discovery of frequent network motifs) or through a rigorous mathematical analysis of the constraints that *any* possible mechanistic model of the type of system must obey. The examples in

[5] For a discussion of adaptationism in this context, see (Green 2014).

[6] The different labels for general principles in the table highlight theoretical differences between the approaches but the notions of design and organizing principles are often used interchangeably and have overlapping historical precursors (Green and Wolkenhauer 2013).

the following exemplify the latter where a biological property (robustness) is articulated as mathematical constraints on possibility spaces.

Design principles for robustness

The emphasis on design principles is particularly prominent in research on biological robustness, i.e. the capacity for a biological system to maintain a given function across a range of perturbations to internal and external conditions (Kitano 2007). Since robustness is also an engineering goal, mathematical tools from control theory are increasingly used to investigate whether design principles underpinning robustness in the two contexts are similar, and to determine the relative dependency of the capacity on fine-tuned mechanisms. Strikingly, many instances of biological robustness appear to result from characteristic ways in which the system is organized (Stelling et al. 2004). This motivates attempting to identify organizational schemes that *in general* afford robustness.

An example is Shinar and Feinberg's (2010, 2011) robustness theorem. Theorem proving is typically not associated with the life sciences but is sometimes used in systems biology to explore the range of logically feasible models for a given property. Shinar and Feinberg (2011) distinguish "designs that work" from "designs that cannot work" by showing mathematically how various network designs can or cannot support the capacity of biochemical reaction networks to display absolute concentration robustness (ACR) for a biochemical species against variations in the concentrations of constituents. Shinar and Feinberg draw on Chemical Reaction Network Theory to identify the necessary and sufficient conditions for ACR. Their mathematical robustness theorem demonstrates that any biochemical mass-action network displays ACR if i) the deficiency of the network is one and ii) two non-terminal nodes differ only in one biochemical species. Deficiency is here a measure of the interdependency of the reactions in the network, calculated by subtracting the linkage class (the number of mutually linked nodes in the reaction diagram) and the rank of the reaction network (the number of linearly independent reactions) from the number of network nodes. These measures are context-independent in the sense that they are stated in general terms for all networks sharing the formally defined set of properties.

What is striking about the result is that the conditions for ACR are expected to hold regardless of the size and the specific biochemical interactions in such networks. The results thus define the properties that any system belonging to a particular category must share and provide understanding as to why particular designs can or cannot be expected to be found in systems with a given capacity (see also Wolkenhauer et al. 2012). Importantly, this type of analysis operates on a meta-level in relation to mechanistic network models, and the analysis explores possibilities beyond what may be biological realized in any concrete system. Accordingly, the aim of the theorem is not a mechanistic explanation but a principle stating a dependency-relation between formally defined structural features of networks and their functional properties. Even though the proof rests on some idealizing assumptions about biochemical networks, it points to crucial architectural

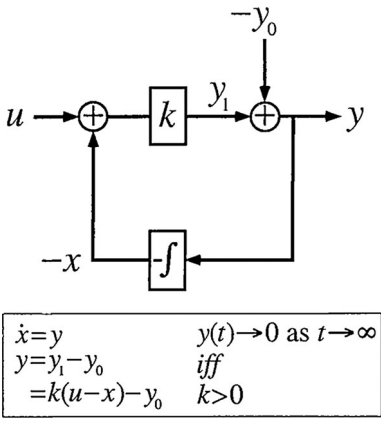


Fig. 2 Diagram illustrating integral feedback control. See text for details. Source: Yi et al. (2000). Copyright (2000) National Academy of Sciences, USA

features of network robustness that are observed in bacteria (Shinar and Feinberg 2011).

To clarify further the difference between causal explanations of specific systems and design principles, consider a theoretical approach to robustness of sensory adaptation in bacterial chemotaxis. Bacterial chemotaxis is the strategy by which bacteria can "swim" toward attractants and away from repellants. Is has been shown experimentally that the system of sensor and flagella motor display so-called 'robust perfect adaptation' (RPA) where the sensitivity of sensors to new stimuli remains stable over a wide range of parameters (Alon et al. 1999). Expressed in engineering terms, perfect adaptation (or perfect desensitization) is the capacity of a system to maintain the responsiveness of sensors by returning to the exact pre-stimulus value. In bacterial chemotaxis, the tumbling frequency responds to changes in stimulus level but then adapts to the new level and returns to its steady-state value through reactivation of the receptor. This enables the system to maintain sensitivity to new changes. The capacity of perfect adaptation is robust over a wide range of stimulus levels and system parameters, and researchers are interested in understanding how this is possible. Two quite different research questions can be asked in this connection. One concerns how RPA is causally produced through interactions among the components in the receptor complex. The other, which I stress here, concerns what principles *in general* underpin RPA (see also Braillard 2010).

