Leading Edge
Essay
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Genetics in the Age of Systems Biology

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Systems biology has become a fashionable label for a new generation of large-scale experiments. This Essay explores how classical approaches such as forward genetics fit into this emerging framework.

There is little doubt that we are witnessing the arrival of the era of systems biology. There is a feeling that something important is going on that may shift the intellectual and experimental landscape on which we stand. Not that we are sure yet precisely what systems biology is. Preliminary definitions either highlight the conceptual aspects of studying complex biological systems (e.g., Kirschner, 2005) or focus more on the technical approaches of large-scale data acquisition and integration (e.g., Liu, 2005). In any case, systems biology has the flavor of something far removed from the gory details of standard molecular biology. We are told that systems biologists see a bigger and more holistic picture, and that the reductionist approach (studying complex systems by investigating only their isolated components) may soon become old fashioned, boring, and perhaps even a little embarrassing.

Although it is true that looking at a biological problem from a larger perspective is intuitively interesting, the current excitement about systems approaches to biological problems raises a number of important issues. There appear to be certain types of approaches that are viewed as synonymous with the notion of systems biology. Large-scale molecular measurements and computational modeling are key elements of a systems biology experiment. Other methods, such as large-scale RNA interference (RNAi) screens, have also become associated with systems biology. One approach that is conspicuous by its absence is forward genetics (the unbiased screening for genetic mutations causing a phenotype of interest). Whereas leading geneticists continue to remind us of the past achievements of the genetic approach and of the promises that genetic toolboxes hold for future research (Nagy et al., 2003; Gregan et al., 2005), one generally fails to find serious consideration of forward genetics in discussions of systems biology. Indeed, it is not uncommon to hear speakers at systems workshops and symposia refer to moving *from* a genetics approach *to* a systems approach. This observation is closely related to the perception that systems biology is here to replace the so-called traditional reductionist strategies. In reflecting on these considerations, we would like to raise the following question: how holistic are large-scale molecular experiments, and what is the nature of the relationship between forward genetics and systems biology? To answer these questions, we would like to briefly consider three topics: (1) the timing of the transition from gene discovery to systems biology, (2) the idea of systems biology as an alternative to a reductionist scientific landscape, and, most importantly, (3) the relationship between forward genetics, quantitative molecular biology, and the systems concept.

The first consideration is rather trivial, as revealed by the following thought experiment. Currently, mutations in less than 25% of all genes have been phenotypically characterized in multicellular model organisms such as the worm *Caenorhabditis elegans*, the fruit fly *Drosophila*, and the mouse. Let us consider the example of the fruit fly genome. Assume that, starting in January 2006, the first characterizations of fly mutants are reported for 50 new fly genes every month. At this unrealistically rapid rate, January 2021 will have passed well before all remaining fly genes are described (and that's assuming only one publication per gene). Clearly, the era of gene discovery is far from over.

This does not mean that the time for an integrative systems approach is not ripe; quite the contrary. Geneticists—perhaps more than biochemists, physiologists, and cell biologists—have been keepers of the myth of the gene as the holy grail of biology. As molecular genetics took center stage, biological processes often became the context in which to understand the function of a given gene, rather than the other way round. Thus, the experimental questions asked and the conclusions drawn became rather gene centric. When thinking at the systems level, geneticists should accept that genes only matter because they are one of many cellular codes. No single gene is more or less important than any other, and the loss of function of gene x causing phenotype X is not itself an interesting observation. It is only interesting if we can begin to quantitatively explain how gene x interacting with genes w, y, and z together produce phenotype X in context A but not in context B, and what predictive value this interaction has on the system. From this perspective, the synergistic combination of quantitative molecular biology, forward genetics, reverse genetics, and computational modeling constitutes systems biology (e.g., Gunsalus et al., 2005).

