Tracing organizing principles: Learning from the history of systems biology

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Abstract

With the emergence of systems biology the notion of organizing principles is being highlighted as a key research aim. Researchers attempt to 'reverse engineer' the functional organization of biological systems using methodologies from mathematics, engineering and computer science while taking advantage of data produced by new experimental techniques. While systems biology is a relatively new approach, the quest for general principles of biological organization dates back to systems theoretic approaches in early and mid-20th century. The aim of this paper is to draw on this historical background in order to increase the understanding of the motivation behind the systems theoretic approach and to clarify different epistemic aims within systems biology. We pinpoint key aspects of earlier approaches that also underlie the current practice. These are i) the focus on relational and system-level properties, ii) the inherent critique of reductionism and fragmentation of knowledge resulting from overspecialization, and iii) the insight that the ideal of formulating abstract organizing principles is complementary to, rather than conflicting with, the aim of formulating detailed explanations of biological mechanisms. We argue that looking back not only helps us understand the current practice but also points to possible future directions for systems biology.

Keywords: systems biology, organizing principles, general systems theory, design principles, mathematical modeling.

Short running title: Tracing organizing principles

1. Introduction

> The historian of science always finds that germinal ideas are limited and that they tend to reappear, spiral-wise, at increasingly higher level of sophistication. - Bertalanffy 1967, p. 60

The focus on general principles of biological organization has greatly increased with the emergence of systems biology a little more than a decade ago. However, this ideal dates back to much earlier systems approaches and in this paper we aim to clarify the epistemic aim that contemporary systems biology has inherited from these. Mathematical and abstract systems theoretic approaches did not become part of mainstream biology in the 20th century, probably because they were outplayed by the successful experimental and technology driven fields that not until recently required mathematical modeling to the extent we now experience in the life sciences. The upshot of these developments has been a realization of the need for a different theoretical perspective to fully understand functional organization of living systems, and some of the previous ideas have therefore now regained their relevance. Several systems biologists have argued that the life sciences currently need approaches complementary to the highly specialized and technology-driven fields that are essentially realizing a reductive agenda. Such an approach should in their view zoom out and focus on key dynamic aspects in terms of general organizing principles in order to integrate research efforts towards an understanding of general biological principles (Mesarović et al. 2004, Wolkenhauer et al. 2012). The aim of the paper is to increase the understanding of the scientific challenges that initially motivated scientists to pursue the possibility of a more abstract (mathematical) approach to biology. Understanding the background is particularly relevant in light of recent proposals to push research forward by exploring the framework of earlier systems theoretic approaches (Mulej et al. 2004, Drack 2009, Wolkenhauer et al. 2011). We highlight the focus on relational and system-level properties emphasized in both previous and current approaches, and the inherent critique of overspecialization and pre-occupation with details in biology. In addition, we emphasize that the epistemic ideal of formulating abstract organizing principles is different from the attempt of formulating detailed causal explanations in biology, elucidating why researchers in systems biology disagree on the most appropriate methods of investigating living systems. However, we shall argue that these aims are in fact complementary rather than conflicting.

We begin by a short introduction to systems biology that is already a heterogeneous approach with several branches. We shall primarily focus on the system theoretical stream of systems biology since the focus on organizing principles has been most explicitly contended within this stream. Section 2 clarifies with examples what we mean by this term. Section 3 provides a reflection on earlier systems theoretic approaches, and Section 4 examines the epistemic strategies in light of the current challenges. Lastly, in Section 5 we ask whether looking back can point to future directions of systems biology.

2. Principles of biological organization in systems biology

Systems biology is a relatively new approach that merges several scientific disciplines to increase the understanding of functional organization of living systems. Systems biology is often defined as a successor of technology-driven –omics research where large-scale data analyses made it necessary to employ statistical, mathematical and computational approaches in order to interpret complex datasets. However, the notion of systems biology covers a range of different practices. Whereas some have emphasized the flood of data from high-throughput techniques as the backbone of systems biology (Aderem 2005), others have argued that systems biology is primarily a merger of systems theory with biology (Wolkenhauer and Mesarović 2005). The differences in these descriptions reflect a difference between at least two streams in systems biology; a pragmatic and a systems-theoretic approach (O'Malley and Dupré 2005). The two streams put different emphasis on the notion of system and differ with respect to the research aim and strategy. For the "pragmatic approach", the term system is seen as a convenient but vague term that covers a set of interacting molecular phenomena analyzed by integration of multilevel data and models. The precursor of this stream is molecular biology and the view of this field is extended but not questioned. In contrast, the system-theoretical approach sets the aim of developing a general systems-theoretical framework alternative or complementary to bottom-up analyses. It is mainly within this stream that the quest for organizing principles has been put forward as the research aim.

To our knowledge the boundaries and epistemic aspects of organizing principles have not yet been given any thorough analysis, and there is no general agreement on a precise definition of the term. There are however general features that serve to explain what we have in mind. Rather than attempting to provide such a definition here, we will use some examples to illustrate common features of general principles.

