

The Science of Every Living Thing

How can our accumulated knowledge of nucleic acids, proteins, and other molecules be translated into an understanding of how the cells, tissues, organs, and ultimately organisms that contain them function? The aim of systems biology is to provide an approach to understand organisms as complex, interacting, and integrated systems that are much more than the sum of their parts.

Integrative approaches to molecular biology began in a small way about 40 years ago with the discovery of feedback regulation of amino acid biosynthetic pathways and the definition of the function and regulation of the lac operon. A bit more recently, molecular biology, aided by automated sequencing and high-throughput technologies, has yielded vast quantities of data and spurred the field of bioinformatics. Two approaches have evolved, one data-driven and looking at one or a small number of components at the gene, protein, and metabolite level, and the other computationally driven to create models to simulate cellular processes and understand how they work. Systems biology can be seen as an integration of many experimental and computational approaches to biologic problems.

The sheer enormity of data will require an effort on the scale of the genome project for analysis and construction of meaningful and useful models. Models of biologic systems, be they cells, tissues, organs, or pathways, can be created to predict responses to various inputs, including changes in diet, development or progression of disease, and therapeutics. These models, therefore, could be used to identify therapeutic targets, identify and design drugs with greater specificity, efficacy, and safety, and predict an individual's risk for disease and response to a given treatment. The ultimate test of a successful model will be the extent to which it correctly predicts the response to defined inputs.

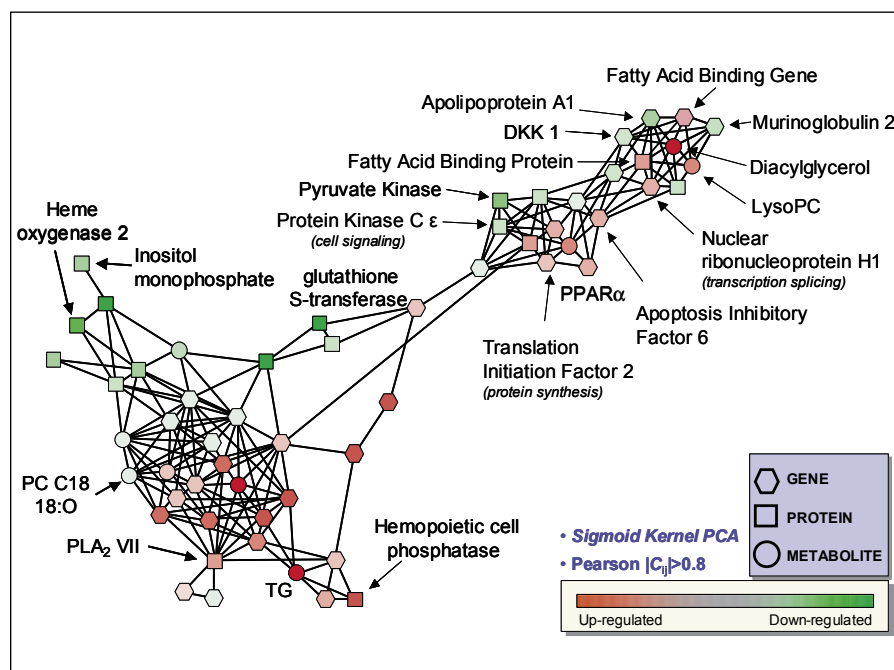
You'll Know It When You See It

Although systems biology-like approaches to life science problems may have been practiced for decades, there seem to be almost as many definitions of what it is, or is not, as there are individuals willing to define

the term. According to Stephen Naylor, Boston University (BU) School of Medicine and Division of Biological Engineering, Computational and Systems Biology Initiative, Massachusetts Institute of Technology (MIT), "It's something everyone thinks they want to do and don't know what it is." He likens trying to identify all the components in a completely darkened room with a laser pointer to what the state of knowledge in the 1990s in molecular and cellular biology had been al-

ary CSBI-related research projects at MIT include gene-protein networks, modeling of cell decision processes, integrative cancer biology, systems and computational approaches to tissue biology and toxicology, and synthetic biology, with other projects being planned.

James Collins, Center for BioDynamics, BU, says "It's a cop-out to say you don't know what systems biology is." His colleague, Timothy Gardner, Department of Biomedical Engineering,



Courtesy of S. Naylor and C. Clish, *Beyond Genomics*, originally published in *OMICS: J. Integ. Biol.* 2004, used with permission.

