Systems Biology: A Shared Goal with Diverse Views

BY FREDERICK P. ROTH AND BRENDA ANDREWS

In a well known Indian tale, blind men offer diverse descriptions of the same elephant ("…seizing on the swinging tail that fell within his scope, 'I see,' quoth he, "the Elephant is very like a rope!" (1)). Systems biology is the contemporary elephant in the room, and it is easy to wonder whether the diverse scientific views operating under this name are of the same beast. However, systems biologists do share a common ultimate goal: to produce a dynamic model that can predict the actions and internal workings of an entire organism.

Currently unachievable in any organism, a predictive dynamic model of an entire organism will require concerted effort on several fronts. Minimally, we must: 1) learn the "parts list" for organisms of interest; 2) obtain a basic understanding of the relationships between all parts; 3) observe system dynamics across time, space, and individuals; and 4) prepare for the global modeling challenge by first modeling small subsystems.

Global Systems Biology: Parts

Ultimate success in systems biology depends on the unfinished task of defining the parts—genes, gene products, and their basic functional role. Current challenges include gene/protein definition, post-translational modifications, phenotyping, epigenomics (*e.g.* heritable chromatin structure), and function annotation. It is clear that the parts list is far from complete. For example, recent work by Takashi Ito (University of Tokyo) and colleagues has expanded the list of *Saccharomyces cerevisiae* (the most extensively studied eukaryote) by dozens of introns, hundreds of new transcription units in regions previously thought to be intergenic, and hundreds of intragenic alternative transcriptional start sites (2). The connection of genes to basic cellular roles, *e.g.* determination of cell shape, also remains incomplete. In a single whole genome phenotyping screen in *Drosophila melanogaster*, Amy Kiger (University of California, San Diego) and colleagues expanded the list of genes affecting cell shape by one-third (3). It is clear that our most basic understanding of genes and gene functions remains vastly incomplete. A current challenge is the integration of disparate sources of data to roughly assign genes to functional roles, which can focus limited experimental resources on the most likely hypotheses (*e.g.* unpublished work by Frederick Roth (Harvard Medical School) and colleagues).

Global Systems Biology: Relationships

Before we can hope to simulate a global system, we must first have a general understanding of how the parts are related to one another. Current challenges include protein networks, genetic networks, gene regulatory networks, and chromatin networks. This area remains even less explored than the parts list. For example, Marc Vidal (Dana-Farber Cancer Institute/Harvard Medical School) and colleagues have roughly estimated that only ~1% of all interactions between human proteins are known (4). We have only begun to learn about genetic interactions (cases in which perturbations of two genes together yield a surprising result that often indicates a functional relationship). For example, Brenda Andrews (University of Toronto), Charlie Boone (University of Toronto), and colleagues are using an automated genetics platform to create a complete map of double-mutant genetic interactions that lead to a significant fitness defect in budding yeast. These groups have also begun to explore the effects of other genetic perturbations, particularly gene overexpression, with the aim of revealing unappreciated functional connections in *S. cerevisiae* (5). Furthermore, much of the dynamic control of biological systems is affected through transcriptional regulation. Unfortunately, we do not yet have a complete map connecting transcription factors to their DNA binding elements in any species. Tim Hughes (University of Toronto), Martha Bulyk (Harvard Medical School), and colleagues are systematically identifying DNA-binding specificity of transcription factors in mouse (unpublished work). In the meantime, it is clear that a comprehensive predictive model of any organism awaits a complete understanding of the relationships between components.

Global Systems Biology: Dynamics

We must also learn how the parts of an organism and their relationships change over time and space within an organism and between organisms and environmental stimuli. Current areas of interest include gene expression, signaling, development, genetic variation, and pathogenic systems.

For example, Jason Lieb (University of North Carolina, Chapel Hill) and colleagues are investigating how the occupancy and activity of human regulatory elements change in living cells (6). One class of circuit that affects dynamics and homeostasis in living organisms is feedback, and our knowledge of the existence of such circuits is incomplete. Rachel Brem (University of California, Berkeley) and colleagues are searching systematically for evidence of regulatory feedback (unpublished work). A major challenge for systems biology will be grappling with complexity and dynamics within multicellular organisms. As an example of current work in this area, Robert Waterston (University of Washington) and colleagues have developed technology for tracking the location and lineage of all cells in real time through the early development of the worm *Caenorhabditis elegans* (7), which they are now scaling up.

Local Systems Biology: Subsystems and Simulation

On the path towards modeling and simulating entire organisms, we can begin by modeling and simulating smaller modules and subsystems. For example, Trey Ideker (University of California, San Diego) and colleagues have been assembling knowledge about individual physical and genetic interactions to model cellular responses to DNA damage (see Ref. 8 for an example). In an example of dynamic subsystem modeling, Alexander Hoffmann (University of California, San Diego) and colleagues are developing temporal models of inflammatory signaling pathways (see Ref. 9 for an example). A major challenge in the modeling of subsystems is that many of our experimental measurements of cellular systems are derived from the study of ensembles of cells rather than individual cells. Alexander van Oudenaarden (Massachusetts Institute of Technology) and colleagues have been exploring stochastic phenomena, (*e.g.* Ref. 10), for which measurements on the single cell level will be critical.

