Rethinking the pragmatic systems biology and systems-theoretical biology divide: toward a complexity-inspired epistemology of systems biomedicine

Srdjan Kesić*

Department of Neurophysiology, Institute for Biological Research "Siniša Stanković," University of Belgrade, Despot Stefan Blvd. 142, 11060 Belgrade, Serbia

* Corresponding author:

Srdjan Kesić, PhD
Assistant Research Professor,
Department of Neurophysiology,
Institute for Biological Research "Siniša Stanković,"
University of Belgrade,
Despot Stefan Blvd., 142, 11060,
Belgrade, Serbia.
Tel: +381 61 3127580
E-mail: srdjan.kesic@ibiss.bg.ac.rs

Short Title: Systems biology and epistemology of systems biomedicine

Abstract

This paper examines some methodological and epistemological issues underlying the ongoing “artificial” divide between pragmatic-systems biology and systems-theoretical biology. The pragmatic systems view of biology has encountered problems and constraints on its explanatory power because pragmatic systems biologists still tend to view systems as mere collections of parts, not as “emergent realities” produced by adaptive interactions between the constituting components. As such, they are incapable of characterizing the higher-level biological phenomena adequately. The attempts of systems-theoretical biologists to explain these “emergent realities” using mathematics also fail to produce satisfactory results.

Given the increasing strategic importance of systems biology, both from theoretical and research perspectives, we suggest that additional epistemological and methodological insights into the possibility of further integration between traditional experimental studies and complex modeling are required. This integration will help to improve the currently underdeveloped pragmatic-systems biology and system-theoretical biology.

The “epistemology of complexity,” I contend, acts as a glue that connects and integrates different and sometimes opposing viewpoints, perspectives, streams, and practices, thus maintaining intellectual and research coherence of systems research of life. It allows scientists to shift the focus from traditional experimental research to integrated, modeling-based holistic practices capable of providing a comprehensive knowledge of organizing principles of living systems. It also opens the possibility of the development of new practical and theoretical foundations of systems biology to build a better understanding of complex organismic functions.

Keywords: Systems biology; Cybernetics; Second order cybernetics; Complexity; Complex biological systems; Epistemology of complexity;

Introduction

In recent years there has been a growing interest in the use of systems biology in a wide variety of biomedical, biotechnical, and agricultural domains [1–4]. As shown by clear historiographical evidence, systems biology has actually resulted from the convergence of multiple theoretical and research pathways such as von Bertalanffy's general systems theory, cybernetics, Claude Shannon's theory of communication, the mathematical theory of systems of nonlinear differential equations, analysis of stability and bifurcations, deterministic chaos theory, cellular automata, complex adaptive theory, fractals, complexity, etc. It has made impressive progress in characterizing molecular interactions underlying multilevel structural and functional complexity of biological organisms indeed. While defining systems biology might be complicated, on the other hand, its emerging “subfields” systems medicine and systems pharmacology significantly contributed to our overall understanding of diseases and their treatments [5].

These fundamental and applied systems research projects differ in their aims, with some attempting a full “top-down” characterization of all gene products (transcripts, proteins, and metabolites) [6, 7], and others trying to exploit systems biology in drug discovery [8, 9], and cognitive and neurodegenerative disease research [10, 11]. In recent years a great deal of attention has been paid to the computational systems biology and the applications of mathematics in systems research. Indeed, to describe the functional integration of biochemical networks and extend their insight into pathophysiology, systems biologists aim to construct complex computer models capable of simulating and predicting the behavior of biological systems in variable environmental conditions [12–14].

Also, the attempts to integrate omics data are common threads that connect systems studies, as well as claims that mathematical-computational simulations (modeling) of these data can provide new insight into the functional and evolutionary dynamics of the living world. Despite the attention paid to the need of developing mathematical methods and computational tools capable of simulating dynamic molecular networks that affect whole-organism physiology, these attempts have not yet yielded results that are satisfactory for explaining the higher-level “emergent” properties of biological systems. In other words, the vast majority of working biologists is unreasonably afraid to creatively include complex systems modeling of higher-level phenomena into their research.

We suggest that this lack of knowledge is the indirect consequence of a somewhat “artificial” divide between two streams in contemporary systems biology practice - dominant pragmatic systems biology and cybernetic-inspired systems-theoretical biology. This stance followed a line of scientists and philosophers such as O’Malley and Dupré [15], and Mazzocchi [16]. These two streams are not theories or perspectives in competition, such as, for example, evolutionism and creationism, the chemical vs. electrical theory of synaptic transmission, statistical mechanics approach based on atomism as proposed by Boltzmann and Gibbs vs. the positivism of Mach and Ostwald in the same period, relativity vs. quantum mechanics, etc. The fact that many systems biologists are currently engaged in producing experimental data and not putting them together back into systems is one of the reasons for fuelling this divide and slowing down the progress of entire systems biology.

Furthermore, both of these streams have their flaws. While it turns out that pragmatic systems biology is no more different than molecular biology except perhaps the total amount of data produced [17], thus far, for some authors, the excessive insistence on the mathematical explanation of biological phenomena fails to provide a deeper understanding of the multilevel complexity of living organisms [18]. But, most scholars would agree that systems biology does not make any sense without both of these streams. Therefore, to provide both pragmatic systems biology and systems-theoretical biology with strong systems principles and to further integrate them into unified systems biology, a long-term and sustainable solution is needed. However, before closing the limitations of the current divide, an agreement on the most important conceptual issues of system biology, including its future best methodology and epistemology, needs to be brought on daylight. This paper, therefore, aims to propose some possible conceptual directions that scientists and philosophers may choose to follow in their consideration of effective ways leading to the integration of systems biology.

In this essay, we start by discussing the methodological, epistemological, and ontological assumptions made to make systems biology a prolific and pragmatic research approach. Next, we outline the difficulties that both pragmatic and system-theoretical biologists are attempting to understand biological systems have faced, especially in terms of linking lower molecular level with higher "emergent" levels. Third, we examine differences between systems biology, cybernetics, and complexity. Finally, we show how the "epistemology of complexity" adds new insight into the study of biological systems, especially in search of "physiological noise" in cancer biology.

Pragmatic systems biology vs. systems-theoretical biology

As a research approach rather than being a discipline [3. 4], systems biology has often looked to other fields, including history and philosophy of science for insight. Nowhere is this more evident than in the ongoing attempts aimed to explain its historical roots. The debate about the rise of systems biology has been the outgrowth of broader discussions on the relationship between systems theory, nonlinear dynamics, and molecular biology. Westerhoff and Palsson [1] concluded this debate by theorizing that systems biology has two independent roots, molecular biology, and nonequilibrium thermodynamics. But what makes systems biology so powerful approach is that it depends on the simultaneous use of "top-down" and "bottom-up" approaches as two significant ways of studying biological phenomena.

