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Systems biology: impressions from a newcomer graduate student in 2016

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Simpson MR. Systems biology: impressions from a newcomer graduate student in 2016. *Adv Physiol Educ* 40: 443–445, 2016; doi:10.1152/advan.00172.2015.—As a newcomer, the philosophical basis of systems biology seems intuitive and appealing, the underlying philosophy being that the whole of a living system cannot be completely understood by the study of its individual parts. Yet answers to the questions "What is systems biology?" and "What constitutes a systems biology approach in 2016?" are somewhat more elusive. This seems to be due largely to the diversity of disciplines involved and the varying emphasis placed on the computational modeling and experimental aspects of systems biology. As such, the education of systems biology would benefit from multidisciplinary collaboration with both instructors and students from a range of disciplines within the same course. This essay is the personal reflection of a graduate student trying to get an introductory overview of the field of systems biology and some thoughts about effective education of systems biology.

high throughput; molecular physiology; biological network

OVER THE PAST 15 YEARS OR SO, there has been a growing interest in "systems biology," with an ever increasing number of publications on the topic (Fig. 1). Intrigued by the increasing use of the term among my own colleagues and excited by the promising potential of so-called "-omics" data and the applications to my own work, I signed up for a graduate course in "Molecular Physiology: Mechanisms and Methods." The first task in this largely self-directed learning course was to write an essay along the lines of "Systems biology: an update." The more I read, the more I appreciated the diversity of this field in both the disciplines and technologies involved and the applications across biological sciences. I came to the conclusion that it was more honest, and less arrogant, to describe this essay as "impressions from a newcomer in 2016." So I approached this essay with two questions that seemed like a natural start for anyone learning about systems biology: "What is systems biology?" and "What constitutes a 'systems biology approach'?" Through this essay, I touch on the philosophical background and practical implementation of systems biology today with the intention of highlighting aspects that may seem vague to other students. I also discuss the unifying potential of the field and some of the criticism faced by systems biology.

A unified definition of systems biology is elusive. In this sense, the philosophical foundations of systems biology seem to be more readily grasped by a newcomer. Underpinning all of the definitions I encountered was an acknowledgment that the whole of a living organism or system cannot be completely understood by the study of its individual parts. As renowned systems biologist Professor Emeritus Denis Noble put it, "biological functionality is multilevel" (17).

The study of individual parts, such as single genes or their protein products, has dominated the field of physiology (20), particularly after the discovery of genetic inheritance and the structure of DNA. Many experiments and projects have focused on finding genes or subsets of genes and/or proteins that cause disease when disturbed. This has been dubbed the "one gene, one enzyme" approach (7), or as the course coordinator suggested, the "one gene, one Ph.D student" approach, and is variously termed "mechanistic" or "reductionist." Contrastingly, implicit in philosophy of systems biology is an intention to study living organisms as a network of interacting parts and a recognition that complex biological systems are dynamic and behave differently under varying conditions. This is nicely exemplified by the following quote: "What is the difference between a live cat and a dead one[1]. One scientific answer is 'systems biology'. A dead cat is a collection of its component parts. A live cat is the emergent behavior of the systems incorporating those parts" (16).

Gaining insights into the dynamics of these individual parts acting within their systems has become increasingly possible with the development of high-throughput technologies. Computing capacity has also increased dramatically over the past 15 years, making modeling of large complex systems a reality. Such models might base their predictions on the biochemical and physical properties of the molecules within a system as well as current knowledge about experimentally confirmed interactions between these molecules. The development of both high-throughput technologies and computing capacity are often identified as the driving force behind the recent enthusiasm and advancements in systems biology (11, 17).