Description	**Examples of general principles**	**References**
Higher Order Laws/ Isomorphic principles	Allometric scaling relations Exponential equation (growth/decay) Logistic law Growth equations Principles of open systems	Bertalanffy (1950a, 1950b, 1967, 1969)
Optimality principles	Branching angle in vascular systems	Rashevsky (1960), Rosen (1967)
	Demand Theory of gene regulation	Savageau (1989)
Design principles	Network motifs	Alon (2006), Savageau (2001)
	Robustness, modularity	Csete and Doyle (2002), Velazques (2009)
Evolutionary Design Principles	The trajectories of evolutionary change leading to design principles	Soyer, ed. (2012)
Organizing principles	Feedback underlying regulation, control and adaptation of dynamical systems	Wiener (1948), Mesarović et al. 2004
	Bounded Autonomy of Levels	Mesarović and Takahara (1970, 1975)
	Closure to efficient causation	Rosen (1991), Letelier et al. (2001) Hofmeyr (2007)
	Coordination principle	Wolkenhauer and Hofmeyr (2007)
	Principles of tissue organization	Wolkenhauer et al. (2011)

Table 1. Examples of general principles in biology. The principles are grouped according to the concepts used by scientists and the lines of research associated with these; i) Bertalanffy's isomorphic principles (Section 3), ii) an engineering- or design inspired approach to design principles, iii) an abstract approach inspired by MGST (Section 5).

Table 1 displays a examples of general principles in biology that have been investigated under different headlines, from higher order laws to design or organizing principles. The list is by no means exhaustive and some of the principles differ considerably. However, the selection of examples can be used to outline characteristic features of these. General Systems Theory (GST) explored systems properties that could be described as *higher order laws* or *isomorphic principles*, often applicable across disciplinary domains (see Section 3). For contemporary systems biologists many of these examples may be considered as mathematical models of general constraints rather than biological principles of functional organization. However, we shall argue that the ideals of GST can be seen as precursors of the motivation behind current systems theoretic developments, although the scope of the principles differs. In contrast to Bertalanffy's broad systems perspective, the search for *design principles* is, as the names say, tightly connected the application of engineering methodologies, and in particular to the strategy of hypothesizing optimal design in biology as a heuristic guide (Savageau 1989, Savageau 2001, Alon 2006, Velazquez 2009). This heuristic has roots in Rashevsky's notion of "optimality principles"; instantiations of (sub)optimal design in biology that can be investigated in analogy to good engineering design (Rashevsky 1954, 1960, 1961). As an example, this method has been used to calculate the optimal branching angles of the vascular system as a basis for empirical investigation of this hypothesis (Rosen 1967). Optimality- or design principles are thus typically connected to design thinking that for heuristic purposes relate engineering design to the outcome of natural selection (e.g. Alon 2006).

Another current, but more abstract, strategy to identify general principles is based on the framework of Mathematical General Systems Theory, category theory and Rosen's work on abstract models of cells and organisms (Hofmeyr 2007, Mesarović et al. 2004, Wolkenhauer et al. 2011, 2012). Proponents of this approach often prefer the notion of organizing principles due to the often criticized adaptationist implications of design thinking, and because they wish to emphasize the difference between living and designed systems. These methodologies also draw on systems engineering principles, but mainly to understand the functional organization of a system regardless of its evolutionary origin. Recently the notion of design principles has however also been is used in *evolutionary* systems biology that goes beyond the adaptationist framework (Soyer, ed. 2012). The notions of design and organizing principles are often used interchangeably, and one should be cautious to give the notion of design a too literal interpretation. Furthermore, the historical trajectories of the methodologies to pursue such principles are intertwined. For instance, Rosen's work is explicitly stated as an important source of inspiration for both approaches (cf. Alon 2006, Hofmeyr 2007). In the following we shall speak of organizing principles to also cover what is sometimes called design principles. Our conclusions based on insights from earlier approaches will apply to all of the above mentioned approaches.

The characteristic epistemic virtues connected to the search for general principles will be clarified in the following section by examining the early traces of systems theoretic approaches. But as basis for the discussion we provide a preliminary definition of organizing principles in terms of characteristic features of the above mentioned examples. Organizing principles are robust generalizations that signify dynamic and functional relations in a class of systems rather than signifying context-dependent mechanisms of concrete systems. They facilitate cross-species and even cross-disciplinary generalizations because they are identified on a higher level of abstraction where many details of the system are excluded from the rigid mathematical framework they are typically investigated in. The potential of gaining insights on biological systems by trans- and interdisciplinary efforts can be illustrated by the notion of homeostasis. This concept was first coined by the physiologist Cannon in 1926 as a generalization of Bernard's idea of the *milieu intérieur* (Bernard 1865/1957) and described as the ability of organisms to maintain internal steady-state despite external perturbations. To give such self-regulating mechanisms a more theoretical basis the notion of feedback was imported from engineering, and feedback models of physiological phenomena, based on perturbation of sodium metabolism in rats, were initiated by biologists from late 1920s and 1930s (Woods and Ramsay 2007). In 1948, the mathematician Wiener formalized the idea of coupled feedback loops in oscillatory systems (Wiener 1948). His seminal book on cybernetics demonstrated the potential of studying control mechanisms in biology in analogy to those in engineered systems. Thus, transfer of resources from other domains often facilitates insights that are not possible to reach with methods from biology alone.