In this respect, two crucial revolutions in our understanding of biomedical methodology inspired the emergence and the growth of systems biology. The first and perhaps the one that approaches systems view of life most literally relates to the shift from the dominant molecular-reductionist "top-down" practice of biology to the holistic "bottom-up" way of observing and explaining biological phenomena [3, 19]. For example, in a relevant article, *The Nature of Systems Biology*, Bruggeman and Westerhoff [19] have argued convincingly that "bottom-up" systems biology deduces the functional properties on higher levels that could emerge from a subsystem that has been characterized using experimental molecular methods. It starts from the constitutive parts by formulating the interaction between the components (e.g., enzymatic process) and then integrates these formulations to predict system behavior.

The second significant methodological revolution relates to the development and successful application of high-throughput technologies in metabolomics, genomics, and proteomics [13]. This “top-down” systems biology starts from the bird-eye view of the behavior of the system – from the whole – and then measure genome-wide or experimental proteome data, with the ultimate goal of discovering biological mechanisms closer to the bottom [19].

Nonetheless, “top-down” and “bottom-up,” approaches to a living world shaped the contemporary study of biological organisms significantly. As suggested by philosophers O’Malley and Dupré [15] and philosopher and biologists Mazzocchi [16], the practice of systems biology consists of two streams. One, which they called “pragmatic systems biology” emphasize large-scale “top-down” characterization of molecular constituents (omics studies) and their interactions, whereas the other, “systems-theoretical ” biology emphasizes systems principles, mathematical biology, “bottom-up” and “top-down” modeling approaches. According to these authors, while pragmatic systems biologists still tend to view biological “systems as mere collection of parts, not as ontological (emergent realities), systems-theoretical biologists are instead committed to adopting a systemic view, that is to refer to systems’ principles, as established in the tradition of systems theory by pioneers such as Wiener, Ashby, and von Bertalanffy [16, p.14]. ” In other words, pragmatic systems biologists do not radically differ from “traditional” molecular biologists, except the fact that they are dealing with the “plurality” of molecules and their large-scale interactions. This belief fostered the widespread understanding that systems biology could be distilled into molecular systems biology [17].

On the contrary, systems-theoretical stream focused on mathematized systems biology stands against endless pragmatic efforts to “molecularize” systems biology. Indeed, for systems biology to prove its worth, it is necessary that scientists shift their primary focus to systems-theoretical biology and computational systems biology. This shift would expand a collective awareness of the strengths of systems theory in providing a holistic understanding of the evolution and physiology of the living organisms. These days there are many voices in the scientific and philosophic community supporting this argument. For instance, according to Mazzocchi [16], the future of systems biology lies in systems-theoretical biology.

There is another less obvious and more interdisciplinary-focused problem of systems biology, especially systems-theoretical biology, which prevents us not only to improve philosophical and historical knowledge of systems biology but also devising its future best research methodology. This problem concerns, I think, unclear and often neglected ties between systems biology and cybernetics, as well as the lack of understanding of the fact that cybernetics can improve theoretical and practical principles of systems biology. Although there is considerable knowledge that suggests common roots between cybernetics and systems-theoretical biology, it is my impression that even systems theoretical scientists quite often neglect the delicate relationship between these two exciting fields of research. The fundamental and correct assumptions here is that systems biology and cybernetics are two intertwined research fields and that the relationship between them is both a two-way street and also at a crossroads. Indeed, biology and especially organismic biology has been an essential inspiration for development in all aspects, including theoretical and experimental of cybernetics during the 20th century [21]. Also, the system's principles proposed by Wiener, Ashby, and von Bertalanffy, as well as nonlinear dynamics, are a common thread that runs through both cybernetics and systems-theoretical biology [16].

However, the essential difference between cybernetics and systems biology is that, unlike systems biology, philosophy played a direct role in the recent development of cybernetics. Indeed, the junction between epistemology, first and second order cybernetics has led to the development of what is called "epistemology of complexity," which quite successfully deals with the astounding relationship between complex systems and the human observer [22–24]. My humble understanding is that it may now be the time for further philosophically-inspired development of cybernetics to be an inspiration for solving some of the arising research problems of systems biology. The way how cyberneticists and complexity scientists discuss complexity can say much about the spatiotemporal organization of complex biological organism, and thus indirectly about the core aspects of systems biology research process.

Problems with systems biology: an insight from research practice

In recent years, systems biologists have focused on the complete spatiotemporal characterization of interactions between molecular constituents of an organism and systems analysis of the "molecular response" of a cell to external and internal perturbations [19]. In addition, systems researchers such as Bruggeman and Westerhoff [19] propose that experimental data must be integrated into mathematical models to enable knowledge-testing by formulating predictions (hypotheses), the discovery of new biological mechanisms, calculation of the system behavior obtained under external and internal perturbations, and finally, development of rational strategies for control and manipulation of cells. To accomplish all of these challenges, they believe, systems biology must integrate methods and approaches developed in other disciplines.

However, there is another critical step that systems biologists should take before developing sophisticated mathematical and computational models. They must be able to provide reliable scientific data on the behavior of molecular components in various physiological and environmental conditions. For philosophers, this entails assumptions regarding a clear and defined experimental practice, yet this aspect of science production lacks rigorous mathematical instructions on how to make a scientific discovery. In this view, the development of new experimental techniques allowing for quantitative measurements and the proceeding level of knowledge in cell biology enables the application of mathematical modeling approaches for testing and validation of hypotheses and the prediction of new phenomena [25]. In other words, along with the rising relevance of mathematical modeling in systems biology, the importance of experimental design (DoE) issues increases; a proper experimental design enables a maximum informative analysis of the experimental data, whereas sophisticated analysis methods cannot compensate an improper design [25]. To my opinion, this issue is one of the most critical shortcomings of systems-theoretical biology, especially considering that some systems-theoretical biologists quite often neglect the importance of experimental data collection method and instead profusely emphasize mathematical modeling.

However, the experimental methodology of systems biology touches upon pragmatic systems biology as well. The fundamental issue at stake here is one of the foundational assumptions of pragmatic-systems biologists that the experimental work is quite powerful in discovering the truths about complex biological phenomena. But this practical reasoning is not without apparent limitations. For instance, in analyzing the living world, the biologist is constrained to focus on a fragment of "biological reality" which he/she arbitrarily isolates to define certain of its parameters, and/or to measure quantities, and /or to identify qualities [26]. This entrenched “top-down” experimental routine may lead to a specific reduction of “ontic complexity” of investigated objects (ontological reduction) and loss of vital information [26, 27]. Stated differently, this widespread experimental routine widely embraced by pragmatic systems biologists fails to produce sufficient data on the adaptive and synergetic interactions between the molecular and cellular components underlying complex dynamics of living systems.

The point here is not that pragmatic systems biologists have failed to provide an integrative understanding of function and evolution of organism which is, by the way, one of the primary goals of systems biology. Indeed, the majority of systems biologists who adopt a large-scale molecular research practice argue that the complete catalogizing of molecular constituents and their interactions may provide an ultimate understanding of life [3, 19]. They have a sense that sum is not just a collection of parts, but they lack appropriate conceptual and mathematical tools to address this ultimate goal of systems research.