In search of an answer to the question "what is systems biology?", I found that most descriptions include a reference to the interdisciplinary nature of the field, the typical data, and the scope. Some explanations of systems biology focus on the integration of computational and mathematical methods into biological knowledge (22), whereas others specifically highlight the almost ubiquitous use of high-throughput or "-omics" data. Some state that the term "systems" encompasses molecules, cells, organisms, and entire species (4, 21), and yet others argue that systems biology concerns itself only with cells and subcellular networks (6). This latter interpretation was admittedly found in a critique of systems biology and does not seem to be a widely held view of "system biologists." One definition I found that concisely describes the purpose and practice of systems biology came from Dr. Ron Germain and appeared in a relatively anonymous article in the internal National Institute of Health (NIH) publication *The NIH Catalyst*: "A scientific approach that combines the principles of engineering, mathematics, physics, and computer science with

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[1] Assuming the cat is not in a state of quantum superposition after being placed in a sealed box with a flask of poison by Erwin Schrödinger.

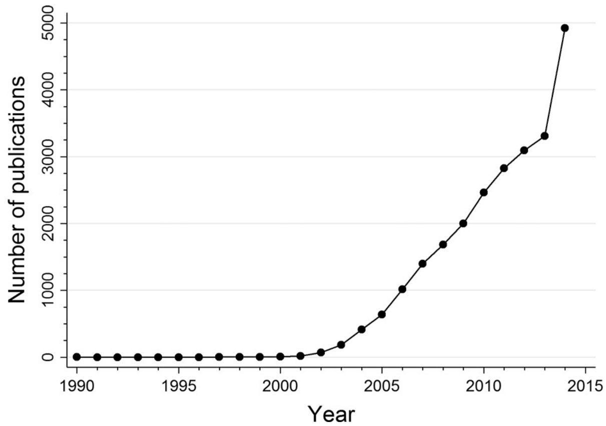

Fig. 1. The increase in systems biology publications. This graph shows the number of publications by calendar year indexed in the National Center for Biotechnology Information (NCBI)'s PubMed using the search term "systems biology" (all fields). Data for 2015 and 2016 are not included.

extensive experimental data to develop a quantitative as well as a deep conceptual understanding of biological phenomena, permitting prediction and accurate simulation of complex (emergent) biological behaviors" (21).

Leaving the nuances of the various descriptions aside, I sought to get an insight into how systems biology is implemented today. The diversity of disciplines involved in systems biology means that there is no single or simple answer to the questions "What does a systems biologist do?" and "What constitutes a systems biology approach in 2016?"

The term "a systems biology approach" is appearing more frequently in the title and abstract of both review and research articles. In review articles, they seem to be predominantly encouraging the use of systems biology thinking when tackling specific research problems rather than advocating a specific method (2, 13). From a random selection of recently PubMed indexed research articles stating in the title that they have used a "systems biology approach," it is clear that the specific computational modeling and experimental techniques vary considerably (3, 10, 19). In his brief overview of systems biology, Dr. Hiroaki Kitano presented an idealized version of how he envisioned that the process of hypothesis-driven research in systems biology should occur (8). He describes an iterative process that uses current biological knowledge and its contradictions to assist in computational modeling and simulation. In turn, these can help predict and direct future experimental work. The data from the experimental work will then contribute to greater biological knowledge and probably more contradictions, which will assist in building improved computational models and so on. All the while, the aim is to understand network structures and dynamics (8). The network(s) of potential interest are numerous and classically include one or more of the following intracellular networks: protein-protein interaction, protein-DNA interactions, noncoding RNA-mRNA interactions, and drug interaction networks (12, 14). With my limited practical knowledge of systems biology, it is difficult to comment on whether Kitano's hypothesis-driven process remains an idealized concept or whether it is realized today. Certainly, the few articles I reviewed employed experiments that aimed to capture the dynamics of a system utilizing high-throughput technologies to construct a predicted network. Sometimes the experiments were inspired by previous computational models. On the whole, I have the impression that publications employing a systems biology approach report one full circle of Kitano's hypothesis-driven process, allowing followup projects to iterate the process. The starting point, i.e., whether one starts with experiments or computational models, and the relative level of focus on the various steps is likely to be influenced by the expertise of the researchers involved and the interests of their laboratories.