Systems biology has further reinforced this view, particularly by exploring resources from graph theory to model large datasets from high-throughput technologies as networks. This framework has afforded a search for general features underpinning the functional organization of biological networks, often investigated in analogy to design principles in artificial circuits (Velazquez 2009). The abstraction from details has revealed new insights to common topological properties of biological networks. While it has been discussed whether biological networks are scale-free or not (Keller 2005), it has generally been accepted that they are modular and hierarchically structured, allowing for cellular networks to display robustness against external perturbation (Hartwell et al. 1999, Csete and Doyle 2002, Steinacher and Soyer 2012). General functional features of small sub-circuits have gained attention with the discovery of overabundant patterns of connectivity, called *network motifs*, found in different regulatory networks and in different species (Milo et al. 2002, Alon 2006). While most of the principles identified in systems biology are on the molecular or cell level there are attempts to identify organizing principles across levels and to go beyond the “flat earth” perspective of network modeling (Mesarović and Sreenath 2006, see Section 4 and 5). The epistemological and ontological status of many organizing principles still remains an issue of debate in systems biology. However, drawing on historical traces of abstract approaches in biology and an examination of the current challenges we shall argue that accurate representation of real-world phenomena is not necessarily a basic requirement for the epistemic value of general principles.

3. Historical trajectories of general principles in biology

This section focuses on some of the important precursors for the current research strategy in systems biology. We do not attempt to provide a historically justified overview of the background of systems biology, but rather to highlight a selection of important precursors of systems thinking that can help to understand the motivation behind the quest for general principles. An obvious way to start such an analysis would be to define what is meant by systems theory. But what Mesarović said in 1968 still seems to be the case; there is no consensus on what constitutes the systems approach to biology (Mesarović 1968). Some would point to systems engineering, some to a “scientific philosophy”, some to cybernetics or mathematical biology, and yet others to classical physiology as pioneered by Claude Bernard (e.g. Noble 2008). Rather than a single historical trajectory that we can trace the ideal of general mathematical principles in biology back to, there are several approaches developed in parallel but connected in the work of key figures to form a society of mathematical biology or systems theory. We have therefore chosen to focus on General Systems Theory (GST) since the "general systemology" (Drack 2009) was based on the aim of integrating achievements in biology into insights on general principles of systems.

GST was first established, not as a scientific theory, but as a methodological and theoretical framework for integrative efforts to formulate general laws and principles of particular interest for biology. The philosopher and biologist Ludwig von Bertalanffy (1901-1972) is generally considered as the father of the approach, but as we shall see in the following section his work was inspired by many previous and contemporary sources. Mihaljo Mesarović (b. 1928) and colleagues later extended the visions into Mathematical General Systems Theory (MGST) that still is highlighted as possible future direction of systems biology (Mesarović et al. 2004).

3.1. Towards a mathematical theory of biological systems

Bertalanffy's 'organismic program' was the first attempt to integrate and institutionalize the efforts to identify general principles in biology. In December 1954, Bertalanffy founded the Society for General Systems Research, together with the economist Kenneth Boulding, the neurophysiologist Ralph Gerard, the mathematical biologist Anatol Rapoport and the psychologist James Miller (Hammond 2003). This institution is now known as International Society for the Systems Sciences (ISSS). SGSR was inspired by earlier attempts to apply mathematical tools to the study of biological systems. The period from 1920 to 1940 is sometimes called the "Golden Age of Theoretical Biology" because of important conceptual shifts in biology based on mathematical descriptions of biological phenomena (Mendoza 2009). A precursor for this development was D'Arcy Thompson's theory of transformation that reduces the problem of morphogenesis to a problem of relative growth relations (Thompson 1917/2004). His proposal was to map shapes of organisms in a co-ordinate system to explore the degree to which morphological changes could be modeled as quantitative transformations. His theory did not have much success in explaining empirical phenomena, but his work inspired a more systematic theory of living systems and raised the question of whether forces other than natural selection could explain the various morphological patterns (Rashevsky 1954, Rosen 1967).

Bertalanffy had initially shared the experimental biologists' skepticism regarding the potential of mathematical tools in biology, because these were associated with a reduction of biological complexity to physico-chemical principles (Pouvreau and Drack 2007). He however radically changed this view as he became familiar with Volterra and Lotka's work on mathematical models of population dynamics, and Fisher, Haldane and Wright's work in population genetics. The value of mathematics in biology became increasingly significant with the foundation of a distinct field called mathematical biology. For the latter part Nicolas Rashevsky's (1899-1972) work was among the key contributions. In 1938, Rashevsky published the first book on mathematical biophysics, and the following year he founded the first international journal for mathematical biology and biophysics, *The Bulletin of Mathematical Biophysics*. Rashevsky also initiated an academic educational program in relational biology, in which one of the now recognised icons of systems biology, Robert Rosen (1934-1998), took part (Rashevsky 1960,1961; Cull 2007). Rashevsky's ideas of relational biology and optimality principles were extended and further developed by Rosen (1967, 1991) and his theoretical cell model was taken up by Bertalanffy as a simple case of an open system and articulated as one of the key 'organismic principles' in biology (Bertalanffy 1950).[1]