The molecular mechanisms underlying bacterial chemotaxis are well-known, as are mechanisms underlying the adaptation to concentrations of attractants and repellants.[7] Barkai and Leibler (1997) developed a model of the receptor complex consisting of a set of differential equations capturing the dynamics of all individual biochemical species through methylation-demethylation processes. Simulations based on this model show that the system does not require specific parameter values

[7] In *E. coli,* chemotaxis involves mediation of a kinase-phosphorylation signal transduction pathway from methyl-accepting transmembrane receptors to six Che proteins that interact with a flagella motor that can change the tumbling frequency according to input signals. Adaptation to concentration of repellants and attractors is causally instantiated by ligand binding, methylation and demethylation of receptors.

for enzyme concentration or kinetic rate constants, and Barkai and Leibler therefore propose that the robustness of the system may be due to intrinsic (topological) properties of the signaling network. John Doyle and colleagues take a rigorous mathematical approach to this question by investigating whether a central principle for RPA in control theory also underpins bacterial chemotaxis.

When designing systems that asymptotically track a fixed steady-state value, engineers rely on the principle of *integral feedback control* (Fig. 2). When environmental inputs u change, the difference between the actual output (y_1) and the desired output (y_0: steady-state receptor activity) is fed back into the system as the integral of the system error $-x$, which becomes an action signal for returning to the pre-stimulus value. By accounting for the difference between y_1 and y_0, the system normalizes the reaction to input u to output y, to maintain the gain k.

Doyle and colleagues reinterpret the Barkai-Leibler model in the framework of control theory and derive an equation characteristic of integral feedback control from the Barkai-Leibler model. The equation guarantees that there is no dependence on the level of the chemoattractant if certain assumptions are satisfied. The mathematical rigor allows the researchers to systematically examine the importance of various model assumptions and demonstrate that four of these are sufficient to ensure RPA (Yi et al. 2002).[8] Moreover, they show how relaxation of any of these leads to non-robust dynamics or deviation from perfect adaptation and the assumptions are therefore considered necessary features of the Barkai-Leibler model.

Could integral feedback control be said to be a design principle for *any* system with the functional capacity of RPA? Doyle and colleagues argue that if a system has robust asymptotic tracking it must be linearized around a fixed ligand equilibrium that confers the conditions for integral feedback control (Yi et al. 2000). They prove this statement for linear systems and consider the result a special case of the internal model principle in control theory, stating that robust asymptotic adaptation requires an internal model of these signals to be present within the system (for proofs of IMP for nonlinear cases, see Sontag 2003). Integral feedback control thus provides a formal constraint on possible mechanistic models capturing the causal operation of chemotaxis in different systems. They argue that "if their [Barkai and Leibler] specific model is later found to be contradicted by experimental data, another mechanism implementing integral feedback is likely to be present" (Yi et al. 2000, 4652). Thus, any system found to display RPA can be expected to belong to the larger class of systems implementing integral feedback control.

Organisms have often found ways to deal with constraints in ways that engineers find to be unlikely or even impossible, and some researchers are reluctant to claim that RPA *necessarily* entails integral control (Briat et al. 2014). Still, Briat et al. contends that integral control seems to be a generic feature of the known biological cases of perfect adaptation, including homeostasis of calcium in mammals and

[8] These assumptions are: (1) CheB only demethylates active receptors, (2) the kinetic rate constants of CheR and CheB are independent of the methylation state of the receptor complex, (3) the activity of unmethylated receptors are negligible, and (4) the concentration of bound CheR is independent of ligand-level.

membrane turgor pressure in yeast.[9] With the investigation of generic features, the focus shifts from uncovering specific causal mechanisms to investigating the types of system organization that *in general* can realize a particular function.

Ma et al. (2009, 761) formulate this shift of focus explicitly: "Here, instead of focusing on one specific signaling system that shows adaptation, we ask a more general question: what are all network topologies that are capable of robust adaptation?" They address this question in the context of enzymatic regulatory networks by computationally searching all possible three-node networks to identify the ones performing RPA. Strikingly, only 395 out of 16.038 possible network topologies show of robust adaptation, and all robust designs display one of two core topologies; either a negative feedback loop with a buffer node (NFBLB) or an incoherent feedforward loop architecture (IFFLP). They further show that the NFBLB class, to which the bacterial chemotaxis system belongs, implies integral feedback control. While the IFFLP class may be an alternative principle accounting for RPA, contradicting Yi and colleagues' general statement, the lack of clear biological cases where this principle is instantiated raises further questions about constraints on biological variation. Whether there are one or two general cases, the example highlights a type of analysis that serves to "unify the organization of diverse circuits across all organisms" (Ma et al. 2009, 760).

I shall further analyze the philosophical implications of this unifying role in the section entitled "How generic abstraction inform biological theorizing". First, I respond to the possible objection that although some functional principles can be abstracted from specific causal models, there is little room for general laws or principles of evolution. Is the quest for general principles compatible with the common view of the contingency of evolution?