The emergence of modern systems biology has brought together expertise from a diverse range of disciplines: biology, engineering, mathematics, computer science, and physics. The exchange of knowledge and ideas provides an exciting potential to make innovative advances based on integrated knowledge from all of these disciplines. Furthermore, the growing spectrum of methods and tools that have been applied in systems biology validates that there is a greater need for forums for exchange of ideas across disciplines to ensure optimal progression of the field. The course I participated in had few students, all within the same discipline of medical science. Given this lack of cross-disciplinary representation, attempting a small systems biology project would have been difficult. However, I note that other universities have successfully conducted multidisciplinary courses, giving students an opportunity to investigate a biological system in small groups consisting of students from different scientific backgrounds (9, 15, 18). Where possible, this must surely help students get a better understanding of what a "systems biology approach" can involve and highlight the benefit of pooling expertise from many disciplines. Certainly, as a student with a medical science background, I feel unsure as to what questions can be examined using, for example, computational modeling. It is clear that systems biology encourages and demands cooperation. However, like any emerging field, there are also critics of systems biology.

In 2010, Nobel laureate Sydney Brenner (1) described today's biology as being dominated by "low input, high throughput, no output" research and that systems biology will ultimately fail to provide unified theories of physiology. Brenner (1) claims that one of the fundamental flaws of systems biology is that it suffers from an "inverse problem," the problem of starting with a set of observations or results and then calculating the cause(s) of these observations. Furthermore, he expresses doubt that meaningful computational models can be constructed from serial snapshots, which still do not capture the dynamics of cellular processes. The remainder of the article outlines Brenner's own vision of how to investigate physiology, arguing that living organisms are reductionist because the molecularly encoded description and not the processes are inherited (1). Brenner (1) states that "The way forward is to continue in the path of molecular biology . . . ," yet in likeness with many descriptions of systems biology, Brenner's "way forward" focuses on understanding the cell as a network of interacting molecules and eukaryotes and networks of interacting cells (1). I am left with the impression that the major difference is that he does not find value in the use of computer modeling to help direct future experimental research. Systems biology and the approach suggested by Brenner (1) otherwise appear to share many similarities, which is perhaps what the author was alluding to with the following quote: "There is a watered-down version of systems biology which . . . does nothing more than give a new name to physiology . . .".

Others have also questioned whether systems biology constitutes a new scientific field or if it is in fact physiology or "integrative physiology" with a fashionable new name (5, 6). At the same time, some "integrative physiologists" criticize systems biology for being too cell-centric and not sufficiently incorporating interactions between cells, organs, organ systems, entire organisms, and the environment to understand the full functional and adaptive capacity of life (6). Indeed, in practice, systems biology appears to be conducted largely on the subcellular level, focusing on genetic and molecular networks. However, several groups express an intention to expand the methods and knowledge to cells, organs, and organisms (4, 21). Once again, I found myself thinking that the philosophical basis of systems biology is easy to fathom, intuitive, and appealing. However, the implementation is complex and still in a state of development.

The diversity of disciplines is both a challenge for newcomers and an enormous benefit for the development of the field of systems biology. I suspect that everyone teaching systems biology describes the field in a slightly different way, yet all would discuss the philosophical basis of systems biology. Recognizing that the complexity and dynamics of biological systems cannot be explained by studying individual parts may not answer the question "What is systems biology?", but rather the more inspiring question "Why systems biology?". As for the question "What constitutes a systems biology approach?," educators should be encouraged to incorporate the multidisciplinary nature of the field. To assist students in gaining an understanding of how systems biology is conducted, I believe it would be highly beneficial to have a range of disciplines represented among both the student audience and team instructors of a course. Particularly at the graduate level, courses could be set up with student participation from several departments, including mathematics, engineering, computing, biology, and physics. Ideally, the students would be given a task demanding cooperation and pooling of knowledge across disciplines to construct a predicted network or determine the consequences of a change in the network. In courses where students are all from the same field, such as the one for which this essay was written, it is still desirable to have teachers from other disciplines. Just as it is for systems biology research, education of systems biology should be a collaborative process.

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AUTHOR CONTRIBUTIONS

M.R.S. prepared figures; M.R.S. drafted manuscript; M.R.S. edited and revised manuscript; M.R.S. approved final version of manuscript.

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