Although the most explicit statements of the need for a general theory of systems is to be found in Bertalanffy's writings in this period, several developments indicate an increasing awareness that many scientific problems could not be solved within the existing disciplines alone. As Klir (1991) notes, the emergence of a number of interdisciplinary fields such as biophysics and biochemistry during the first half of the 20th century was probably the first step to recognize the existence of general properties across disciplinary boundaries. Bertalanffy's role in the theoretical and organizational aspects of the program of GST was complemented by the experimental approach of the biologist Paul Weiss (1898-1989) in the field of animal behavior and developmental biology (Drack and Wolkenhauer 2011). Weiss's experimental work pointed in the same direction as Bertalanffy's theoretical approach, namely to the conclusion that the reductionist analytico-summative approach in biology had severe limitations because it neglected the organizational aspect of the living world (Weiss 1970). To address relational aspects of biological systems, they both

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[1] For an insightful description of Bertalanffy's inspiration from philosophical sources see (Pouvreau and Drack 2007).

called for a conceptual and methodological framework that could bridge between theory and experimentation and between micro and macro levels (Drack and Wolkenhauer 2011). Two milestones of the coupling of mathematical modeling and experimentation came with the 1952 Hodgkin-Huxley model of action potentials in neurons, and the first mathematical model of the hearth rhythm (Noble 1962).

It should also be mentioned that the developments in systems theory and mathematics are closely connected to industrial developments that forced the invention of control systems for steam engines and feedback amplifiers to improve communication systems. Already in the late nineteenth and early twentieth century electrical engineers faced an increasing need for mathematical descriptions to deal with modular control systems (Wellstead et al. 2008). The methodologies to design control mechanisms for the growing body of new technology was later also applied to living systems. William Ross Ashby (1903-1972) and Norbert Wiener (1894-1964) were influential figures within the emergent field of cybernetics that tied together different lines of scientific developments such as electrical engineering, information theory and early research on neural networks (Pickering 2010). Bertalanffy acknowledged the importance of cybernetics in accounting for control mechanisms but argued that the focus on feedback-mechanisms could only account for a sub-set of the system properties addresses in GST (Bertalanffy 1967, 1969). He maintained that a broader and less mechanistic and technology-focused framework was needed to accommodate the active and open nature of living systems, as reflected in biological phenomena such as development, evolution, differentiation and creativity (Hammond 2003).

Like Bertalanffy, the systems engineer Mesarović also wanted to expand systems theory beyond properties that could be investigated in cybernetics. He was the first to use the notion of systems biology to describe the strategy to use systems theory for explaining living systems (Mesarović 1968). Systems theory traditionally referred to the theory of control systems but Mesarović explicitly aimed to broaden the notion to include the emerging field of *Mathematical* General Systems Theory; an extension of Bertalanffy's framework. In the following section we examine the ideals of (M)GST in further detail.

3.2. The quest for isomorphic relations

From the 1930s on Bertalanffy noted a broad interest in "systems" in many different scientific disciplines such as physics, biology, psychology, engineering and social sciences (Bertalanffy 1950a). He saw this development as an increasing realization of the limitations of studying phenomena in narrowly confined contexts on lower and lower levels. He defined the problem addressed in systems sciences as "essentially the problem of the limitation of analytical procedures in science" (Bertalanffy 1969). Thus, systems problems stem from phenomena that cannot be explained as a conglomeration of parts but exhibit what Warren Weaver called "organized complexity" with dynamic features changing over time (Bertalanffy, 1969, 34). Bertalanffy further noted that completely different fields arrived at isomorphic formalizations or homologies to account for similarities in the patterns of organization in different systems.

An example is the exponential law that with a positive exponent applies to as different phenomena as the unrestricted growth of bacterial, plant or animal populations and to the number of papers published on *Drosophila* (Bertalanffy 1950a). With a negative exponent the law can be applied to e.g. the decay of radioactive elements, the killing of bacteria by antibiotics, the loss of body substances in an animal upon starvation, and the decrease of populations with a death rate that exceeds the birth rate. For all these phenomena the exponential curve is the same. Another example is the logistic law of Verhulst that in physical chemistry describes the autocatalytic reaction; in sociology the growth of population under the conditions of limited resources and space; and within the domain of technological inventions, it can describe the growth of the railway system in the US during the 19th century. The corresponding s-shaped sigmoid function only signifies the rather general system of equations, namely an increase in elements, originally exponential, that at a certain point becomes limited due to restricting conditions. To use the equation to explain concrete phenomena we need to address the causal factors that explain the curve shapes. On the level of higher order laws there need however not be any overlap between the causal constraints in different cases where the law applies (Bertalanffy 1950a). Additional examples, to mention a few, are equations describing flows of energy and heat, equilibrium in chemical kinetics or population dynamics, fluctuations in business and populations cycles, and oscillations in electronic and biological systems. Bertalanffy further developed Huxley's principles of allometry, or relative growth, and identified different morphological types. The scope of general principles did not only include quantitative laws but also qualitative principles characterizing types of systems, such as the previously mentioned definition of organisms as open and fundamentally active systems, maintaining themselves in a nonequilibrium steady state through interaction with the environment (Bertalanffy 1950b).