In summary, systems biologists have a shared vision for where the field must ultimately go, but the scale of the challenge is immense and demands a diversity of vision as we proceed.

REFERENCES

1 Saxe, J. G. (1873) *The POEMS of John Godfrey Saxe*, James R. Osgood and Company, Boston, Massachusetts

2 Miura, F., Kawaguchi, N., Sese, J., Toyoda, A., Hattori, M., Morishita, S. & Ito, T. (2006) A large-scale full-length cDNA analysis to explore the budding yeast transcriptome. *Proc. Natl. Acad. Sci. U. S. A.* **103,** 17846-17851

3 Kiger, A., Baum, B., Jones, S., Jones, M., Coulson, A., Echeverri, C. & Perrimon, N. (2003) A functional genomic analysis of cell morphology using RNA interference. *J. Biol.* **2,** 27

4 Rual, J. F., Venkatesan, K., Hao, T., Hirozane-Kishikawa, T., Dricot, A., Li, N., Berriz, G. F., Gibbons, F. D., Dreze, M., Ayivi-Guedehoussou, N., Klitgord, N., Simon, C., Boxem, M., Milstein, S., Rosenberg, J., Goldberg, D. S., Zhang, L. V., Wong, S L., Franklin, G., Li, S., Albala, J. S., Lim, J., Fraughton, C., Llamosas, E., Cevik, S., Bex, C., Lamesch, P., Sikorski, R. S., Vandenhaute, J., Zoghbi, H. Y., Smolyar, A., Bosak, S., Sequerra, R., Doucette-Stamm, L., Cusick, M. E., Hill, D. E., Roth, F. P. & Vidal, M. (2005) Towards a proteome-scale map of the human protein-protein interaction network. *Nature* **437,** 1173-1178

5 Sopko, R., Huang, D., Preston, N., Chua, G., Papp, B., Kafadar, K., Snyder, M., Oliver, S. G., Cyert, M., Hughes, T. R., Boone, C. & Andrews, B. (2006) Mapping pathways and phenotypes by systematic gene overexpression. *Mol. Cell.* **21,** 319-330

6 Giresi, P. G., Kim, J., McDaniell, R. M., Iyer, V. R. & Lieb, J. D. (2007) FAIRE (Formaldehyde-Assisted Isolation of Regulatory Elements) isolates active regulatory elements from human chromatin. *Genome Res.* **17,** 877-885

7 Bao, Z., Murray, J. I., Boyle, T., Ooi, S. L., Sandel, M. J. & Waterston, R. H. (2006) Automated cell lineage tracing in Caenorhabditis elegans. *Proc. Natl. Acad. Sci. U. S. A.* **103,** 2707-1272

8 Workman, C. T., Mak, H. C., McCuine, S., Tagne, J. B., Agarwal, M., Ozier, O., Begley, T. J., Samson, L. D. & Ideker, T. (2006) A systems approach to mapping DNA damage response pathways. *Science* **312,** 1054-1059

9 O'Dea, E. L., Barken, D., Peralta, R. Q., Tran, K. T., Werner, S. L., Kearns, J. D., Levchenko, A. & Hoffmann, A. (2007) A homeostatic model of IkappaB metabolism to control constitutive NF-kappaB activity. *Mol. Syst. Biol.* **3,** 111

10 Kaufmann, B. B. & van Oudenaarden, A. (2007) Stochastic gene expression: from single molecules to the proteome. *Curr. Opin. Genet. Dev.* **17,** 107-112

Systems Biology Thematic Meeting

ORGANIZERS:
Brenda Andrews, *University of Toronto*
Fritz Roth, *Harvard Medical School*

Symposium: Global Systems Biology: Parts

Unexpected complexity of the budding yeast transcriptome, *Takashi Ito*

Functional genomic analysis of morphogenesis, *Amy Kiger*

Systematic function annotation in microbes and mammals, *Fritz Roth*

Symposium: Global Systems Biology: Relationships

Interactome networks and human disease, *Marc Vidal*

Genetic interaction networks in yeast, *Brenda Andrews*

Cracking the second genetic code, *Tim Hughes*

Symposium: Global Systems Biology: Dynamics

Genome-wide identification of active human regulatory elements by formaldehyde-assisted isolation of regulatory elements, *Jason Lieb*

Expression variation and regulatory feedback, *Rachel Brem*

Title TBD, *Robert Waterston*

Symposium: Local Systems Biology: Subsystems and Simulation

An integrated physical and genetic interaction map of genotoxicity, *Trey Ideker*

A temporal code to generate specificity in inflammatory signaling, *Alexander Hoffmann*

***Dynamics of signal transduction and gene expression in single cells: feedback*, inheritance and survival,** *Alexander van Oudenaarden*