

The systems biology cycle can be stated as: perturbation-measurement-model-hypothesis-perturbation, and so forth. In his article that reviews Hood's six points, John Russell points out that not all the technologies to handle these requirements are currently available, yet they are critical to achieving systems biology's goals.¹⁶

2.1. Bioanalytical Technologies

The omic technologies have been reviewed extensively elsewhere, and their fundamentals will not be described herein. Suffice it to say that DNA microarrays generate large data sets relevant to gene expression and genetic variation (primarily SNPs [single nucleotide polymorphisms]); mass spectrometry and gel electrophoresis generate smaller, but still extensive, data sets for protein expression; nuclear magnetic resonance (NMR) and mass spectrometry provide modest-sized data sets for metabolite levels in living systems; and yeast two-hybrid assays and mass spectrometry provide data on protein-protein interactions. The remainder of this section deals with how these bioanalytical modalities have been combined in systems biology to provide the multifaceted data sets that act as inputs for the sophisticated computational systems, which generate models for further hypothesis generation.

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Academic Perspective: Institute for Systems Biology

The ISB focuses mainly on understanding the function of cells, and in pursuit of this goal it recognizes the need to process "minute quantities of large numbers of samples on which thousands of measurements can be made simultaneously."¹⁷ Since current omic methodologies are insufficient to generate very high throughput on very small samples, the ISB aims to focus on new nanotechnology and microfluidic devices. Such devices, which could be used in both research and diagnostic applications, have been under investigation by a research consortium called the NanoSystems Biology alliance, formed at the instigation of the ISB.

A key missing link in bioanalytical technology centers on the ability to measure large panels of protein biomarkers. According to ISB, such a system should:

- Quantitatively sense over a fairly broad dynamic range
- Scale to thousands of measurements or more
- Pass tests of sensitivity and specificity (i.e, avoid false negatives and false positives)

2.3. Bioinformatics Technologies

Bioinformatics for systems biology is in itself a huge subject, and a comprehensive review would require a separate report. Here we provide a brief survey of some common methods used for pathway analysis, cell modeling, and disease modeling.

Pathway Analysis

From the perspectives of drug discovery and diagnostics, cellular pathway analysis is currently the prevalent branch of systems biology. It is also an elementary entry point for systems biology when one considers the added complexity of taking higher levels of biological organization into account. Technologies for pathway analysis were reviewed recently by Andrey Sivachenko, PhD, and Anton Yuryev, PhD (of Ariadne Genomics [Rockville, MD], one of several key small-company players in the field).²⁷

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Most diseases of interest to pharma today are complex in the sense that they are thought to be caused by defects in multiple genes working in concert with environmental factors. Therefore, it is not surprising to find great complexity in associated networks of interacting expressed genes, proteins, and metabolites. An understanding of disease-relevant biological pathways and their interactions is considered crucial to the future development of effective therapies. According to Sivachenko and Yuryev,²⁷ “Pathway is ultimately a paradigm used to denote a group of genes, proteins, metabolites, or other entities acting together to achieve some function, shape the flow of information, enable sequential interaction of a chemical reaction ‘conveyor,’ and so on.”

Databases

Enormous amounts of relevant information that are currently available (much of it from academic investigation of model systems) must be subject to extraction and suitable representation in order to be useful. Increasingly, sets of relevant human data are becoming available. For example, Prolexys Pharmaceuticals (Salt Lake City, UT) sells access to its database of more than 120,000 protein-protein interactions, which it claims is the world’s largest such collection.

emergent behaviors at higher levels. A related concept, self-organization, implies that components are inherently capable in predetermined ways of generating emergent behaviors. Complexity in biological systems also implies nonlinear interactions among components.

To reiterate, a simple system would have few components with little interaction among them, and emergent behaviors tend to be predictable. A complicated system is likely to have many components, but interactions among them would still permit prediction of emergent behaviors, at least in principle. Complex systems possess components that interact so as to pose inherent limitations in predicting emergent behaviors.