3.3. From fragmentation to unification

Bertalanffy proposed that logical homologies of typified systems could counterbalance the increasing problem of overspecialization and fragmentation of knowledge in science. This he saw as a problem of wasted resources and inefficiency because the same scientific discovery was duplicated or triplicated in different fields (Bertalanffy 1950a, 1969). What was needed, he argued, was a re-orientation of scientific thinking to accommodate integrative efforts. GST was thought to work as a regulative device in science to encourage and codify the investigation and exploration of the cross-disciplinary application of methods, concepts and principles, and to develop a more exact theory in non-physical fields. He stressed that mathematics was the key tool to go beyond vague descriptions of principles and functions in biology because the mathematical framework provides the right kind of rigidity and abstraction from lower-level details (Bertalanffy 1950a). Inspired by Lotka's work, the higher order laws could take a similar role as statistical thermodynamics in physics where exact laws are formulated even though the lower-level causes are ignored (Pouvreau and Drack 2007).

An enforced quest for isomorphic laws across disciplines was thought to provide a methodological unity across disciplines (Bertalanffy 1950a, 1969). At first sight, this seems to be at odds with his insistence on the epistemological parity between physics and biology. However, when Bertalanffy spoke of unification of science he had in mind a correspondence on a higher level of abstraction. The aim was not to reduce biological explanations to physical laws but quite the opposite; instead of studying concrete instances of what Rosen called "thinghood properties" GST should aim for general principles addressing dynamic "systemhood similarities", and this framework also led to identification of principles specific for biology (Klir 1991). The systems perspective is therefore anti-reductive in this sense but embraces another form of reduction; a reduction of complexity by abstraction for the sake of generality (Nurse and Hayles 2011).

Bertalanffy emphasized that the isomorphisms are often only formal since the systems (e.g. populations of bacteria and radioactive elements) do not have any causal relations in common. What is common is the higher order *type* of constraining relations. Other examples, such as Bertalanffy's growth equations, do however have ontological anchoring and signify both formal and causal constraints that (a class of) organisms have in common. His growth equations represent growth as the imbalance between assimilation and dissimilation processes where assimilation is correlated to surface area, linking what he called 'growth types' to 'metabolic types'.[2] The growth equations do not account for all growth types but the equations signify a "causal basis" for more exact descriptions. Thus, general laws and principles can be more or less abstract, representing relations of different formal and causal similarity across different systems. Accordingly, the types of explanations we can derive from them may also differ in their predictability and accuracy. Bertalanffy proposed that there are degrees of scientific explanation. When the research objects are complex, as it is in biology, or when we enter fields that are not yet theoretically developed we often have to be satisfied with what he called "explanation in principle" (Bertalanffy 1969, 36). He borrows the concept from the economist Hayek that used the term to make sense of the value of economic models despite their inability to make accurate predictions of the stock market. These can be valuable when no other explanation exists – as tools to constrain the problem space for further investigations. Furthermore, the abstraction from details allows for a comparison of dynamics properties of different systems, thereby facilitating the transfer of methods across disciplines. Thus, the simplicity of the principles is not the result of a reductionistic view on biological systems but rather an awareness of our inability of comprehending biological systems in all their complexity from a study of the systems' components. In the following section we shall argue that this is also what motivates contemporary systems biologists to return to the ideals of earlier systems approaches.

4. Current challenges in the life sciences

Some systems biologists have stressed the need for a more 'holistic' approach to account for 'emergent systems properties' but it is not clear what is meant by these rather metaphysically loaded terms. Often 'emergence' simply signifies properties that cannot be found from a study of the parts of a system alone. For Bertalanffy, the need for a systems approach was not a result of special 'vitalistic' properties in the realm of biology that could not in principle be grasped in an extended physical science. Rather, the irreducibility of biology to physics reflected limitations *in practice*. If all parts *and* relations of biological systems could be known, Bertalanffy argued, it would in principle be possible to have a full understanding of these systems (Pouvreau and Drack 2007). However, he was far from optimistic that this would ever be a realistic option because of the complexity of organisms. Bertalanffy did not experience the revolutionary development of new experimental techniques that now have brought about optimism for what he thought was not possible. It is however not certain that awareness of today's experimental achievements and computational power would have changed his view. In fact, many contemporary systems biologists share his view. The two different streams of systems biology described by O'Malley and Dupré (2005) reflect a disagreement on the prospects of large-scale modeling. Whereas many proponents from the pragmatic approach aim for progress in understanding by extending the methodologies of molecular biology, the systems theoretical approach questions the potential of this strategy and proposes a more theoretical approach. In the following section we characterize the developments and challenges that motivate the latter proposal.