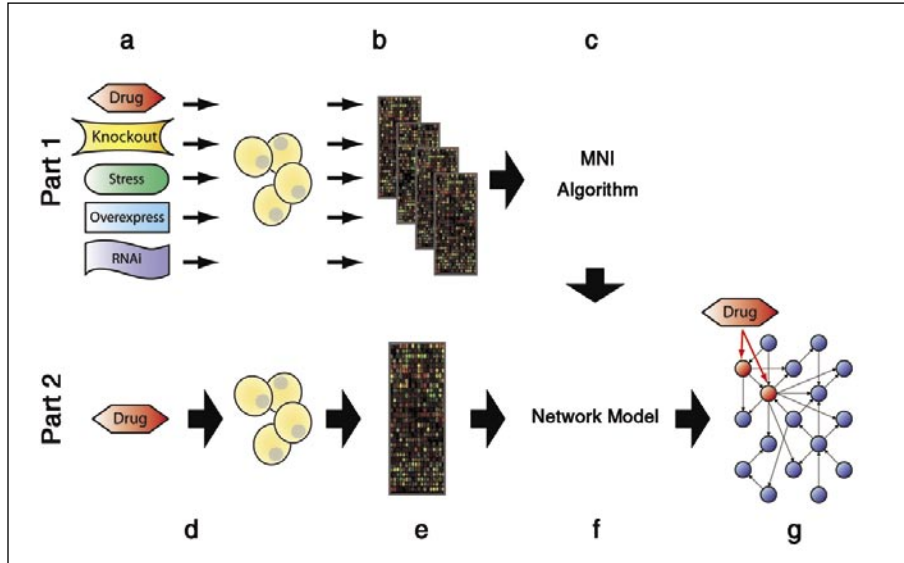
Correlation network: output from a systems biology experiment on transgenic versus isogenic control mouse.

lowing scientists to understand about disease processes. "Systems biology is trying to focus a searchlight on things," he says.

Brigitta Tadmor, Executive Director, Computational and Systems Biology Initiative (CSBI), MIT, focuses first on what systems biology is not. She says it is not an approach merely to mine the literature and databases to build a model, nor is it a form of theoretical biology, but a fusion of once-disparate fields, including experimental biology, computational sciences, and multiple engineering disciplines. The six multi-investigator interdisciplin-

BU, observes that some people think systems biology is "just physiology revisited." "It isn't just physiology," notes Collins, defining it as the study of interacting components, such as genes and proteins, rather than looking at what goes on in one tissue or organ at a time, as physiology does. "It's a great time to be in this space," he adds.

David E. Hill, Center for Cancer Systems Biology, Dana-Farber Cancer Institute, Boston, MA, is one of many who knows system biology when he sees it. There is more to it than knowing everything about all the things