The primary problem of both pragmatic-systems biology and systems-theoretical biology has been a failure to appropriate the philosophical conception of “emergence” scientifically. Much of this resistance to the genuinely scientific embracement of “emergence” has its roots in both philosophy and more traditional science. As Ryan [28, p.2] argues

> “As the only commonality amongst the alternative positions is their failure to gain sufficient traction to generate consensus, their variety has only reinforced the status of emergence as an enigma.”

Ryan [28] also criticizes systems researchers for their adoption of the conception of “emergence” as a relation between levels, which have diverged to include a remarkable number of different positions. In this respect, philosophers and systems-theoretical scientists inadvertently accept the hierarchical theory of living organisms, which consequently fueled the existing disagreement about “emergence." Quite understandably, there has been an ongoing aversion to the misconceptions of philosophical concepts such as “emergence” in science, especially in experimental sciences. For example, according to philosophers David Chalmers [29] and Mark Bedau [30], there are two entirely different concepts of “emergence," “strong” and “weak," which often confuses scientists and philosophers. The former - most common in philosophical discussions since the 1920s and the British emergentist movement. According to Chalmers this form of “emergence” suggests [29, p. 244] “that a high-level phenomenon is strongly emergent with respect to a low-level domain when the high-level phenomenon arises from the low-level domain, but truths concerning that phenomenon are not deductible even in principle from truths in the low-level domain.” Unlike “strong emergence,” “weak emergence” concerns our cognitive and scientific inability to make epistemological predicaments about high-level phenomena [30].

In contrast, some complexity scientists, for example, Ryan [28] and Bar-Yam [31] who are firmly against “hierarchical” thinking in biology, contend that systems scientists should reflect upon “emergence” and “emergent properties” in terms of scope and resolution. Accordingly, first comes settings of the scope of the system, and then we are left to decide the resolution, which is usually straightforward. As far as systems theorists concerns, they are entrenched in believe that mathematized theory of “emergence” can ultimately make this concept scientifically appropriated. As Ryan [28] and Bar-Yam [31] argue, “strong emergent properties” cannot be found in an individual state of the system but rather in the ensemble, or the relationship of a system to the environment. In other words, there is no “strong emergence” when constraints that act on each component define the system.

On the contrary, when constraints are known that act on collectives and not on parts does “strong emergence” occur. In this view, the use of the mathematical study of multiscale variety is the evidence that forms of “strong emergence” can be scientifically considered at least in case of parity bit systems [31]. In this study, Bar-Yam [31] showed that it is possible to use mathematics to demonstrate “strong emergence.” But, Bar-Yam’s research deals with the “simple” complex system, and therefore, it is hard to say whether the multiscale variety can, in the same way, describe and predict the cases of “strong emergence” found in the biological domain. However, there are models in neurobiology with a long history, such as the Hodgkin-Huxley (H-H) model of nerve excitability that is capable of predicting emergent neural dynamics.

Nevertheless, “bottom-up” model such as the H-H model and “top-down” models of working memory and decision-making are studied by mathematics (theoretical neuroscience) and computational science (computational neuroscience) [32]. Although somewhat different, these two branches of neuroscience work in a complementary manner. According to Gerstner et al. [32, p. 60]: “Theory has the advantage of providing a complete picture of the model behavior for all possible parameter settings, but analytical solutions are restricted to relatively simple models. The aim of theory is therefore to purify biological ideas to the bare minimum, so as to arrive at a “toy model” that crystallizes a concept in a set of mathematical equations that can be fully understood. Simulations, in contrast, can be applied to all models, simplified as well as complex ones, but they can only sample the model behavior for a limited set of parameters”. Stated differently, before the typical model-building process begins, scientists must refine their ideas in the theoretical and most likely philosophical domain. I would complement this view by adding that this process of model production must undoubtedly include the selection of valid experimental data. Therefore, the above assessment of the validity of the combined use of “bottom-up” and “top-down” models in the study of working memory and decision-making could be complemented with the conclusions on the importance of collecting valid and fresh experimental data on these processes (experimental neuroscience).

As a computationally effective and straightforward model, H-H predicts quite successfully the propagation of action potentials, pacemaking activity or bistability, which are not a property of the individual components and processes (sodium, potassium, leakage permeation pathway, membrane capacitance) [32, 33]. It is based on the composition of ion channels, with specific time constants and gating dynamics that control the momentary state (open or closed) of a channel [32]. Although skepticism about its accuracy and usefulness has been raised over recent years [34], this model is still of vital importance in computational electrophysiology and neuroscience. In other words, the H-H model is “bottom-up” detailed biophysical model of a single neuron that allows scientists further development of macroscopic models of neural activity [32]. It is quite often combined with “top-down” computational models to quantify the brain dynamics, which is operating on multiple time scales. For, example, sophisticated modeling has provided a way to identify the connection between the simulation-based biophysical level and the phenomenological drift-diffusion models that were used to quantify decision-making behavioral data [32]. These above examples suggest that it is possible to predict specific “emergent” biological phenomenon if the mathematical model of the system is accurately defined, and the behavior of low-level components is realistically recognized.

In a similar vein, as part of Human Brain Project, Markram et al. [35] were able to reproduce in computational simulations a wide variety of spontaneous and evoked regenerative and non-regenerative firing patterns in “*in vitro*” and “*in vivo*” experiments, without any additional tuning of model parameters. This experiment was done on a neuronal microcircuit of a column in the rat primary sensory neocortex.

Despite this strong evidence that mathematics, theoretical and computational neuroscience can demonstrate the “biological emergence,” still some scholars and thinkers are not convinced in the unquestionable power of mathematics to explain the most if not all “emergent phenomena” in nature. According to them, in principle, mathematics is not necessary to demonstrate “emergence.” The first and second laws of thermodynamics, for instance, can be considered as emergent, in the sense that they apply to macroscopic phenomena that do not depend on microscopic details. In other words, Kinetic theory of gases shows how they can emerge in the limit of large numbers of particles. Robert B. Laughlin [18], a Nobel Prize winner, systematizes this “anti-mathematical” view of emergence in the book “*A Different Universe*: *Reinventing Physics from the Bottom Down*.” He argues that although the myth of absolute power of mathematics is still entrenched in our culture, the transition to the Age of Emergence brings to an end this myth. In his opinion, mathematics fail to deal with “emergent phenomena” adequately. Likewise, in the Philosophy of Mathematics, there is currently a fierce controversy about whether there are genuine “extra-mathematical” explanations in science, which are independent of the physical description of natural phenomena [36–38]. This debate is certainly not in favor of those systems-theoretical scientists who claim that it is possible to explain “emergence” in nature and society in a purely mathematical manner. Hence, the advocates of systems-theoretical stream in systems biology need to be aware of these shortcomings of mathematized systems biology.