Constraint-based generality in evolution

The famous statement by Stephen Jay Gould (1982) that a "replayed tape" of evolution would yield a completely different outcome is often taken to support the view that biology can only be a historical science with highly context-dependent explanations. Yet, Gould's work as a whole reminds us that there are different dimensions to generality. We therefore need to specify which features of biology we take to be general or context-dependent. Some research in evolutionary biology is focused on adaptive differences among species or populations, whereas other research aims to explain the generality of some phenotypic patterns. From the perspective of the first approach, evolution appears highly contingent in the sense that evolution can explore an infinite number of roads for adaptive specialization, making it highly unlikely that something like *Homo sapiens* would result from a rewound tape. But it does not follow that evolutionary roads—from a higher-level perspective—are random and exhibit unlimited degrees of freedom.

[9] For practical implications of this principle for designing synthetic homeostatic circuits in synthetic biology, see also (Ang et al. 2010).

Gould was just as fascinated by the common morphological patterns across phyla as by the diversity of species (Haufe 2015; Sterelny 2007). In this own words "[H]owever much we celebrate diversity and revel in the peculiarities of animals, we must also acknowledge a striking 'lawfulness' in the basic design of organisms" (Gould 1977/2006, 319). Gould saw this as evident in the general relations between size and shape, and in the limited variation in functional designs for respiration, flying etc. Whereas science fiction books often describe giant insects with current insect morphology scaled up, Gould cheerfully points out that the evolution of such organisms is not possible as "their sheer bulk would have grounded them permanently" because the weight that must be supported by the wings increases as the cube of the length (Gould 1977/2006, 321). Similarly, the combined effect of the law of gas diffusion and physiological requirements for gas exchange means that open respiratory designs can only support organisms with large surface-to-volume ratios (see also Wouters 2007). Insects are therefore constrained to be small.

Reflections of this type are not just amusing intellectual exercises but also bring insights to whether the characteristic patterns result from conservative, convergent or constraint-based processes (or a combination of these). Gould (1983/2006) calls for a shift in focus from what he calls 'vulgar Darwinism'; the attempt to analyze organisms 'part by part' from selectionist explanations of evolution towards adaptive endpoints. From the perspective of adaptationists, the endpoints signify 'good adaptive tricks' that sometimes can be general, but the paths to get these are considered random (Dawkins 1978; Dennett 1995). Gould takes the opposite stand in viewing the specific endpoints as largely contingent but the processes leading to these as constrained.[10] Although the difference between these viewpoints are sources of many scientific controversies, paying attention to the level of abstraction in the two cases opens the possibility that they can be viewed as complementary focal points within the same theoretical framework (Gould 1977/1996; Green et al. 2015a). While particular traits may be explained by adaptive specialization to specific types of environments, understanding the stability of dis-continuous phenotypic patterns in the larger landscape of possible phenotypes requires something other than selectionist explanations (Wilkins and Godfrey-Smith 2009).[11]

The adaptationist approach has been dominant after the modern synthesis, and the issue of constraints on form and morphological shapes has been taken up mainly by neo-Rationalists and developmental biologists. But the recent emergence of fields such as EvoDevo (Collins et al. 2007; Müller and Newman 2003) and evolutionary systems biology (ESB) (Soyer 2012) signifies a renewed interest in filling in the gap that Darwin described as our profound ignorance of the laws of variation (Darwin 1859, 167). In these fields, the quest for general principles of evolution is captured by notions such as 'generic principles', 'generative principles', 'isomorphic principles', or 'evolutionary design principles'. The principles are framed in different conceptual frameworks, but the common idea is that

[10] Whereas Gould initially believed that laws of evolution could be based on regular adaptive processes, he came to realize that generality in evolution was most likely to be found in evolutionary processes that are insensitive to specific adaptations and variations (Haufe 2015).

[11] Huang (2004) refers to these different focal points as Type I and Type II explanations in evolutionary biology (the latter investigating what I call constraint-based generality).

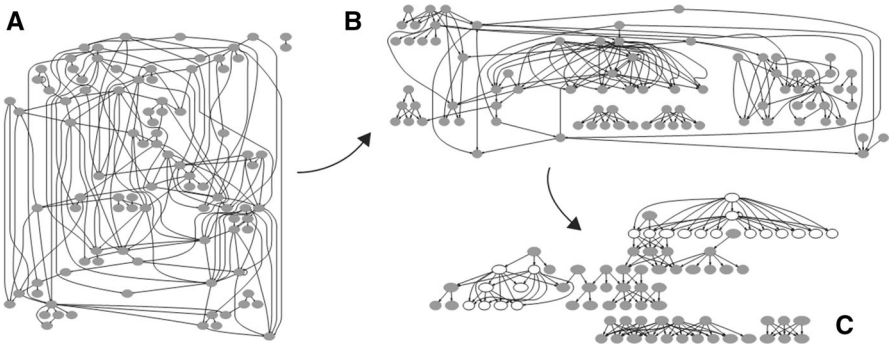


Fig. 3 Generation of hierarchical network structures from mutational dynamics over 2000 generations. Cordero and Hogeweg (2006). Reprinted by permission from Oxford University Press

investigations of general constraints and principles of evolution can be informative about biological variation and stability of evolutionary trajectories.