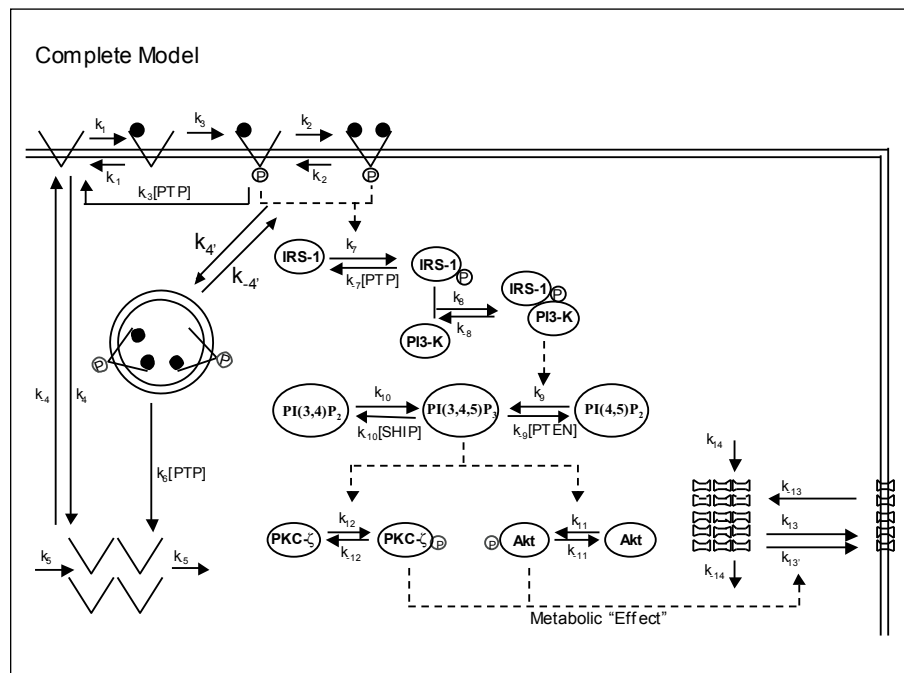


Courtesy of J. Collins and T. Gardner, Boston University

Overview of the mode of action by network identification (MNI) method. In part 1, an organism is exposed to treatments (a), and RNA expression is measured for each (b). A model is inferred by the MNI algorithm (c). In part 2, the RNA expression in response to a drug (d) is compared with that in part 1 (e) and used to infer a model (f) of the regulatory influences (arrows) between genes (blue circles) and targets (red circles) (g).

that affect a single gene, its RNA, and its protein. He observes that it will be essential not only to have comprehensive collections of data resources, but also a way to make them available. Even more important, he says, will be

more of an effort to standardize the technologies used, such as microarrays. "The resources won't truly be useful without standards to evaluate the data," Hill notes.



Developed in the laboratory of Michael J. Quon, Diabetes Unit, Laboratory of Clinical Investigation, NCCAM, NIH

Schematic of mathematical model of insulin signaling.

Networks and Maps

Zoltan Szallasi, Children's Hospital and Informatics Program, Harvard Medical School, defines systems biology as "producing predictions or hypotheses by non-obvious computational means for biological systems, where a biological system is defined as a regulatory network of heterogeneous biochemical entities." Depictions of these networks, in the form of increasingly complex maps, are being produced for a variety of biological systems. Michael J. Quon, Chief, Diabetes Unit, National Center for Complementary and Alternative Medicine (NCCAM), National Institutes of Health (NIH), Bethesda, MD, and his group apply systems biology to their research in two areas. One is to use detailed mathematical models of insulin signaling pathways in cells to understand the molecular mechanisms of insulin action and insulin resistance in adipose cells and endothelial cells. The other is to use mathematical modeling to predict insulin sensitivity in humans based on fasting blood glucose and insulin levels.

Mirit I. Aladjem, National Cancer Institute (NCI), Bethesda, MD, sees systems biology as a way of taking into account the complexities of biologic systems and trying to make sense out of them. She points out how differently the information being gathered at NCI on regulatory interactions is being depicted compared with the biochemical pathways of yesterday, with their clear paths from substrates, to interactions with enzymes, to products. Bioregulatory pathways, such as those a cell uses when it "chooses" between normal or malignant growth, require a different language as well as graphics; both the substrates and enzymes are modified and affect the interaction, so a linear model won't suffice. She works with molecular interaction maps (MIMs), developed in the late 1990s at NCI by Kurt Kohn, which contain conventions used as a language to represent networks containing multiprotein complexes, protein modifications, and enzymes that are substrates of other enzymes. Interactive MIMs allow all the interactions in which a given molecule to be viewed is involved. Aladjem sees her work, currently looking mostly at systems relevant to cancer, as providing tools that can be used by others interested in drug development to clarify the

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role of genes identified through microarrays.

Gardner is looking at microbial systems and how they respond to environmental stresses. These systems have the advantage of allowing faster, easier, and more efficient construction of models than do the mammalian systems that Aladjem and Quon are working with. He and his colleagues are creating networks that can ultimately be used to predict the mechanism of action of drugs. The goal is to find less toxic, more bioavailable, and more effective drugs. "Everybody is struggling to figure out how systems biology will be useful," he observes. It is going to shape the way people do research in drug discovery, he predicts. Collins is also working in bacterial and yeast

systems because of their simplicity compared with eukaryotic organisms. He notes that although one might have the impression that there are a lot of data available from microarrays' many genes, the reality is that these data are from a limited number of time points and conditions. In order to analyze a sufficiently large number of expression pathways, more resources and time will be required.

Future Directions

The NIH in the U.S. and the Biotechnology and Biological Sciences Research Council in the UK have both made systems biology approaches part of their near-term strategic focus. Universities are beginning to offer doctoral programs in systems biology (in name or in intent), including

MIT and Harvard University and the University of California at San Diego, CA, among others. The successful amalgamation of computer modeling with biologic and biomedical sciences may one day fully illuminate how organisms develop and function, inform clinical diagnosis and treatment, and improve drug discovery and agriculture. Systems biology approaches to data are likely to yield more useful results than the approaches that have been used in the past.

Lynne Lederman is a freelance medical writer in Mamaroneck, NY.