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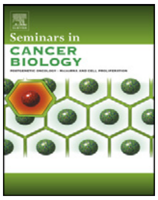

Review

Systems biology beyond networks: Generating order from disorder through self-organization

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ABSTRACT

Erwin Schrödinger pointed out in his 1944 book “What is Life” that one defining attribute of biological systems seems to be their tendency to generate order from disorder defying the second law of thermodynamics. Almost parallel to his findings, the science of complex systems was founded based on observations on physical and chemical systems showing that inanimate matter can exhibit complex structures although their interacting parts follow simple rules. This is explained by a process known as self-organization and it is now widely accepted that multi-cellular biological organisms are themselves self-organizing complex systems in which the relations among their parts are dynamic, contextual and interdependent. In order to fully understand such systems, we are required to computationally and mathematically model their interactions as promulgated in systems biology. The preponderance of network models in the practice of systems biology inspired by a reductionist, bottom-up view, seems to neglect, however, the importance of bidirectional interactions across spatial scales and domains. This approach introduces a shortcoming that may hinder research on emergent phenomena such as those of tissue morphogenesis and related diseases, such as cancer. Another hindrance of current modeling attempts is that those systems operate in a parameter space that seems far removed from biological reality. This misperception calls for more tightly coupled mathematical and computational models to biological experiments by creating and designing biological model systems that are accessible to a wide range of experimental manipulations. In this way, a comprehensive understanding of fundamental processes in normal development or of aberrations, like cancer, will be generated.

1. Introduction

Fifty years ago at the dawn of the molecular biology revolution, unprecedented enthusiasm was generated by the idea that biology was finally reduced to chemistry and consequently, the proposed way to understand organisms was to study them from the bottom up. Central to this view was genetic determinism, i.e. the perception that the organism was determined by a genetic program. The origin of systems biology, in contrast, attributed to von Bertalanffy, a biologist and philosopher, and Paul Alfred Weiss, a biologist, emphasized an organicist view where both bottom-up and top-down causation are considered. These two opposed views are represented by two discrete approaches in a new version of the systems biology discipline. O'Malley and Dupre call the genetic approach ‘pragmatic systems biology,’ which is centered around large-scale molecular interactions, such as gene networks, while the organicist approach, called ‘systems-theoretic biology’, is centered on system principles [1]. The differences between both approaches are not technical but rather philosophical, given that both are committed to mathematical modeling.

Philosophy is central to all scientific endeavors, including experimental and systems biology. Although many biologists ignore it, their research is guided by unstated ontological and epistemological stances. The inescapable fact is that, whether biologists like it or not, there are no theory-free data. As put by the philosopher Daniel C. Dennett: “There is no such thing as philosophy-free science; there is only science whose philosophical baggage is taken on board without examination” ([2], p. 21). Hence, in this review we will address the philosophical underpinnings of systems biology and of the science of complex systems. The incorporation of network models in the practice of systems biology over the theoretical framework of an interacting bottom-up and top-down system suggest a reductionist slant that hinders research on emergent phenomena. In addition, we are proposing a systems biology approach beyond networks.

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2. Philosophical underpinnings

2.1. Reductionism

There are three types of reductionisms, namely, ontological, methodological, and epistemic [3]. Ontological reductionism, also called physicalism, claims that organisms are made up by molecules and their interactions. This form of reductionism represents the worldview of the practitioners of the other two kinds of reductionism. Epistemic reduction claims that higher order phenomena can be reduced to another more basic level. This line of thought entails a 'hard-core' view, whereby biology could be reduced to chemistry and physics and, hence, biology would not be an independent science. According to the Stanford Encyclopedia of Philosophy [4], "methodological reduction is the idea that biological systems are most fruitfully investigated at the lowest possible level, and that experimental studies should be aimed at uncovering molecular and biochemical causes." This is another way of saying that molecular biology can, in principle, fully explain all biological facts. This type of reductionism is also pervasive in other fields of biology where causality is sought using a bottom-up approach. A great number of biologists insist that explanations should always be sought for at the gene and/or gene product level, regardless of the level of organization at which the phenomenon of interest is observed. Thus, genetic reductionism together with its twin, genetic determinism, predicates that everything in biology may be reduced to genes because the genome is the exclusive repository of transmissible information. It then follows that genes are the only units of selection [5] and development is just the unfolding of a genetic program. In sum, genes would be the building units of the organism and have a privileged metaphysical status (for an extended analysis of this subject, see [6]).