Evolutionary principles are called for to illuminate why some phenotypic patterns (leaf structures in plants, segment and stripe patterns in insects etc.) are general and discrete, rather than exhibiting continuous variation filling the scope of logical possibilities (Soyer 2012). Why, for instance, are only a small set of logically possible network motifs observed in regulatory networks? Are these the effects of selection? Or a by-product of genome evolution, obeying structural constraints, akin to the process Kauffman described? Or perhaps a combination? By mathematical and computational modeling of detailed experimental data, evolutionary systems biologists can now address such questions in novel ways. Evolutionary simulations can largely extend and complement experimental approaches by searching for evolutionary patterns across multiple levels of biological organization, allowing the researchers to focus on "evolutionary trajectories and transitions, rather than the substrates or end projects of natural selection" over a large time span (Jaeger and Crombach 2012, 106). In particular, non-goal directed simulations have great potential for informing about the structural side effects of evolutionary dynamics and for outlining the range of possible future trajectories of the evolving in silico system (Hogeweg 2012).

An example is Cordero and Hogeweg's (2006) evolutionary network model that demonstrates how hierarchical structures with an overabundance of network motifs (feedforward loops) can emerge by non-selective tinkering of promoter regions in simulations of evolving yeast networks. The researchers use experimentally measured rates of mutational dynamics (deletion, mutation, duplication and recombination of genes and transcription-factor binding cites) in transcriptional regulatory networks of yeast and simulate the network evolution over 2000 generations. Due to the high degree of freedom in such a model, one might expect the network structure to evolve in a random fashion. But surprisingly well-organized patterns evolve in the model (Fig. 3).

The white nodes in the network have the same connectivity-pattern as Alon's FFL network motif ("Systems biology and the quest for general principles" section). These structural patterns were unexpected as the model does not select for

functional motifs, and patterns shown in Fig. 3 with many closely overlapping FFL structures were found to match empirical data for transcriptional networks in yeast (Cordero and Hogeweg 2006).[12] The demonstration that non-random patterns can result from constraints on random mutational dynamics questions the assumption that the generality of organizational patterns, such as network motifs, could only be explained by natural selection.

To extend the list of examples, the computational biologist and evolutionary theorist Eugine Koonin (2011) uses mathematical tools to search for "laws of evolution" in comparative studies of prokaryote and eukaryote genomes. As examples of such "universal" quantitative laws of evolution he mentions the negative correlation between a gene's sequence evolution rate and expression level, and the distinct scaling of functional classes of genes with genome size. Similarly, the population geneticist Michael Lynch (personal communication) stresses the existence of a universal scaling between the number of genome-wide deleterious mutations and effective population size, where the latter plays a role akin to temperature in statistical mechanics. Thus, the quest for laws or principles of evolution need not rest upon the assumption that natural selection alone provides this regularity. Taken together, the cases stress the importance of answering questions related to the actual level of randomness in variation, and the level of contingency versus generality for evolutionary trajectories and endpoints.

How generic abstraction inform biological theorizing

In this section we further examine the difference between i) generalizations based on causal similarities in specific systems, and ii) general principles that define the generic features of a typified class of systems. Whereas the former gain stability from empirical observation of causal homogeneity in nature, the latter play a theoretical role in categorizing general functional dependencies which specific systems of a given type must instantiate. Returning to the example of bacterial chemotaxis, a mechanistic model of how RPA is causally produced can be generalized only if the causal operations are similar in other systems. In contrast, the principle of integral feedback control is taken to generically achieve RPA in *any* system exhibiting this functional capacity. The significance of the latter research aims is stated by Ma et al. (2009, 760) when highlighting that the aim to "construct a unified function-topology mapping […] may otherwise be obscured by the details of any specific pathway and organism". Thus, we may miss out on important aspects of biological research practice if we insist on the focus on causal explanations of specific systems and take all generalizations to rely on the scope of this type of explanations.

The examples in this paper may been seen as instances of what philosophers of science recently have described as *topological explanations* (Huneman 2010; Jones

[12] In the network model based on empirical data, they find that many of the motifs are closely overlapping and "more than 30 % of the FFL circuits are formed by 5 pairs of regulators with significant homology at the protein level" (Cordero and Hogeweg 2006, 1934). This finding speaks counter to the assumptions that the motifs result from selection of individual functional units (see also Green 2014).

2014) or non-causal *design explanations* (Braillard 2010; Wouters 2007). These explanations identify functional dependencies that deliberately abstract from the causal basis for these properties in specific systems. My aim in this paper, however, is not to engage in a discussion about explanatory and non-explanatory features of design principles, but rather to highlight a theoretically important role of constraint-based reasoning that complement explanations of causal specifics.