Further, Steven Weinberg [39], a Nobel Prize-winning physicist, stresses the importance of the pluralistic scientific research of “emergence.” Weinberg in his well-acclaimed book entitled “*Dreams of a Final Theory*: *The Scientist's Search for the Ultimate Laws of Nature*” stated that the "reductionist" approach of finding a final theory of physics would by no means represent the end of special sciences such as biology. He supports his view by arguing that every hierarchical level of complexity will bring new “emergent phenomena,” for whose understanding even a unified physics wouldn’t be enough. He also claims that the level of resolution or detail in modeling complex systems needs to be limited. This stance complies with the requirement of the Occam razor or principle of parsimony. This philosophical principle states that one should not make more assumptions than the minimum needed or in a modeling context it is interpreted as: “Simpler models should be favored over more complex ones" (https://canworksmart.com/model-complexity/). In other words, this is a severe problem of modeling practice because the need for empirical or "raw" data and datasets is significant not only for the understanding of complex phenomena but also for calibrating and validating the models for improved usefulness in predicting, forecasting, and managing the behavior of the system [40]. In addition to finding the right variables, finding the balance between avoiding both overfitting and oversimplification is the grand challenges of computer science and complex modeling [40].

Furthermore, Alexander Rosenberg [41, 42], a well-respected philosopher of science and biology, considers "strong emergence" to be nothing more than an artifact of our limited cognitive, mathematical, and computational abilities. Although Rosenberg still maintains a strong reductionist view on the metaphysical ground, the possibility to reduce the sciences of complex (biological) systems to physics and chemistry turned, however, to be unfeasible. In Rosenberg's perspective, currently limited cognitive and computational abilities of human civilization, which prevent us of identifying universal laws in a biological domain such as those of physics or chemistry preclude the reduction of biology to physicochemical sciences. Similar to Weinberg, Rosenberg argues that the progress in physical sciences, at least for some time, will not lead to the end of sciences dealing with the astonishing complexity of a living world. My impression is that the consensus about "weak emergence" among scientists and philosophers has been reached more or less. However, when it comes to the "strong emergence," things are much more complicated because even within the sciences of complex systems there is no consensus reached about how to understand and study "emergent phenomena." Therefore it is unlikely that there is even a minimum consensus among scientists and philosophers on this issue.

From what we discussed so far, it is evident that both pragmatic and systems-theoretical approaches have their drawbacks that affect the attempts to explaining the cases of "strong emergence." It is, therefore, quite problematic to choose one over other perspectives as the basis of the future best methodology of systems biology. This is a diagnosis of the methodology of systems biology until the pragmatic-systems biologists start including systems principles in their work, and systems-theoretical biologists do not begin considering the importance of proper experimental design for modeling efforts. But, despite these shortcomings, there is a practical and theoretical need for both of these streams as well as for their more close ties through continuous integration. Of course, this integration has sense only in parallel with the elimination of their apparent limitations.

The integration between, on the one hand, the "top-down" experimental and computational approaches and "bottom-up" computer systems biology on the other is the best way to continue with the further integration of systems biology. There are many ways how this general model of integration could be realized in practice. One of them is above described, combined use of "top-down" and "bottom-up" modeling in neuroscience. The other, proposed by Wukketis [20], is more of general and philosophical nature. He suggests that biology in the 21st century must find the ways to overcome the historical and practical differences between analysis ("top-down") and synthesis ("bottom-up") and use them as complementary perspectives.

Perhaps one of the most impressive attempt to bridge between these two ways of observing complex organisms is the "theory of biological relativity," which underlies that there is no privileged level of causation in biology and that the biological functions are controlled simultaneously from higher and lower levels. Considering the multidirectional signal flow through biological hierarchies, Denis Noble [43] in an article entitled "*Claude Bernard, the first systems biologist, and the future of physiology*," proposed that there is no privileged level of causation in complex biological systems. The main conclusion of his exhaustive and in-depth analysis of system biology as a genuinely multilevel approach is that the insights obtained from the higher-level analysis (emergent properties) are even necessary to succeed at a lower level. In his view, in addition to reductionist "bottom-up" causal chain, there is also the higher level of control of cell signaling and gene expression via "downward causation." In a way, studying the control and integration of the flow of information in biological systems must combine "top-down" and "bottom-up" approaches, in both computational and experimental domain.

The "epistemology of complexity" is another significant conceptual way that can integrate and accommodate "top-down" and "bottom-up" approaches for the discovery of "emergent processes and structures." It relies on concept and methods devised in cybernetics and complexity such as self-organization, synergetics, complex adaptive theory, Maturana's and Varela's autopoiesis theory, second-order cybernetics (SOC), Morin's complex thinking, biological complementarity [23, 24, 44–48]. It highlights the importance of the observer systems role in the process of gathering knowledge and "co-construction" of the world environment [22–24, 49, 50], and can be seen as another proposal to integrate system biology. The "epistemology of complexity" may have the same role as the theory in neuroscience in Gerstner et al. [32] example. It has the potential to purify biological ideas to the bare minimum, to include the role of the observer in complex model building, and to ensure a simple model building with a set of mathematical equations that can be fully understood, and easily manipulated. It also has the potential to encourage the pragmatic - systems biologists to start putting the bricks together into a system.

Considering all this, we argue that a new complexity-oriented epistemology is a starting point for re-questioning the problems of the systems research and convincing pragmatic biologists to be more open for the principles of system theory. But above all, it should stimulate systems-theoretical biologists to include the epistemological considerations into model-building processes.

Systems biology from the perspective of cybernetics and complexity

Systems research now requires a new epistemological perspective that embraces complexity considered in all of its theoretical and practical aspects. We submit that a step toward the integration of systems biology particularly leads through "epistemology of complexity." At the root of "epistemology of complexity" is the cybernetic thinking and cybernetics, which both has a long history. First, it is hard to define cybernetics precisely. In its most general meaning cybernetics is a science that deals with the natural, technical and social process of change, which generates novelty, variety, and increase of organization; in one aspect all reality we experience is cybernetic [51]. Cybernetics is interdisciplinary and transdisciplinary because it provides the links between different knowledge domains and at the same time it abstracts the universal phenomena of control and communication, learning and adaptation, self-organization and evolution from the many areas it adumbrates [21, 22, 51, 52].

Norbert Wiener, one of the founders of cybernetics, established the permanent links between biology and cybernetics by defining cybernetics as the science of “control and communication in the animal and the machine” [21]. But, the word cybernetics dates back to ancient Greek and then later in modern times André-Marie Ampère used it in his essay on the “*Philosophy of the Science*” published in 1884 [53]. Cybernetics and General systems theory (one of the founders of General systems theory was Austrian biologists Karl Ludwig von Bertalanffy) are shown to be the same in motivation, requirements, characteristics, attributes, and behavior [53]. While cybernetics emphasized coordination, regulation, and control using feedback loops at the same time general systems theory attempted to elucidate profound principles underlying all types of systems whose components are linked by feedback loops [54]. Later on, advances in nonlinear dynamics in the second half of the 20th century influenced the further development of system theory, cybernetics, and complexity theory [54–56].