4.1. Large-scale modeling vs. abstract approaches

With the possibility of studying cell processes *in vitro*, main-stream biology became an inherently experimental and observational science, and the role of theories was in many contexts outplayed by the drive for developing increasingly sophisticated techniques for the isolation and manipulation of

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[2] For further details see (Pouvreau and Drack 2007).

systems (Klir 1991). The resulting specialization and context-dependency of results has been a consequence of the inherent complexity of biological systems. Not only is the number of interacting components overwhelming; biological entities are constantly changing and are organized through nonlinear and cross-level relations. Furthermore, organisms and cells are fragile in the sense that the research object - a *living* system – will easily be destroyed as we try to study it. Therefore, the history of the life sciences has to a large extent been a story about the development of increasingly sophisticated techniques to visualize, manipulate, isolate, purify and imitate biological processes inside and outside the cell (Rheinberger 1997). Many of these strategies have been reductive in the sense that they zoom in on isolated molecular components and pathways in order to make the investigation of cellular processes tractable. Such approaches have been extremely successful, and biological research has repeatedly crossed the boundaries of what was thought possible to investigate experimentally. However, as the knowledge increased so did the realization of the limitations of reductive approaches for understanding the overall functional organization of living systems. Previously it was thought that the ability to predict phenotypic functions, and thus also malfunctions or diseases, would increase rapidly with the sequencing of genomes. But with the rise of functional genomics, it became clear that the data of the human genome was quantitatively smaller, but qualitatively much richer, than expected. The difference between a fruit fly and a human is not fully understandable from the sequence alone but requires knowledge of complex intra- and extracellular processes that regulate the expression of genes and subsequent interactions of proteins (Dupré 2008). Similarly, complex diseases such as cancer can rarely be explained by studying single pathways. The focus of research efforts on a specific molecule (say p53, E2F1) or a specific pathway (say Jak-Stat, MAPK) are justified by their relevance for a particular cell function (proliferation, differentiation or apoptosis) that in turn is relevant to tumor growth and progression. However, the integration of research results is complicated by the context-dependency of the individual efforts while no overall theory, e.g. of the cell, is present (Loscalzo and Barabasi 2011). As a consequence, researchers have argued that a theoretical reorientation of biological and biomedical research is necessary (Wolkenhauer et al. 2012, Nurse and Hayles 2011, Wolkenhauer and Hofmeyr 2007).

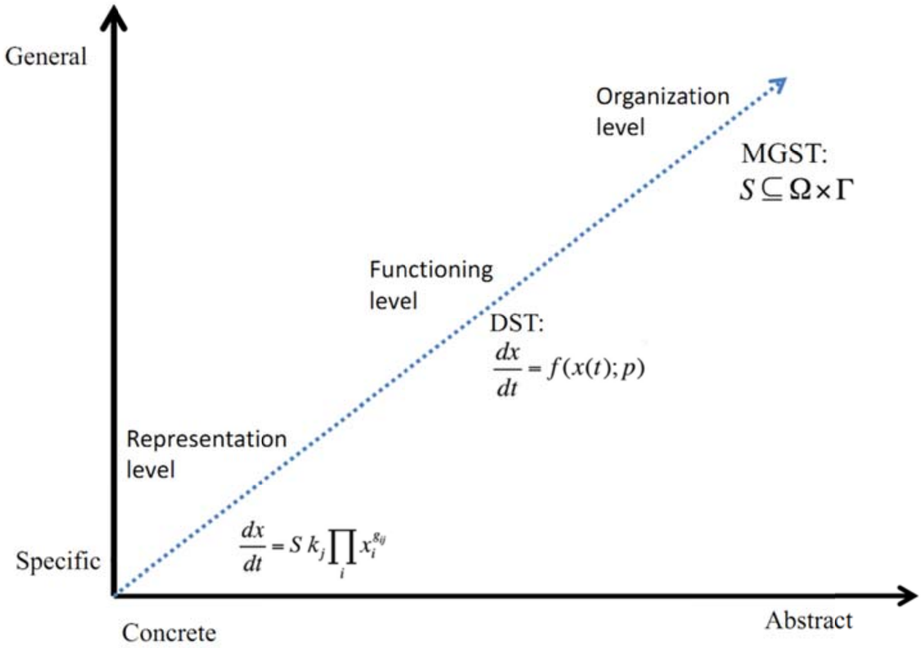
The emphasis in systems biology on higher-level abstractions is an attempt to counterbalance the (over)specialization associated with reductionist approaches (Alberghina and Westerhoff 2005). Whereas many research results in molecular biology have been diagrammatic representations of molecular structures and pathways, systems biologists investigate cross-level and time-dependent quantitative relations by modeling numerous relations using ordinary differential equations and network modeling (Wiggins 2003, Palsson 2011). The main reason to employ systems theory in the description of molecular networks is the dynamical component, but recently also to include multilevel factors such as environmental influences and spatio-temporal aspects, e.g. the spread of cancer cells in a tissue. The latter can be investigated using agent-based simulations to investigate pattern formation arising from molecular and cellular components interacting in space and time. Even though high-quality time-series data are still lacking, the impressive production and management of data may provide reason to think that we are on our way towards having sufficiently detailed information to realize what for Bertalanffy was utopic speculation: to model all relevant parts and operations in living systems. However, a new problem faced as the agent based modeling techniques develop is the complexity and intractability of models due to computational requirements of simulations or the lack of interpretability of the model's coding. The problem of large-scale modeling is therefore somehow analogue to Lewis Carroll's and Jorge Borge's fictional stories where maps as big as the countries they represent cause practical problems, not because of the *lack* of precision, but because of their *exact* accuracy (Carroll 1939/1988, Borges 1960/1998).