Asking how effects are causally produced is not the only important research question in biology. Researchers may also be interested in understanding the spaces of possibilities that biological systems must operate within, why certain patterns are observed in many (biological) systems, and why the same model can be applied to study diverse systems despite differences in their causal make-up.[13] *Design principles* identify formal rules about what organizational structures can achieve a particular type of biological function. Formalizations are important for this purpose because they can highlight and clarify similarities of form regardless of materiel context (Griesemer 2012). Design principles thereby signify general dependency-relations between structures and functions, given a set of formally defined constraints. Research may either start from an investigation of organizational features to infer functional capacities (as in Kauffman's or Alon's work), or—as in the examples on robustness—start from a formally defined functional capacity to determine the organizational designs that will work. This way, design principles helps researchers to understand the particular cases as instantiations of a more general type, e.g., as an instance of amplifiers, feedback control systems, persistence detectors etc. As I shall further clarify below, they unify causally different systems through generic abstraction.

Unification without reduction

The role of formalizations in biology is sometimes taken to imply a reductive subsumption strategy. For instance, Winther (2009, 138) argues that the increasing use of abstract formalizations, e.g. in mathematical analysis of gene regulatory networks (GRN), has affinities with the aim of providing reducing theories. Winther contends that these explanatory functions are important aspects of theoretical biology and suggests that a mathematical model of a GRN can be seen as a *mathematical reducing theory* whereby qualitative phenotypic characteristics (e.g. tissue differentiation) are derived from and reduced to more general GRN models. Meanwhile, he acknowledges that the biological world may be too diverse to be adequately characterized by a global mathematical structure. I do not dispute that subsumption strategies may play a role in some biological contexts. Yet, the practice of systems biology shows that general principles can play a unifying role that is not realized through reduction.

[13] This role is akin to answering Batterman's (2002) type II questions, described through case studies in physics. But whereas Batterman emphasizes how what he calls minimal models explain mainly by showing why details don't matter, I emphasize the generic features that the functional equivalence class (or universality class) have in common. Thus, the accounts differ with respect to what is taken to be the salient feature of the answer to the why-question.

I have argued that general principles inform biological theorizing by establishing connections between higher-level descriptions of different systems and therefore unify these through generic abstraction. This role is akin to the one described by Kitcher:

> Understanding the phenomena is not simply a matter of reducing the 'fundamental incomprehensibilities' but of seeing connections, common patterns, in what initially appeared to be different situations. Science advances our understanding of nature by showing us how to derive descriptions of many phenomena, using the same patterns of derivation again and again, and, in demonstrating this, it teaches us how to reduce the number of types of facts we have to accept as ultimate (or brute). (Kitcher 1989, 432)

I share with Kitcher the view that a great part of scientific understanding relates to seeing and establishing connections and patterns across different contexts. The systems theoretic approach in biology is largely inspired by the attempt to search for unified schemas accounting for systems phenomena to counterbalance fragmentation in science (Bertalanffy 1969). But unlike Kitcher, I do not define scientific explanations solely in terms of deductive argument patterns. And unlike Friedman, I do not see unification as the "essence of scientific explanation" (Friedman 1974). Science is diverse and researchers have different explanatory and theoretical aims because there are different types of questions one may ask about the world. For the same reason, I am not claiming that constraint-based generality is equally important in all research fields of biology.

Importantly, general principles do not replace specific models. Specific models cannot be derived from or reduced to general principles. Neither can we get to insights about possibility spaces from detailed models of specific systems. They are simply answers to different questions. Whereas causal explanations specify how operations are produced in concrete systems, the abstract analysis highlights the functional dependencies that enable and limit the space of possibilities for the type of systems that the specific cases are instantiations of. Both types of insights are necessary if we want to understand not only the causal operations of concrete systems but also how these relate to other phenomena, and whether these relations could have been different. Also in evolutionary biology, these two explanatory strategies are compatible in the sense that a full explanation requires an uncovering of the "interplay between stable, predictable patterns (laws) and unpredictability of specific outcomes" (Koonin 2011, 5).

The unifying role of formalizations in biology is akin to Kuhn's (1962/1996) description of how *exemplars* guide science education and research by representing general solution to problems. In systems biology, a characteristic feature is that such exemplars are adopted from other disciplines such as physics and engineering.[14] This observation may bring back Beatty's (1995) worry that the generalizations are physical or chemical, rather than biological. Yet, reasoning about possibility spaces

[14] I thank Mads Goddiksen for suggesting a comparison between the transfer of higher-order formalisms in systems biology and exemplars. One disadvantage of seeing design principles as examplars is, however, that it is not a part of Kuhn's account to make sense of the redefinition of exemplars through interdisciplinary 'bootstrapping' (Nickles 1990, 24).

is conducted within a functional framework and also involves constraints which are distinctively biological.