One of the central issues of the science of cybernetics concerns the origin, maintenance, and evolution of complexity, which goes beyond the cybernetics itself [57]. We submit that it is reasonable to argue that complexity delves deep into the sphere of transdisciplinary attempts to formulate a complete knowledge of the world. It surprises its cybernetic roots in many ways and more profoundly emphasizes the discovery of “emergent properties” across biological hierarchies. As history teaches us, complexity has actually resulted from the convergence of different research and theoretical pathways (e.g. nonlinear dynamics, cellular automata, self-organization, synergetics, Maturana’s and Varela’s autopoiesis theory, Morin’s complex thinking, systems theory, etc.), which have dealt with issues at multiple levels (e.g., mathematical, computational, experimental, etc.).

Furthermore, complexity is a theory, with accompanying mathematical models, about the behavior of systems [56]. Although cybernetics and complexity are two similar and interconnected fields of research, their difference may be reflected in the next paragraph [56, p.141–142]:

> “Complexity theory is related to both ecosystems and chaos theory, all three of which have been used to conceptualize biological, social, and psychological systems. However, to a greater extent than ecosystems theory, complexity theory attempts to explain why systems demonstrate emergent patterns that are greater than the summed effects of the original parts”.

Unlike complexity studies where the concept of “emergence” plays a vital role, in cybernetics, historically speaking, much of it revolves around the terms “positive and negative feedback control loops” [58]. Hence, complexity studies of the living world aim to reveal and describe the cases of both “weak" and “strong emergence,” whereas cybernetics is more concerned with the study of information flow within and throughout the system.

While experimental and mathematical observations about concepts and theories of complexity are abundant, the exact processes underlying generation of complexity remains unclear [55]. There is no unified theory of complexity, as well [55]. Also, there are many subjectively-bounded measures of complexity. Indeed, Rosen [59] portrayed complexity as a system’s characteristic corresponding to the difficulty in describing and modeling it: there is no single account capable of fully explaining complex systems. Many different ways of investigating and interacting with them are instead needed. But what scientists and philosophers dealing with complexity have in common is the doctrine that the evolution of complexity, the production of the living world, and later intelligent human and his civilization- are the results of the same process of self-organization governed by the same general principles.

Several concepts and theories of first-order cybernetics like synergetics, autopoiesis, or complex adaptive systems theory are proposed to explain and describe complex biological systems [44– 49]. But “Morin's complex thinking” and the “principle of complementarity” significantly influenced the formation of epistemological views on cybernetics. These two perspectives considerably deal with the ways of acquiring knowledge of the complex phenomena from the apparent theoretical and practical contradistinctions [23, 24, 49, 60].

Starting from the development of cybernetics as a holistic tradition in the 1950s and 1960s, it also becomes essential to address the role of an observer who distinguishes a system as such [22, p.1370]:

> “It was understood that the epistemology of the observer, how she, as a system comes to observe and know her world and the systems therein, was a complex matter.”

This thinking has led to the development of SOC. An essential contribution to the development of SOC gave Heinz von Forester, Humberto Maturana, Ernst von Glasersfeld, Gordon Pask, and others [22]. The following description made by Scott [22, p.1372], best explains von Forester understanding of cybernetics:

> “He shows that as we draw on our science to explain how we ourselves work, we find ourselves in a hermeneutic circle of explanation.” In other words, first-order cybernetics and first-order systems are explained from the perspectives of second-order cybernetics.

The epistemological scheme of the observer circularity in the domain of explanation includes the following steps [22, p.1374]:

> (1) First order study of observed systems distinguishes systems that are energetically open and organizationally closed (autopoietic).
>
> (2) Evolution and ontogenetic development of systems that observe and converse.
>
> (3) Second order study of observing systems: the observer explains himself to himself.

By taking into account these points, we might conclude that scientific knowledge is not directly taught and conceived as being a representation of an external and mind-independent reality. In other words, our scientific descriptions of the complex world should be seen as “world version” or better yet, these “world version” are “relative to us,” although it is possible that there is the “world itself” independent from our existence. Therefore, at this point, it is clear why the epistemological consideration of “emergence” (weak emergence) precedes the ontological and scientific study of it. This critical primacy of epistemological reflection points purposely to the shortcomings of our cognitive abilities, and perhaps it may reveal the paths that need to be taken to improve our knowledge of the “world itself.” For these reasons, the “epistemology of complexity” somehow reflects our constant need to return to fundamental philosophical aspects underlying the formation and growth of scientific knowledge.

Furthermore, as indicated, a better understanding of the coupling of the observer to the observed in biology is possible from the perspective of “Morin’s complex thinking” that invokes epistemological scheme of the observer circularity [23, 24, 49, 60]. What is important here is that “complex thinking” does not necessarily imply that “everything is complex,” meaning ‘what cannot be understood.” In other words, “complex thinking” allow scientists to articulate all sort on first sight distinct concepts and approaches such as the whole and the parts, as well to distinguish complex from complicated [61]. It allows combination several factors at the same time, “Where principles of regulation and non-equilibrium are combined, where contingency and determinism, order and disorder are; where levels of the organization and nonlinear dynamics can be identified by feedback between the levels [61, p. 3].” It seems that this perspective is promising, in integrating between opposites such as “holism” and “reductionism,” “top-down,” and “bottom-up” systems biology, pragmatic-systems biology, and systems-theoretical biology. However, one can object that “Morin’s complex thinking” is a more conceptual approach rather than a scientific method. But, here everything is about reconciliation between concepts, and therefore, the use of theoretical tools is also understandable. But such a conceptual strategy must be reflected directly on the biomedical research-practice itself. To provide this translation into research, let us discuss what the connections between “epistemology of complexity” and systems biology are.

Toward an epistemology of complexity in systems biology

Knowledge as something that has meaning for a subject (knowledge is our experience of the world that cannot be symmetrical, pure, or complete) is always contextualized, in a sense that it is always bounded to boundaries, or to our ways of producing descriptions when dealing with complex systems [50, 62]. For example, hypothetically speaking, if scientists had detailed knowledge of the fertilized egg, including the concentrations and locations of transcription factors and the relevant epigenetic influences, we could imagine solving the ultimate puzzle of development by devising equation involving gene expression patterns determined by both the genome and epigenome [63]. However, we cannot yet characterize all the relevant concentrations of transcription factors and epigenetic influences; and in the case that we could provide this information, there are “boundary conditions,” which determines the context of expression of these factors and their activity within the cell, tissues, and organs [54]. In other words, the “boundary conditions” are set by the higher level and determining those conditions at that level either by measurement or by computation can enable them to be inserted into the equations at the lower level [63]. Even more so, the notion of “boundary conditions” remind me of Davies notion of the epigenome as useful but virtual objects as there is no ‘command and control center,’ or instructions etched into a physical system, from which epigenetic control ultimately emanates [64]. Hence, it is challenging to qualitatively determine boundary conditions (to list them all), not to mention their small and large variations that may affect the behavior of molecular interaction network topology.