Systems theoretic proponents complain that our understanding of the functional organization of organisms and disease states has not been proportional to the production of the flood of data and scientific publications. This is a controversial discussion that we cannot cover in detail here. For understanding the motivation behind the abstract approaches it is however important to note the suspicion that adding further layers of complexity of biochemical details to the vast amount of publications will not help us understand living systems (Mesarović et al. 2004). Even though large-scale modeling projects of systems biology can be seen as important developments towards integration of research results, it is argued that to fully answer the questions associated with complex systems, novel and more abstract approaches are needed (Wolkenhauer and Mesarović 2005). Thus, rather than meeting biological complexity by analyzing interrelationships of *all* of the elements in the system, alternative strategies are chosen that explore the logical and biological range of possible principles of system organization. Thus, the two different approaches within systems biology pursue considerably different epistemic aims to solve the same problem; the fragmentation of research results. In the following section we shall however argue that the systems-theoretic approach is complementary to, rather than conflicting with, the aim to model biological mechanisms in greater detail. We shall return to the visions of (Mathematical) General Systems Theory to illustrate this point.

4.2. The complementarity of organizing principles

The ideal of organizing principles draws on the belief that not all details are necessary for understanding systems properties and that principles applying to a range of systems can be formulated. Critics have questioned whether such principles can be found and generalized across different biological contexts. We do not doubt that the belief in the existence of such general causal relations is an important part of the motivation for the search for such principles. However, it was important for Bertalanffy to distinguish between the regulatory value of higher order laws and the (lack of) ability of these to account for detailed causal relations. Following this line of thought it is relevant to ask whether organizing principles need to signify causal or ontological real-world phenomena for this strategy to be useful.

Bertalanffy used the notion of “explanations in principle” to denote the explanatory value of general principles and higher order laws. There is however an ambiguity in the notion that is also reflected in the examples used – it can signify sketches of “how-possible explanations” for more accurate causal descriptions *or* identify the ‘principal’ or fundamental higher order properties of systems. Rather than see this as a weakness, we might take advantage of this duality to explain two complementary epistemic virtues that organizing principles may alternate between. First, organizing principles may be conceptualized as how-possible explanations towards more detailed explanations of real-world systems. Secondly, organizing principles may take a role as higher-order laws or principles that signify the most fundamental characteristics of types of systems. For this purpose it is not an aim to lower the level of abstraction by adding further details, since the higher level of abstraction affords a facilitation of conceptual and mathematical frameworks that serve to inform and constitute biological theory. Below we describe this dual aim of working as templates for detailed explanations and of guiding conceptual precision of dynamic relations by introducing a distinction between different levels of understanding (Figure 1).



The *representation level* describes the behavior of concrete systems in detail and the models often apply to a narrow range of specific systems. Research on this level involves identification of molecular details in a network and their biophysical interactions. The *functioning level* includes generalizable mechanisms that determine the dynamic behavior of a system, and the models underlie observations made in experiments. Some of the examples in Table 1, e.g. network motifs, are represented as a diagram with arrays of signs that can serve as templates for more detailed models on the representation and functioning level. Another example is the study of a positive feedback loop in a mutual activation network which leads to a bistable behavior that describes a specific class of concrete systems (Tyson et al. 2003). However, for these examples and for organizing principles in general, their epistemic value is not reducible to the role of templates for the making of more detailed models. The aim of research on the *organization level* is to identify rules, principles and laws of which some functioning is an instantiation. If, say, bistability is found to be a necessary condition for cell function (e.g. cell differentiation, apoptosis etc.) across different cell types and species, bistability would define an organizing principle that generalizes relations by *defining* them as examples of a specific types. On this level, organizing principles can provide a more fundamental understanding of why the system behaves in specific way, independent from a particular manifestation of the type of system in the real world. Instead of assigning epistemic virtues to general principles on only one of these levels, the ambiguity in Bertalanffy’s distinction allows us to recognize that organizing principles may be valuable for understanding on all of these levels, depending on the epistemic cultures they are investigated in.

In summary, organizing principles can thus be fruitful as a means towards more detailed descriptions as well as clarify the most fundamental properties that can account for a *type* of systems behavior. The latter epistemological role is possible in virtue of, rather than despite of, the lack of details taken into account. Just like the purpose of a good map is useful because it omits unnecessary details while representing only the essential features for the purpose of navigation, so is modeling an art of making appropriate assumptions for specific purposes, i.e. of finding the relevant level and units of abstraction essential for understanding the system (Wolkenhauer & Mesarović 2005). Unlike the analogy to cartography, in science it is often the iterative process of modeling that matters, and not the model itself. General principles need not signify ontological or “real-word” counterparts in order to serve a purpose in biological research. What is now announced as design or organizing principles may turn out to be a too simple characterization of the functional organization of biological systems, as it has been argued in the case of network motifs (Solé & Valverde 2006). Nevertheless, the investigation of general principles may serve an important role as a framework for conceptualizing and comparing biological functions in a more precise mathematical language and across various systems. It is here important to note that mathematical frameworks with potential application in biology should not be narrowly identified with computability. As Rosen noted, this would exclude almost all of mathematics (Hammon 2003). Recent projects in systems biology explore the potential of MGST, and theorem proving in particular, for increasing the understanding of biological organization by identifying how biological systems work with *necessity*. Such projects raise the question of whether looking back is the key to push systems research forward.