Physical constraints are important for understanding spaces of possibilities in biology. As Polanyi (1968) argued, the boundary conditions imposed on physico-chemical processes by the structure of biological systems is what enables the system to harness the functional utilization of these. But these are not explanatory in biology outside the functional context of the organism. Polanyi therefore argues that the controlling principles of life cannot be reduced to the laws of physics and chemistry. Similarly, contrary to the expected reconnection to reductionism, the quest for general principles in systems biology reflects a step towards a focus on relational or systemic properties (Klir 1991). Rather than stressing the reduction of biological complexity to physical principles, systems biologists emphasize that many biological properties are only visible when we understand living systems as functional wholes in interaction with their environment. From this perspective, the search for abstract principles may indicate an increasing awareness of our inability to understand how living systems function from a bottom-up study of components, or how these evolve without an understanding of the constraints on biological variation.

Concluding remarks

The philosophical literature on formalizations in biology has primarily focused on how inferences in a formalized model relate to inferences made about causal relations in a target system, or to derivations in reductive explanations. On this background, the possibility for general laws or principles in biology is dismissed due to the diversity and contingency of biological phenomena or as a result of a demonstration of the problems with theory reduction. I have argued that an examination of the scientific practice of systems biology challenges the view that there could be no role for laws and general principles in biology. Yet, I argue that we need not assume any connection between general principles and reductionism. Rather, the views can be reconciled if we distinguish between different types of generality. In particular, I have argued that *constraint-based generality* is compatible with the rejection of generality based on strong causal regularities in the biological world and even with the contingency of evolution.

When scholars have argued that there is no room for generality in biology, they have typically addressed this question at a level where individual traits, organisms or molecular structures are compared. But a similar conclusion could be reached if we studied the behavior of individual molecules in a gas. In the context of physics and chemistry, the observation of various trajectories of individual molecules is perfectly compatible with the possibility of identifying common organizational patterns and laws if we treat these entities as ensembles of particles and pursue a higher-level analysis of their projected long-term states. Similarly, biological systems can be observationally and experimentally studied for purposes of identifying causal operations in specific systems *or* be treated as particles with common relational or dynamic properties that enable a categorization of biological

possibilities and stable types (see also Haufe 2015). I have argued that the quest for general principles is compatible with the view that specific endpoints of evolution are highly contingent. The need to recognize these different and compatible approaches increases as researchers within systems biology reintroduce the quest for design principles through mathematical and computational modeling of biological 'big data'. These research practices indicate a renewed interest in understanding how constraints on dynamic trajectories drive living systems towards particular equilibrium states, why some system-level properties are insensitive to many lower-level perturbations, and why characteristic patterns are observed across causally distinct systems.

I have argued for a unifying role of general principles, exemplified through case studies in systems biology where researchers identify design principles. Design principles signify general dependency relations between biological structures and functions through formally defined constraints. The principles are identified by deliberately abstracting from causal details to identify the generic features that functionally equivalent systems (must) have in common. Although the empirical value of such general principles is dependent on specific systems instantiating the types of relations described, causal differences between the systems of the class are irrelevant to the formal rules signifying the generic systems properties. The epistemic power of such principles lies in this lack of context-dependency because it affords an understanding of why a set of systems behaves in a specific way independently of the particular manifestation of the functions.

Philosophers often associate the question about generality in biology with the question about theory reduction to physical laws or principles. I have argued that the current situation in systems biology gives no indication of theory reduction. General principles in systems biology are not derived from physical or chemical laws but are additional to these and specific for functional systems. Moreover, the formalization of general principles in systems biology is not introduced as an alternative to detailed causal explanations. General principles address a different type of question. Biologists may ask which network designs can possibly afford the type of robustness observed in biological systems, or why some logically possible phenotypic patterns are not realized in any real-world biological system. These conclusions cannot be reached by detailed modeling of the existing phenotypic traits alone. Thus, the quest for general principles highlight the wish to understand what generic features characterize pattern-producing systems in biology and beyond, and why we should expect particular organizational patterns to arise in evolution.

Acknowledgments I would like to thank William Bechtel, Maria Serban, Nicholaos Jones and two anonymous reviewers for very helpful comments to earlier versions of this paper.

References

Alon U (2007) An introduction to systems biology: design principles of biological circuits. Chapman and Hall, Boca Raton

Alon U, Surette MG, Barkai N, Leibler S (1999) Robustness in bacterial chemotaxis. Nature 397:168–171

Amundson R (1994) Two concepts of constraint: adaptationism and the challenge from developmental biology. Philos Sci 61:556–578