Furthermore, complex systems have a history, and without taking their history and context into account, they cannot be adequately understood [62]. For complex systems, for which the boundaries of knowledge (boundary conditions) are hard to set, knowledge comes to be in a dynamic network of interactions (in a state of constant transformation) without distinctive borders - this has to do with nonlinear dynamical interactions in a complex open system as a result of autopoiesis (self-production of living systems) process [62]. In other words, there are no accurate or perfect representations of an open system, which is more straightforward than the system itself (this is so-called the problem of boundaries). The fact is that when we build representations of biological systems (by employing models and nonlinear measures), we are forced to leave many things out; these omissions are nonlinear, and therefore it is hard to predict their magnitude [62].

Luisa Damiano [50] presents a compelling rational-based view of acquiring knowledge of the complexity from the research practice itself. What she emphasizes is the difference between “theoretical problem” and “epistemological problem” of complexity research. The theoretical problem requires “theoretical innovations”; it requires “the elaboration of models able to explain how nature can disobey the old reductionist postulate “the whole is the sum of its part” [50, p. 274].

In contrast, “epistemological problem” requires an epistemological innovation [50, p. 274]:

> “The suspension and, possibly, the substitution of the classical objectivist principle which relates the values of scientific descriptions to the characterization of a reality that is free from subjective influence.”

What is emphasized by Damiano is not the revolutionary role of SOC in describing “emergent properties," but rather a greater involvement of “epistemology of complexity” together with experimental sciences and mathematics to represent, explain and reproduce dynamic behavior of complex biological systems. What one might consider from Damiano’s distinction is that systems biology at first should resolve its “theoretical problem” before moving on to discuss its more serious “epistemological problem.” This common practice somehow belongs to the traditional school of thought in terms of how to solve scientific problems. According to this conventional reasoning, to be able to discuss epistemological issues of systems biology properly, we should first address and explain its experimental, mathematical, and computational problems, and then implement them into research practice. However, considering the epistemological scheme of the observer circularity in the domain of explanation, one can expect the resolution of experimental, mathematical, and computational issues only at the outset of the proper consideration of “epistemological problem.” In other words, back to the scientific and philosophical basis of the possibilities of human knowledge of complexity is the right way to establish trustworthy and productive pragmatic and systems-theoretical biomedical research practice.

Practical implications: epistemology of complexity of cancer research

The main question is how to use the “epistemology of complexity” to settle between conceptual and research contradictions found throughout systems biomedicine? In principle, comprehensive knowledge of complexity, as Cilliers [62] suggests, should be in the first place defined by dialectical relationship (beyond the object/subject dichotomy) between knowledge and the system within which this knowledge is constituted. Similarly, Mazzocchi [23], Theise and Kafatos [60] propose that the principle of complementarity, used initially in quantum mechanics, can successfully bridge between opposing perspectives and epistemological limitations associated with biomedical research. With this in mind, the gap between "weak emergence" and “strong emergence” and “bottom-up” and “top-down” analysis, pragmatic-systems practice and systems-theoretical practice should be closed at the interface between the complex biological system and the knowledge of the biomedical researcher. How can this be applied and refined in biomedical practice?

SOC provides valuable conceptual resources for system biology and can provide a completely new scientific and even philosophical perspective on how we approach information and causality in cancer biology, for example. For someone to determine whether the data from a particular level are relevant or irrelevant for understanding the phenomenon investigated, one must consider the context and the ways of producing descriptions of information content. In other words, one must be able to provide clear evidence that the measured “bottom-up” or “top-down” information is not a nonlinear artifact of measuring process itself. To support this thesis, it would be useful to stress that environmental factors (“boundary conditions”) are also inevitable in the process of cancer treatment, such as the temperature, radiations, chemical drugs, the immunological state of the host, individual quality of life factors, etc. [65–67]. So, it is essential to consider the probable influences of the different kinds of stochastic fluctuations on the process of cancerogenesis before the start of the therapy [66].

Current approaches to detect stochastic fluctuations information flow pretty much rely on the analytical derivation of the signal-to-noise ratio (SNR) from stochastic resonance estimation techniques. Using this approach, Li et al. [66] showed that weak environmental fluctuations could induce the extinction of tumor cells in the subthreshold periodic treatment. But, the authors of this study are cautious in their conclusion as the environmental fluctuations could also induce the appearance of stochastic resonance effect which is not beneficial to the extinction of tumor cells in the process of treatment. According to these authors, if the positional fluctuations are included in the equation, then it will enhance the stochastic resonance effect; however, the correlation length of positional fluctuations will play a decisive role during the treatment of cancer.

What can we conclude from this example? The history and context (the type of cancer, previous treatment, quality of life, etc.) play a significant role in estimating the effect of stochastic fluctuations on cancer treatment. Given that there are a large number of central and internal physiological and genetic factors affecting the treatment of cancer, it is challenging in this situation to evaluate the flow of stochastic fluctuation and its relation to positional variations. However, the method itself that provides the knowledge of the effects of stochastic change and noise on complex systems, including biological organisms, raises many questions. The stochastic resonance (SR), extensively studied by physicists in recent decades, has been described in a plethora of physical and biological systems, including the central nervous system [68]. It occurs when increases in levels of unpredictable fluctuations such as random noise cause an increase in a metric of the quality of signal transmission, or detection performance, rather than a decrease due to the nonlinearity of system and parameter ranges being ‘‘suboptimal’’ [68].

As we mentioned, biologists and physicists quite often use signal-to-noise ratio (SNR) to quantify stochastic resonance (see 66). But according to credible scholars such as McDonell and Abbot [68], SNR is unlikely to be a useful way of quantifying SR in biology since it is a measure designed for linear systems and artificial electronic systems. If instead biologists want to prove that biological function may rely on random noise, it makes more sense to measure variations in function with changing internal noise level. McDonell and Abbot [68] further criticize the use of SR in biomedical research. I will mention only a few critics they raise. The first criticism relates to our limited methodological capacity to devise an experiment that can undoubtedly reveal intrinsic stochastic resonance by removing naturally occurring healthy variability and thus demonstrating that function is impaired solely due to that removal.

The second critique stresses the epistemological problems of explaining positive noise because if noise benefits are found, then that means that an alternative, superior, non-noisy mechanism is not efficiently feasible or robust. This fact implies that our current knowledge of dominantly non-noisy cellular mechanism should be reconsidered from the ground up. Their third critique suggests that use of SR as a signal-processing strategy in its own right is misleading because it confuses cause with effect [68, p.7]:

> “In this circumstance, the system itself is capable of SR, and the technique that is employed is that of modifying the noise intensity.”

Now, after this consideration, it becomes clearer why many complexity theorists such as Mazzocchi [23] insists on Morin’s complex thinking as a promising theoretical tool that can help unravel the biological role of noise. The search for “positive” or “constructive“ meaning of noise makes sense only if the role of the observer (experimenter) and his epistemological status is included in the broader “noise” equation. Even then, boundaries of knowledge that determine the biological effects of noise are hard to understand due to nonlinear dynamical interactions in a complex open system. In other words, there are no accurate or perfect representations of noise and SR in, for example, cancer biology, which is more straightforward than the system itself. But the truth is that when the “epistemology of complexity” is employed, then we can, at least, be aware of the necessity of distinguishing between naturally occurring healthy variability and experimentally-generated noise. In other words, if we include epistemology in the research agenda, we can at least look at the limitations of the existing cognitive, experimental and mathematical techniques for the study of the origin, source, and physiological significance of noise. This practice would make it possible to discriminate between the biologically relevant effects of stochastic fluctuation and “negative noise” that is an artifact of our limited cognitive, mathematical, and computational abilities.