A main obstacle to the success of reductionism is the historicity of the organism, i.e. evolution and ontogeny. As François Jacob noted, nature is not an engineer, but a tinker—a given molecule is put to different uses [7]. Evolutionary history confronts us with the fact that these transformations were lost with the extinction of over 95% of the species that once existed. We are then forced to reconstruct this history from the organisms that exist today. This reconstruction is further hampered by evidence pointing to the fact that even in the same organism a protein may have different functions in different cells. For example, lactate dehydrogenase and crystalline are the same molecule; the former is an enzyme in muscle while the latter plays a structural role in the eye's lens. Beta-catenin is both a transcription factor and a cell-adhesion protein [8]. Also, a signal pathway effector may lead to the induction of different gene products and therefore distinct differentiation programs in different cell lineages [9]. This lack of a unique correlation between a given protein and its function was addressed by Hull as the problem of "the many and the many" [10]. In other words, one phenotype may result from several different molecular mechanisms, while a single molecule may be involved in different phenotypes. A clear example of this divergence is polyphenism, where a single genotype produces different phenotypes. These examples of diversity make reduction difficult, if not impossible.

2.2. Organicism and emergentism

Organicism is a philosophical stance that, contrary to reductionism, considers both bottom-up and top-down causation. It claims that "...Wholes are so related to their parts that not only does the existence of the whole depend on the orderly cooperation and interdependence of their parts, but the whole exercises a measure of determinative control over its parts" [11]. Implicit in this description is the concept of emergence, meaning that at each level of biological organization new properties manifest, which could not have been predicted from the analysis of the lower levels.

The existence of emergent properties is dismissed by physicalists because in their metaphysical stance, the belief on the causal closure of the physical word precludes the existence of emergents. However, as organisms are open systems, external constraints are always operating on them. The internal constraints defining a system are always disturbed by external ones; thus, in order to understand what is going on in a system, we must jump simultaneously to multiple levels on which this system is integrated [12]. For instance, a cell is integrated in a more complex system, the tissue. Organisms and their cells are ontogenetically linked. For example, a zygote is a cell as well as an organism. It divides, producing more cells, which are organized in a three-dimensional pattern. When gastrulation takes place, cells dramatically change their positions relative to one another followed by the formation of germ layers and a new series of rearrangements, local cell proliferation, cell movement, cell migration and cell specialization resulting in the emergence of tissues and organs. Even in a simpler system, like a muscle cell in the heart, its components are proteins that channel calcium and potassium ions, and they carry currents that change the cell voltage, which in turn changes the ion channels [13]. Thus, the components alter the behavior of the heart and the heart alters the behavior of the components, yet both components and the heart are integrated in a higher multi-cellular structure, the organism. This means that the working of such systems is never defined by initial internal constraints. When dealing with open systems, new systemic properties emerge as time elapses which can modify the initial properties. Thus what is described at an early time point (T1) is not the essence of the system. In other words, when one states that the biological facts at T1 cause physical facts at a later time point T2, and that they compete with the explanation of these facts as purely physical ones, we are making a mere idealization. At T2, the system is not the same as the one at T1, because it has acquired new properties that were absent at T1. Therefore, a system's description of natural events is not a complete description of what this system does. Diachronic emergence then means that in specific natural or formal systems the initial relations and properties of elements cannot teach us how they would be applied as the system evolves. Thus, the historical way by which a system of natural events operates is not a consequence of its description. It acts and it produces novelty in the real world (novel qualities and novel structures). In conclusion, emergence has an ontological meaning [14] and is not a simple epistemic property [15].

2.3. Complex systems

The last half of the 20th century and the first decade of the current one were characterized by the dominance of reductionist approaches to biology which were mainly driven by molecular biology. This type of reductionism was inspired by the influential 1944 book "What is life" by Erwin Schrödinger [16] who postulated that the chromosome formed an "aperiodic crystal" that is durable, an important prerequisite for hereditary matter. Schrödinger called it the "material carrier of life". Parts of the chromosomes are formed by genes, which themselves are large, durable and responsible for the observed inheritance mechanism, thus making animate matter unique. Schrödinger's ideas were driven by quantum mechanical reasoning applied to biology and were seminal in triggering the molecular biology revolution and lead to an increasingly gene-centric view of nature, a view further extended by another influential book, "The selfish gene" by Richard Dawkins [5]. However, now that the human genome has been decoded (see e.g. [17]), one may ask whether (a) knowing all parts of the system, can we fix or repair it if something goes wrong, and (b) can we put the parts back together?