5. Going forward by looking back

In the first section we speculated that the reason why systems theoretic approaches did not gain as much attention during the 20th century as its proponents hoped for was that they were outplayed by the successful experimental and technology-driven approaches. Another important reason is the conceptual and methodological gap between systems sciences and experimental biology. The framework of many systems sciences were originally developed to solve problems in engineering and not to address biological phenomena. Many experimental biologists were skeptical of the practical value of MGST, and systems engineers were not trained to deal with problems in the life sciences. Mesarović noted the importance to overcome this challenge already in 1968:

> The real advance in the application of systems theory to biology will come about when biologists start asking questions which are based on system-theoretic concepts [...] then, we will have a field of *systems biology* with its own identity and in its own right (Mesarović 1968).

Mesarović had to wait many years for this breakthrough, and even now systems biology has not succeeded in developing the general theory of biological systems he called for. The gap still exists, as an obstacle to fully explore the potential of MGST (Mesarović et al. 2004).

Other researchers follow this attempt of bridging the gap between systems theoretical and experimental approaches and between earlier approaches and modern research projects (Mulej et al. 2004, Pouvreau and Drack 2007, Wolkenhauer and Hofmeyr 2007). An example of a strategy argued to carry a great potential for future biology is theorem proving. Theorems have been used to identify necessary conditions for any model of a system with a specific property, e.g. absolute concentration robustness, and thereby to categorize classes of (network) models of systems from abstract statements (Wolkenhauer et al. 2012). The lack of context-dependency of mathematical proofs allows researchers to explore logical possibilities of relations in systems and between models of systems with the aim of increasing the clarity and consistency of functional descriptions. For instance, mathematical proofs drawing on MGST and category theory have been used to formulate cross-level principles that define the relation between propensities of differentiation in stem cell lines and tissue-fate in colon cancer (Wolkenhauer et al. 2011). Another example is the attempt to formalize an abstract cell model that signifies self-organization of cell functions. This approach combines Rosen’s idea of closure to efficient causation with the mathematical framework of Mesarović and Takahara to postulate the existence of a ‘coordination principle’ that determines cell function (Mesarović and Takahara 1970, 1975, Wolkenhauer and Hofmeyr 2007). These and other recent publications on abstract descriptions of cells reflect an increased interest in the old problem in theoretical biology of understanding life from a general organizational perspective. Apart from the theoretical interest these are argued to be of practical importance for understanding complex diseases such as cancer as the loss of systems property of functional organization rather than a cell-based disease. From this perspective, the key to understand cancer is not to investigate molecular pathways in detail but to understand the principles underlying the organization of processes across levels.

The empirical value of many of these abstract approaches is still to be determined. Despite many efforts to develop abstract models to understand life in general and cell functions in particular, progress in terms of empirical application remains dubious. Letelier and colleagues review theoretical developments in defining life throughout the last 70 years and conclude that different approaches to the same question have been developed almost in isolation from each other without major improvements (Letelier et al. 2011). They therefore propose that the way forward is to make an effort to understand the paths already explored and extend and integrate these. Thus, there seems to be an increasing need for integration of methods and conceptual frameworks on various levels: of old and modern approaches, of epistemic units in different disciplines, and of abstract and experimental methodologies. The reluctance from experimental biologists to adopt the mathematical and systems theoretic framework is understandable since the practical value of these approaches is heavily dependent on what problem is being addressed and what data are available. However, it should be noted the systems theoretic framework foremost presents a way of thinking about biological organization that redefines and reevaluates the visions and methods of the life sciences, and its influence should rather be judged by the extent to which the shift of perspective develops and informs theory. The use of theorems and graphical proofs is not introduced to formulate detailed causal explanations but to explore the logical possibilities of a system. We should not necessarily expect organizing principles to provide detailed explanations of biological phenomena. Their epistemic virtue lies elsewhere; as general and de-contextualized principles they can facilitate the transfer of methods across disciplines and signify the essential dynamic features for the behavior of systems. While organizing principles may not always have *accurate* predictive power for a particular system, their power lies in the fact that they express something fundamental about types of system properties in general, possibly about *any* cell, *any* organism or *any* control system.

Even though the practical use of organizing principles is still debatable, it is important to note that the increasing interest for such strategies reflects a self-critical tendency in the life sciences, questioning the abilities of reaching the goals of science with further specialization and by adding layers of complexity to models and scientific literature. It is thus inherently motivated by the need for a change of perspective. The practical prospect of the alternative strategy is that the approach may help avoid re-invention of the wheel by looking back (to earlier systems approaches) and to the side (to other disciplines). The epistemic prospect is that the ideal of organizing principles represents optimism that not all details are needed to understand biological phenomena, and that more abstract approaches can facilitate the transfer of methods across disciplines – hopefully leading to a greater understanding of the functional organization of living systems.

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