Conclusion

Mainstream systems biology has adopted a model of “expanded” molecular biology. For this and other reasons, reductionist “top-down’ research approach and reductive explanation are still dominant in contemporary biomedicine. As De Vreese et al. [69] notes, reductionist methodological practice is still prevailing in medicine, and medical research and practice is not fully and genuinely explanatory pluralist yet. This legacy in systems biology dates back to one of its roots, molecular biology and scientific methodology meant adopting a reductionist “top-down” research program in science. There can be no doubt that there are many fundamental aspects of systems biology, which is made clear by utilizing a reductionist methodology [3, 19].

Advocates of systems-theoretical biology and holistic understanding of life have been confronted with questions of the value of reductionist research program, implying that the essence of systems biology relegates their work outside the framework of molecular systems biology. These critiques miss the point of the importance of such large scale pragmatic molecular studies precisely because they assume that the mathematically-based model-driven approach is capable of discovering mechanisms operating at higher levels. But, the efforts to mathematically describe and predict “ontological realities” at higher levels (“strong emergence”) also did not produce a consensus on a universal mathematical theory of emergence. This doesn’t mean that there are no models in systems biology and neuroscience that cannot predict and describe certain “emergent phenomena.” In this regard, it is sufficient to look at the value of the H-H model that describes the overall single-neuron activity in computational electrophysiology [32, 33]. It, therefore, seems that both streams have their advantages and disadvantages. But I would say that there is no symmetry in this diagnosis because the essence of system biology lies primarily in the theoretical landscape of systems science [15, 16]. That is, the system principles should “absorb” the pragmatic stream in systems biology. And not the way around.

Consequently, we must consider carefully projecting the future of systems biology from the angle of a non-critical narrative that does not perceive the strengths and weaknesses of the current experimental and modeling research practice. We suggest that further integration and some agreed complementarity between these two streams are of essential importance for the future progress of systems biology. On this path, a better and more detailed view of the relationship between cybernetics and system biology can lead us in search of successful bridging principles that will unite contemporary systems research efforts.

I have concluded that pragmatic-systems biologists and systems-theoretical biologists at first focus their attention to “theoretical problem” and “theoretical innovation.” Unfortunately, this sequence of events only amplifies the existing “epistemological problem” of complexity research. By contrast, “epistemology of complexity” moves in the opposite direction, and the first place addresses important knowledge-related aspects underlying conceptual and research distinctions that could inhibit the proper practical implementation of "theoretical innovation." In this way, “epistemology of complexity” maintains the epistemic reliability of systems research just like in our example of noise in cancer biology. But above all, it creates preconditions necessary for the development and implementation of sophisticated mathematical and computational models (“theoretical innovations”) powerful enough to deal with the elusive “emergent principles and properties.” Indeed, to explain the emergence scientifically, the inclusion of the notion of an observer in definition and formal models is needed. For example, Baas and Emmeche [70] recognized and included the role of the observer in their formal mathematical framework for modeling “emergent phenomena.” So what we see in this example is that the complexity-inspired “epistemological innovation” can be reliably used to advance “theoretical innovation.” Therefore, I think that the general idea of cybernetics, in particular, second-order cybernetics and “epistemology of complexity,” can improve the multilevel linear and non-linear modeling methodology used in systems research of life.

However, I have only sketched the possibility of using "epistemology of complexity" in systems biology and systems medicine. In general, a problem with the "epistemology of complexity" is sometimes imprecise definition of how it can improve the acquisition of the knowledge in research practice, but this is a circumstance to be expected with freshly introduced concepts whose potential range of applications is still to be explored. To provide accurate analyses of this notion I have presented, the basic idea to approach systems biology here must be refined against concrete examples of biomedical practice. More detailed studies are needed to improve our understanding of how "epistemology of complexity" can solve persistent problems of current systems-based biomedicine.

Acknowledgments

The author would like to thank the reviewers for all of their constructive and insightful comments that improved the first draft of this manuscript.

References

[1] Westerhoff HV, Palsson BO. The evolution of molecular biology into systems biology. Nat Biotechnol 2004;22:1249–1252.

[2] Hood L, Heath JR, Phelps ME, Lin B. Systems biology and new technologies enable predictive and preventative medicine. Science 2004;306(5696):640–643.

[3] Ahn AC, Tewari M, Poon CS, Phillips RS. The Limits of Reductionism in Medicine: Could Systems Biology Offer an Alternative? PLoS Med 2006;3:e208.

[4] Kohl P, Crampin EJ, Quinn TA, Noble D. Systems biology: an approach. Clin Pharmacol Ther 2010;88(1):25-33.

[5] Stéphanou A, Fanchon E, Innominato PF, Ballesta A. Systems Biology, Systems Medicine, Systems Pharmacology: The What and The Why. Acta Biotheor 2018;66(4):345-365.

[6] Weckwerth W. Metabolomics in systems biology. Annu Rev Plant Biol 2003;54:669-689.

[7] Nicholson JK, Lindon JC. Systems biology: metabonomics. Nature 2008;455(7216):1054.

[8] Butcher EC. Can cell systems biology rescue drug discovery?. Nat Rev Drug Discov 2005;4(6):461.

[9] Cortopassi WA, Celmar Costa Franca T, Krettli AU. A systems biology approach to antimalarial drug discovery. Expert Opin Drug Discov 2018;13(7):617-626.

[10] Geschwind DH, Konopka G. Neuroscience in the era of functional genomics and systems biology. Nature 2009;461(7266):908.

[11] Wang ZT, Tan CC, Tan L, Yu JT. Systems biology and gene networks in Alzheimer's disease. Neurosci Biobehav Rev 2019;96:31-44.

[12] Kitano H. Computational systems biology. Nature 2002;420:206–210.

[13] You L. Toward computational systems biology. Cell Biochem Biophys 2004:40:167-184.

[14] Materi W, Wishart DS. Computational systems biology in drug discovery and development: methods and applications. Drug Discov Today 2007;12(7-8):295-303.

[15] O'Malley MA, Dupré J. Fundamental issues in systems biology. BioEssays 2005;27(12):1270-1276.

[16] Mazzocchi F. The limits of reductionism in biology: what alternatives? E-LOGOS: Electronic Journal of Philosophy 2011;11:1−19.

[17] De Backer P, De Waele D, Van Speybroeck L. Ins and outs of systems biology vis-à-vis molecular biology: continuation or clear cut?. Acta biotheor 2010;58(1):15-49.

[18] Laughlin RB. A Different Universe: Reinventing Physics from the Bottom Down. Basic Books; 2005

[19] Bruggeman FJ, Westerhoff HV. The nature of systems biology. Trends Microbiol 2007;15:45–50.