Ang J, Bagh S, Ingalls BP, McMillen DR (2010) Considerations for using integral feedback control to construct a perfectly adapting synthetic gene network. J Theor Biol 266:723–738
Barkai N, Leibler S (1997) Robustness in simple biochemical networks. Nature 387:913–917
Batterman RW (2002) The devil in the details: asymptotic reasoning in explanation, reduction, and emergence. Oxford University Press, Oxford
Beatty J (1995) The evolutionary contingency thesis. In: Wolters G, Lennox J, McLaughlin P (eds) Concepts, theories and rationality in the biological sciences. University of Pittsburgh Press, Pittsburgh, pp 45–81
Bertalanffy Lv (1967) Robots, men and minds. George Braziller, New York
Braillard P (2010) Systems biology and the mechanistic framework. Hist Philos Life Sci 32:43–62
Briat C, Gupta A, Khammash M (2014) Integral feedback generically achieves perfect adaptation in stochastic biochemical networks. http://arxiv.org/pdf/1410.6064v3.pdf
Brigandt I (2015) From developmental constraint to evolvability: how concepts figure in explanation and disciplinary identity. In: Love A (ed) Conceptual change in biology. Springer, Amsterdam, pp 305–325
Burian R, Richardson RC, Van der Steen W (1996) Against generality: meaning in genetics and philosophy. Stud Hist Philos Sci 27:1–29
Collins JP, Gilbert S, Laubichler MD, Müller G (2007) Modeling in EvoDevo: how to integrate development, evolution, and ecology. In: Laubichler MD, Müller G (eds) Modelling biology: structures, behaviors, evolution. MIT Press, Cambridge, pp 355–378
Cordero OX, Hogeweg P (2006) Feed-forward loop circuits as a side effect of genome evolution. Mol Biol Evol 23:1931–1936
Csete ME, Doyle JC (2002) Reverse engineering of biological complexity. Science 295:1664–1669
Darwin C (1859) On the origin of species by means of natural selection. John Murray, London
Dawkins R (1978) The selfish gene. Oxford University Press, Oxford
Dennett DC (1995) Darwin's dangerous idea: evolution and the meanings of life. Penguin, London
Depew DJ, Weber BH (1995) Darwinism evolving: Systems dynamics and the genealogy of natural selection. MIT Press, Cambridge
Dupré J (2007) Is biology reducible to the laws of physics? Am Sci 95:274–276
Friedman M (1974) Explanation and scientific understanding. J Philos 71:5–19
Goodwin B (1994) How the Leopard changed its spots. The evolution of complexity. Phoenix, London
Goodwin B (2009) Beyond the Darwinian paradigm: understanding biological forms. In: Ruse M, Travis J (eds) Evolution: the first four billion years. Harvard University Press, Cambridge, pp 299–312
Gould SJ (1977/1996) Size and shape. In: McGarr P, Rose S (eds) The richness of life. The essential Stephen Jay Gould. Vintage Books, London, pp 317–323
Gould SJ (1982) Darwinism and the expansion of evolutionary theory. Science 216:380–387
Gould SJ (1983/2006) How the zebra gets its stripes. In: McGarr P, Rose S (eds) The richness of life. The essential Stephen Jay Gould. Vintage Books, London, pp 325–332
Green S (2014) A philosophical evaluation of adaptationism as a heuristic strategy. Acta Biotheor 64:479–498
Green S, Wolkenhauer O (2013) Tracing organizing principles: learning from the history of systems biology. Hist Philos Life Sci 35:555–578
Green S, Fagan M, Jaeger J (2015a) Explanatory integration challenges in evolutionary systems biology. Biol Theory 10:18–35
Green S, Levy A, Bechtel W (2015b) Design sans adaptation. Eur J Philos Sci 5:15–29
Griesemer J (2012) Formalization and the meaning of "Theory" in the inexact biological sciences. Biol Theory 7:298–310
Hamilton A (2007) Laws of biology, laws of nature: problems and (dis) solutions. Philos Compass 2:592–610
Haufe C (2015) Gould's laws. Philos Sci 82:1–20
Hofmeyr J (2007) The biochemical factory that autonomously fabricates itself: a systems biological view of the living cell. In: Boogerd FC, Bruggeman F, Hofmeyr J-H, Westerhoff HV (eds) Systems biology: philosophical foundations. Elsevier, Amsterdam, pp 217–242
Hogeweg P (2012) Toward a theory of multilevel evolution: long-term information integration shapes the mutational landscape and enhances evolvability. In: Soyer O (ed) Evolutionary systems biology. Springer, London, pp 195–223
Huang S (2004) Back to the biology in systems biology: What can we learn from biomolecular networks? Brief Funct Genomic Proteomic 2:279–297

