The elusive field of systems biology

“Systems biology” is quickly emerging as the popular term describing many exciting scientific activities of postgenomic biology. There is now even a department of systems biology (Harvard Medical School, Boston, MA), and an institute of systems biology (The Institute for Systems Biology, Seattle, WA) associated with prestigious academic institutions, and many of these same elements are being put into place at others. As with any rapidly evolving area of science, it is not easy to formulate a precise definition of “systems biology,” nor should we try to put boundaries around it by doing so. At the moment there is clearly uncertainty over what the field is and what it represents. There are a number of reasons for this. One understandable and acceptable reason is that many of the traditional scientific disciplines are a part of systems biology, so each one feels that it can and does represent this exciting new field. Another understandable but unacceptable reason is that some individuals and institutions are recognizing the popularity of this term and applying it to advance their own special interests without adding any value to this truly expansive field. Along with this scenario comes the danger with all buzzwords du jour, that it will be overused and wind up conveying no meaning at all. This would be truly unfortunate, because systems biology, as used by its serious scientific proponents, represents what may be the most important new and revolutionary endeavor of 21st century biology.

So what does systems biology really mean, and what is the science that it encompasses? Before attempting to define this new field, it is useful to define some things that it is not. It is not an expansion of any single existing scientific discipline or field of biological research. It is not just a catchy new phrase for “integrative physiology” or “computer modeling” or “systems analysis.” Nor can it be characterized by the tools used in a DNA microarray or proteomics facility. It cannot be wholly captured by annotation and correlational analyses using genomic-scale data sets. It cannot be defined as merely descriptions of cellular gene expressions and diagrams showing the clustering of function or interactions of thousands of genes or proteins. Systems biology cannot be defined as the high-throughput phenotyping of thousands of mutated fish, worms, flies, mice, or rats. So, although systems biology is none of these alone, each of these elements represents an essential component of this emerging new discipline. Systems biology, therefore, is not a scientific discipline in its traditional sense. At its core, systems biology represents a renewed recognition that biology is best understood by taking a coordinated, integrative systems view. In practice, systems biology means the application of many currently defined disciplines with the goal of bringing together information from the smallest units of the biological system (genes) to help understand the function of the whole organism. To accomplish this goal, these efforts must also incorporate not only what we know about biology, but also the expertise of our colleagues in the sciences of physics, chemistry, mathematics, and the computer sciences.

An increasing number of scientists have recognized that in this postgenomic world, it is imperative that our institutions of science be proactive in creating ways to converge functional genomics and integrative physiology. The limitations of pure reductionism to help us understand complex function have become abundantly apparent. It can be argued that this type of restructuring work is premature. But many, including me, have chosen to believe that now is the time to begin building the scientific infrastructures that will enable an integrated understanding of the function of complex organisms and chronic diseases. How much more data do we need to add to the already more than 12,000,000 computer searchable references represented in PubMed before we begin to take this task seriously? I suggest that now is the time for interdisciplinary groups of scientists to converge in ways that will enable the linking of genomes/proteomes/metabolomes/interactomes (and the other “-omes”) to complex cellular function and ultimately the function of the whole organism. It is this goal that is represented by the term “systems biology.”

So if we take this to be our definition of systems biology, how do we translate it into practice? I would argue that no single center has yet achieved a working model encompassing all of the needed elements of a systems biology center, either real or virtual. It would appear that to reach the goals expected of systems biology research, these centers must encompass many elements in a cohesive whole. One is the use of the high-throughput analytical, robotic, and computational approaches required for genomic sequencing, microarrays, proteomics, large-scale phenotyping, bioinformatics, etc. These centers would embrace physiologists with broad knowledge and experimental skills, capable of hypothesis development and testing at the cellular, organic, and whole organism levels. At the center of all of this must be a team of skilled mathematicians, engineers, and computational biologists for collaborative design and analysis of large-scale data sets and predictive modeling. All of these skill sets must converge, with the individuals working in concert to design and implement testable, quantifiable studies that link genes to the function of complex biological pathways.

To have all of these elements working collaboratively in an administratively coordinated unit would indeed be revolutionary: it does not yet exist. Granting agencies and academic institutions are structured to support individual, traditional research disciplines, although elements of the needed restructuring are evolving as part of the new National Institutes of Health Roadmap (http://nihroadmap.nih.gov/). At the moment, it is a struggle to maintain and support large interdisciplinary groups, but such groups will be necessary for the study of systems biology, and both government agencies and academic institutions must now engage in planning for this type of unit if systems biology is to become a reality.

I don’t pretend that this will be an easy task. Revolutions never are. Each of the existing disciplines, departments, and centers will have to contribute to the essential elements of such a center. There must be convergence and collaboration between scientists working at the extreme ends of the scientific spectrum, i.e., those representing the ultimate in scientific reductionism (molecular genomics, proteomics, etc.) and those working with complex functional pathways of cells and organisms. A “systems biologist” must speak and understand the languages of these different disciplines. And as difficult as this
may be to structure, it is this challenge that will bring about stimulating new approaches and lead to the convergence of these historically divergent fields. The convergence must encompass scientific experts in genomics, proteomics, metabolomics, biochemistry, bioinformatics, biophysics, cell and molecular biology, the physiological sciences, and computer modeling, as well as the technology experts that provide the underpinning required to bring this about. Systems biology represents the work that will emerge from these collaborations and lead to truly new levels of understanding of the emergent properties and functions of living systems.

So let us strive not to trivialize or obfuscate what systems biology really is. As revolutionary as is the science required for systems biology, so too will be the changes in the ways in which we carry out and fund this science. This will require rethinking the ways in which the departments and research centers within our academic institutions are integrated, as well as the ways in which academia and industry interact to develop the technologies required to advance these exciting goals.

Allen W. Cowley, Jr.
Editor-in-Chief
Physiological Genomics
E-mail: pgeditor@mcw.edu