Our second consideration relates to the perception that, as the star of system biology rises, that of reductionism must fade. Curiously, however, it is not a great achievement per se to approach

a given problem more holistically. Most visionaries of the past are forgotten because their grand ideas and books became useless once the pedestrian way of experimental science revealed their incompatibilities with the facts of nature. Science remains the art of the solvable. Traveling the systems road, we must constantly ask ourselves how appropriate the big picture is and how adequate the systems approach is to the level of the question we are trying to answer. The fundamentally new characteristic of systems biology is its way of thinking, rather than its way of doing. Systems thinking realizes that the phenotype of a system (from the shape of a cell to an evolutionary stable strategy) is the emergent property of the interactions among all of the components of this system. Thus, it is neither the scale of the system nor the particular approach used to arrive at a list of its functional components that defines a systems approach. In fact, perhaps paradoxically, for research driven by this concept to succeed, it may be necessary first to isolate a reduced system to provide an experimentally testable hypothesis. For example, to understand the molecular changes that occur in a cell upon binding of a ligand to its receptor, most quantitative biologists largely query well-defined in vitro cell culture systems, which do not necessarily reflect the in vivo responses of a complex developing system. Thus, for the time being, the practical (as opposed to the conceptual) translation of systems biology is much better referred to as large-scale reductionism.

A further complication is that every system can be described at numerous levels, but only very few of these are relevant to a useful understanding of the system. To give an example, the early universe, a car engine, and a boa constrictor are all products of quantum interactions of subatomic particles. Yet a quantum description of these interactions is only useful for one of the three systems: it can neither tell us if the engine is working nor what the snake had for lunch. Richard Dawkins refers to this necessary feature of scientific inquiry as "hierarchical reductionism" (Dawkins, 1986). So, although large-scale measurements are imperative for a comprehensive description of the system, the level at which both measurements and integration occur must vary depending on the system being studied and the question being asked.

Our third consideration questions the assumption that if systems biology is holistic, then genetics is reductionist. Let us first have a closer look at the *"omics"* approach. It is now possible to measure, with increasing precision and in some cases in real time, the molecular constituents of a system and their variations across a series of dynamic phenotypic changes. These measurements are collectively referred to as *"omics"* (as in gen*omics*, transcript*omics*, prote*omics*, lipid*omics*, and so on). But not every *"omics"* experiment is systems biology. It depends on the question. If the purpose of a microarray experiment, for example, is to identify a few target genes for a transcription factor and then validate the "most promising candidates," then this is not systems biology. If, on the other hand, the purpose is to describe the global transcriptional response of the cell to changes in the level, localization, or sequence of the transcription factor and then ask how the new molecular conditions created in the cell interact to produce the phenotype, then that is systems biology. Thus, the tools put constraints on the task at hand, but they do not define it. So, what about the genetic approach?

We argue that the assumption that genetics, and especially forward genetics, is a reductionist approach is simply erroneous. Like a microarray experiment, a genetic screen is not itself reductionist or holistic. It is the use of the genetic toolbox that defines its outcome. It seems that, by mistaking the *"omics"* wave for the systems approach *itself*, we are forgetting some of the most influential systems approaches of the past: when Christiane Nusslein-Volhard and Eric Wieschaus (Nusslein-Volhard and Wieschaus, 1980) targeted the whole *Drosophila* genome using random mutagenesis to unravel the riddle of embryonic pattern formation, they were doing systems biology. Other classical examples include the *Drosophila* screens of Seymour Benzer (for example Hotta and Benzer, 1972) and the *C. elegans* screens of Sydney Brenner (for example, Hodgkin and Brenner, 1977). How conceptually different is a genome-wide forward genetic screen from genome-wide RNAi screens (reviewed in Friedman and Perrimon, 2004)? Today, mouse RNAi screens and proteomics measurements can only be done in vitro. As such, is a forward genetic screen for behavioral defects in the living mouse not at least as much, if not more, relevant to systems biology? In general, a genetic screen addresses the following questions: what is the total number of components required to build a given phenotype (system) and what is the contribution of each of these components to the phenotype? To answer these questions, genetics assumes (correctly) that perturbation of these components should result in some change in the expression of the phenotype. Furthermore, our ever-increasing capacity to visualize and quantify subtle and dynamic phenotypes—from cell shape to behavior—in live animals means future genetic screens will provide an unprecedented wealth of physiologically relevant information. Genetics is not only compatible with systems biology, it is a corner stone of any useful form of it. But if all it takes to remain fashionable is a fresh label, "Forward Genet*omics*" might do nicely.

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