Types of Biological Networks

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Component interactions lie at the heart of biological systems, and various types of interaction networks have been established. In some instances, two or more different kinds of networks have been overlaid and linkages among them established. The underlying goal in this work is to learn what these networks have to teach us. The hope is that these teachings will reveal how to predict emergent properties of the networks, particularly disease phenotypes, and to provide important clues suggesting radically new approaches to therapeutics.

DNA microarrays enabled transcriptomics, which permitted construction of genome-wide networks in which nodes are expressed genes with edges connecting those genes that are coexpressed under a given set of conditions. By now, thousands of such networks representing differential gene expression in two or more conditions (e.g., control vs. drug treatment, mutation, gene knockout, or disease) have been established in universities and in biomarker and drug discovery organizations. Analysis of these networks has given important and practically useful clues concerning the pathways relevant to disease processes and the effects that drugs might have on them. One downside of such studies is that researchers sometimes drown in a plethora of rich clues without being able to determine which ones are the best to pursue.

Similarly, genome-wide studies of genetic markers (particularly single nucleotide polymorphisms [SNPs]) and their associations with disease have suggested disease-relevant pathways and associated new approaches to therapy. Such studies identify areas (loci) in chromosomes that are likely to contain relevant genes. Identifying such genes, determining their function, and tracing their pathways in the search for likely drug

Chapter 4

APPLIED RESEARCH IN SYSTEMS BIOLOGY

The previous chapter focused on basic systems biology research, which aims to establish the fundamental principles and concepts that promise to extend our understanding of living systems and their pathologies while providing the new paradigms for future therapeutic and diagnostic applications. Although applied systems biology is far from reaching its full potential, it has already begun to impact the way researchers think about diseases, therapies, and biomarkers. This chapter discusses some of this early applications work, which promises to set the tone and direction for future efforts.

4.1. Impacts of Systems Biology on Specific Disease Areas

In this section, we consider impacts of systems biology on several major disease areas: cancer, cardiovascular diseases, neurological diseases, and metabolic disorders. One dilemma facing pharmaceutical companies today has been stated eloquently by GlaxoSmithKline's Colin Dollery, MD,⁴⁷ who points out that the classical reductionist approach of controlling for as many variables as possible while varying one of them worked very well in physiological and pharmacological studies of the cardiovascular system. However, today's major unmet clinical needs, such as arthritis, cancer, schizophrenia, and chronic obstructive pulmonary disease (COPD) are more challenging and have not so far proved particularly amenable to traditional experimental approaches. Furthermore, genetics has not been able to identify single factors that contribute strongly to their pathology. He concludes that an alternative systems biological approach may be in order. Focus on the pathways and control systems that influence the disease state in order to identify nodes suitable for intervention, and on combination therapies involving modulation of multiple nodes, is likely in order.

5.2. Approaches of Selected Drug Discovery and Development Organizations

Cellicon Biotechnologies

Cellicon Biotechnologies spun off in 2002 from the Center for Biodynamics and the Center for Advanced Biotechnology at Boston University with the aim of applying systems biology methodologies to the creation of new antibiotics. Its approach is described in a 2007 paper in the journal *Cell*.⁶⁸ It determined that the three major classes of bactericidal antibiotics worked by varying mechanisms that all ended up triggering a common process in bacteria leading to the production of lethal hydroxyl free radicals, and started to develop new antibiotics that would target this mechanism more directly than prior entries. The company is currently dormant, without employees, and operating as an academic program.

CombinatoRx

Founded in 2000, CombinatoRx (Cambridge, MA) is a pioneer in the systems biology-intensive field of combination pharmaceuticals. The company is publicly traded and reported nearly \$15 million in revenues for the year 2007, \$12.2 million from collaboration and the remainder from government contracts and grants. The net loss for the year exceeded \$53 million, while liquid assets totaled nearly \$110 million. Partners include Angiotech Pharmaceuticals, Bio*One Singapore, and Fovea Pharmaceuticals. The company has more than 160 employees.