[20] Wuketits MF. The status of biology and the meaning of biodiversity. Naturwissenschaften 1997;84:473−479.

[21] Andrew AM. Cybernetics and system concepts in the natural sciences. Kybernetes 1982;11:9–13.

[22] Scott B. Second-order cybernetics: a historical introduction. Kybernetes 2004;30:1365−1378.

[23] Mazzocchi F. Complementarity in biology: A reassessment in relation to molecular-reductionist and systemic approaches. EMBO reports 2010;11:339−344.

[24] Morin E. Complex thinking for a complex world-about reductionism, disjunction, and systemism. Systema: connecting matter, life, culture, and technology 2014;2:14–22.

[25] Kreutz C, Timmer J. Systems biology: experimental design. The FEBS journal 2009:276:923−942.

[26] Rheinberger HJ. Experiment and orientation: Early systems of in vitro protein synthesis. J Hist Biol 1993;26:443−471.

[27] Rheinberger HJ. Experimental complexity in biology: some epistemological and historical remarks. Philos Sci 1997;61:S245−S254.

[28] Ryan AJ. Emergence is coupled to scope, not level. Complexity 2007;13(2):67-77.

[29] Chalmers DJ. Strong and weak emergence. The re-emergence of emergence. In: Clayton Davies, Paul, and Clayton, Philip, editors. The re-emergence of emergence: The emergentist hypothesis from science to religion. Oxford University Press; 2006. p. 244–256.

[30] Bedau MA. Weak Emergence. Noûs 1997;31:375−399.

[31] Bar-Yam Y. A mathematical theory of strong emergence using multiscale variety. Complexity 2004;9(6):15-24.

[32] Gerstner W, Sprekeler H, Deco G. Theory and simulation in neuroscience. Science 2012;338(6103):60−65.

[33] Herz AV, Gollisch T, Machens CK, Jaeger D. Modeling single-neuron dynamics and computations: a balance of detail and abstraction. Science 2006;314(5796):80-85.

[34] Meunier C, Segev I. Playing the devil's advocate: is the Hodgkin–Huxley model useful? Trends Neurosci 2002;25(11):558-563.

[35] Markram H, Muller E, Ramaswamy S, Reimann MW, Abdellah M, Sanchez CA, ... Kahou GAA. Reconstruction and simulation of neocortical microcircuitry. Cell 2015;163(2):456-492.

[36] Steiner M. Mathematical explanation. Philos Stud 1978;34(2):135−151.

[37] Baker A. Are there genuine mathematical explanations of physical phenomena? Mind 2005;114(454):223-38.

[38] Longa G. Mathematical Explanation, in PhilPapers: Online Research in Philosophy 2015.

[39] Weinberg S. Dreams of a Final Theory: The Scientist's Search for the Ultimate Laws of Nature. Pantheon, New York; 1993.

[40] San Miguel M, Johnson JH, Kertesz J, Kaski K, Díaz-Guilera A, MacKay RS, ... Helbing D. Challenges in complex systems science. Eur Phys J Spec Top 2012;214(1):245-271.

[41] Rosenberg A. Instrumental Biology, or The Disunity of Science (Science and Its Conceptual Foundations series). The University of Chicago Press, Chicago; 1994.

[42] Rosenberg A, McShea DW. Philosophy of biology: a contemporary introduction. Routledge, Taylor and Francis Group, New York; 2007.

[43] Noble, D. Claude Bernard, the first systems biologist, and the future of physiology. Exp Physiol 2008;93(1):16-26.

[44] Maturana HR. The organization of the living: A theory of the living organization. Int J Man Mach Stud 1975;7:313−332.

[45] Varela FJ. Describing the logic of the living: The adequacy and limitations of the idea of autopoiesis. In: Milan, Zeleny, editors. Autopoiesis: A theory of living organization. North-Holland; 1981. p. 36–48.

[46] Haken H Synergetics: An Introduction Nonequilibrium Phase Transitions and Self-Organization in Physics, Chemistry, and Biology. Springer-Verlag, Berlin; 1978.

[47] Holland JH. Complex adaptive systems. Daedalus 1992;121:17–30.

[48] Kauffman SA. The origins of order: Self-organization and selection in evolution. Oxford University Press; (1993).

[49] Chia R. Complex thinking: Towards an oblique strategy for dealing with the complex. In: Steve, Maguire, Bill, McKelvey, editors. The SAGE handbook of complexity and management. SAGE Publications; 2011. p. 182–198.

[50] Damiano L. Co-emergences in life and science: a double proposal for biological emergentism. Synthese 2012;185:273–294.

[51] Beer S. What is cybernetics? Kybernetes (2002);31:209–219.

[52] Glanville R. Second-order cybernetics. Cybernet Syst 2002;3:59–85.

[53] Dutta Majumder D. Cybernetics and general systems—a unitary science? Kybernetes 1979; 8:7–15.

[54] Anderson P. Perspective: Complexity theory and organization science. Organiz Sci 1999;10:216–232.

[55] Chu D, Strand R, Fjelland R. Theories of complexity. Complexity 2003;8:19–30.

[56] Woehle R. Complexity theory, nonlinear dynamics, and change: augmenting systems theory. Advances in Social Work 2007;8:141-151.

[57] van Dijkum C. From cybernetics to the science of complexity. Kybernetes 1997; 26:725‒737.

[58] François C. Systemics and cybernetics in a historical perspective. Syst Res Behav Sci 1999;16:203–219.

[59] Rosen R. On complex systems. Eur J Oper Res 1987;30:129-134.

[60] Theise ND, Kafatos MC. Complementarity in biological systems: A complexity view. Complexity 2013;18:11‒20.

[61] Ferrara NF. The Complex Thinking: building of a new paradigm. V! RUS 2010; (3).

[62] Cilliers P. Knowledge, limit, and boundaries. Futures 2005;37:605–613.

[63] Noble D. A theory of biological relativity: no privileged level of causation. Interface Focus 2012;2:55−64.

[64] Davies PC. The epigenome and top-down causation. Interface Focus 2011;2:42−48.

[65] Kim R, Emi M, Tanabe K. Cancer immunoediting from immune surveillance to immune escape. Immunology 2007;121(1):1−4.

[66] Li D, Xu W, Guo Y, Xu Y. Fluctuations induced extinction and stochastic resonance effect in a model of tumor growth with periodic treatment. Physics Letters A. 2011;375(5):886−890.

[67] Üstündağ S, Zencirci AD. Factors affecting the quality of life of cancer patients undergoing chemotherapy: A questionnaire study. Asia-Pacific journal of oncology nursing. 2015;2(1):17.

[68] McDonnell MD, Abbott D. What is stochastic resonance? Definitions, misconceptions, debates, and its relevance to biology. PLoS computational biology. 2009;5(5):e1000348.

[69] De Vreese L, Weber E, Van Bouwel J. Explanatory pluralism in the medical sciences: Theory and practice. Theor Med Bioeth 2010;31:371−390.

[70] Baas NA, Emmeche C. On Emergence and Explanation. Intellectica 1997;2(25):67‒83.