Huneman P (2010) Topological explanations and robustness in biological sciences. Synthese 117:213–245
Jaeger J, Crombach A (2012) Life's attractors. Understanding developmental systems through reverse engineering and in silico evolution. In: Soyer O (ed) Evolutionary systems biology, advances in experimental medicine and biology. Springer, London, pp 93–119
Jakobsen L (2010) Vespertilionid bats control the width of their biosonar sound beam dynamically during prey pursuit. Proc Natl Acad Sci 107:13930–13935
Jones N (2014) Bowtie structures, pathway diagrams, and topological explanation. Erkenntnis 79:1135–1155
Kauffman S (1969) Metabolic stability and epigenesis in randomly constructed genetic nets. J Theor Biol 22:437–467
Kauffman S (1993) Origins or order in evolution: self-organisation and selection. Oxford University Press, New York
Kitano H (2007) Towards a theory of biological robustness. Mol Syst Biol 3:137
Kitcher P (1989) Explanatory unification and the causal structure of the world. In: Kitcher P, Salmon WC (eds) Scientific explanation. University of Minnesota Press, Minneapolis, pp 410–505
Klir GJ (1991) Facets of systems science. Plenum Press, New York
Koonin EV (2011) Are there laws of genome evolution? PLoS Comput Biol 7:e1002173
Kuhn TS (1962/1996) The structure of scientific revolutions. University of Chicago Press, Chicago
Letelier JC, Cárdenas M, Cornish-Bowden A (2011) From L'Homme Machine to metabolic closure: steps towards understanding life. J Theor Biol 286:100–113
Ma W, Trusina A, El-Samad H, Lim WA, Tang C (2009) Defining network topologies that can achieve biochemical adaptation. Cell 138:760–773
Mayr E (2005) What makes biology unique? Considerations on the autonomy of a scientific discipline. Cambridge University Press, Cambridge
Mesarović M, Takahara Y (1970) Theory of hierarchical, multilevel systems. Academic Press, New York
Mesarović M, Takahara Y (1975) General Systems Theory: Mathematical Foundations. Academic Press, New York
Mesarovic M, Sreenath SN, Keene JD (2004) Search for organizing principles: understanding in systems biology. Syst Biol 1:19–27
Müller G, Newman SA (2003) Origination of organismal form: beyond the gene in developmental and evolutionary biology. MIT Press, Massachusetts
Nersessian NJ (2008) Representation and reasoning: analogy, imagery, thought experiment. In: Nersessian NJ (ed) Creating Scientific Concepts. MIT Press, Cambridge, pp 131–181
Nickles T (1990) Discovery logics. Philosophica 45:7–32
O'Malley M, Dupré J (2005) Fundamental issues in systems biology. BioEssays 27:1270–1276
Polanyi M (1968) Life's irreducible structure. Science 160:1308–1312
Rashevsky N (1961) Mathematical principles in biology and their applications. Springfield, LA
Rosen R (1967) Optimality principles in biology. Butterworths, London
Rosen R (1991) Life itself: a comprehensive inquiry into the nature, origin, and fabrication of life. Columbia University Press, New York
Savageau M (1989) Are there rules governing patterns of gene regulation? In: Goodwin B, Saunders P (eds) Theoretical biology, epigenetic and evolutionary order from complex systems. Edinburgh University Press, Edinburgh, pp 42–66
Shanks N (2001) Modeling biological systems: the Belousov–Zhabotinsky reaction. Found Chem 3:33–53
Shinar G, Feinberg M (2010) Structural sources of robustness in biochemical reaction networks. Science 327:1389–1391
Shinar G, Feinberg M (2011) Design principles for robust biochemical reaction networks: what works, what cannot work, and what might almost work. Math Biosci 231:39–48
Smart J (1963) Philosophy and scientific realism. Routledge & Kegan Paul, London
Sontag ED (2003) Adaptation and regulation with signal detection implies internal model. Syst Control Lett 50:119–126
Soyer O ed (2012) Evolutionary systems biology. Springer, London
Stelling J, Sauer U, Szallasi Z, Doyle FJ III, Doyle J (2004) Robustness of cellular functions. Cell 118:675–685
Sterelny K (2007) Dawkins vs. Gould, survival of the fittest. Icon Books Ltd., Cambridge

Tyson JJ, Chen KC, Novak B (2003) Sniffers, buzzers, toggles and blinkers: dynamics of regulatory and signaling pathways in the cell. Curr Opin Cell Biol 15:221–231
Velazquez JL (2009) Finding simplicity in complexity: general principles of biological and nonbiological organization. J Biol Phys 35:209–221
von Bertalanffy L (1969) General systems theory. Foundations, development, applications. George Braziller, New York
Wiener N (1948) Cybernetics: or control and communication in the animal and the machine. MIT Press, Paris
Wilkins JF, Godfrey-Smith P (2009) Adaptationism and the adaptive landscape. Biol Philos 24:199–214
Winther RG (2009) Schaffner's model of theory reduction: critique and reconstruction. Philos Sci 76:119–142
Wolkenhauer O, Hofmeyr J (2007) An abstract cell model that describes the self-organization of cell function in living systems. J Theor Biol 246:461–476
Wolkenhauer O, Shibata DK, Mesarović M (2011) A stem cell niche dominance theorem. Syst Biol 5:1–16
Wolkenhauer O, Shibata D, Mesarović M (2012) The role of theorem proving in systems biology. J Theor Biol 7:57–61
Wouters A (2007) Design explanation: determining the constraints on what can be alive. Erkenntnis 67:65–80
Yi TM, Huang Y, Simon MI, Doyle J (2000) Robust perfect adaptation in bacterial chemotaxis through integral feedback control. Proc Natl Acad Sci USA 97:4649–4653