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CombinatoRx seeks synergistic combinations of mainly pre-existing compounds that will equal or enhance currently therapeutic capabilities. It starts with the CRXX library, which contains chemical probes and compounds from the global pharmacopoeia. It next conducts combinatorial high-throughput screening (HTS) using millions of pairwise combinations, and uses its Chalice database and analysis system for automated selection and prioritization of results. CombinatoRx has several combinations in the clinic. Its lead program, CRx-102, in Phase IIb trials for the treatment of arthritis, combines low-dose prednisolone and the cardiovascular agent, dipyridamole, to provide a multitarget mechanism of action that is claimed to synergistically and selectively amplify the anti-inflammatory activity of glucocorticoids. Efficacy results to date appear rather promising.

Early clinical programs in topical dermatology include two combinations, one of mometasone and nortriptyline in the treatment of psoriasis and corticosteroid-responsive dermatoses, and nortriptyline plus

Table 5.2. Selected Recent Deals in the Systems Biology Space (cont.)

Company	Partner	Description
Health Discovery Corporation	Clariant	7/07 Clariant gains exclusive license to HDC 4-gene prostate cancer test; 30% royalty
Health Discovery Corporation	Pfizer	12/06 Pfizer licenses HDC pattern recognition technology for identification of new targets/biomarkers
Ingenuity Systems	GlaxoSmithKline	3/08 Extends enterprise-level agreement with GSK for access to Ingenuity Pathways Analysis software
Ingenuity Systems	XDx	7/07 XDx licenses Ingenuity Pathways Analysis software to help identify and understand transcriptomic biomarkers for diagnostics
Ingenuity Systems	FDA	11/07 Ingenuity granted 3-year CRADA to expand Ingenuity's system capability to enable research and regulatory review of biomarker, pharmacogenomic, and toxicogenomic data

Source: Insight Pharma Reports

Several deals go beyond fee-for-service or similar arrangements. For example, BG Medicine exclusively licensed a cardiovascular biomarker from a research institute for development as its own product. Drug developer CombinatoRx is offering licenses to a subset of its lead candidates. For example, Angiotech Pharmaceuticals (Vancouver, BC, Canada) has taken a royalty-bearing license, permitting it access to as many as 10 compounds for further development plus an option to license 5 more. Fovea Pharmaceuticals (Paris, France) has taken a license to CombinatoRx compounds for development in a particular therapeutic area, ophthalmology. Health Discovery Corporation (Savannah, GA) granted a royalty-bearing license to its prostate cancer biomarker.

a function of deep pockets, but rather the corporate philosophy. If you have deep pockets, it makes the investment easier, but you still have to prioritize. If you do systems biology, that means you're not doing something else.

CHI: Is there anything you'd like to add?

Dr. Edmonds: I do consider myself a systems biologist, but clearly not on the computational side. I like to see how things interconnect and how they relate to each other. I have great hope that this will have an impact, not just on drug discovery and development, but also on medicine. Take the OncoDx 80-gene chip for prognosis of breast cancer recurrence and the associated algorithm—that's a form of systems biology. You will see more of these technologies and approaches penetrate into the clinical arena. That's the way it's going and I don't really see the trend reversing itself.

Colin Hill

CEO, President, Chairman, and Co-Founder, Gene Network Sciences, Cambridge, MA

CHI: A number of companies currently act as service providers for pharma to generate predictive models based on omic and phenotypic data. What are the main ways in which Gene Network Sciences (GNS) is distinctive and advantageous compared to some of the others?

Colin Hill: We come at the problem using increases in supercomputing power and newly generated omic data in what I consider a data-driven fashion, which is somewhat unbiased. One of the distinctions between biology and drug discovery versus the engineering disciplines is that in both cases you're dealing with complex systems, but in the world of engineering you have the wiring diagram, analogous, for example, to the blueprint of a Nokia cell phone. While it might be very complicated, with switches turning each other on and off and affecting each other in complex ways to produce the overall behavior of the phone, the engineer has an actual blueprint and can predict how the system is going to behave after various perturbations. You push on this part of the system, it will do this; push on another part, it will do that—and you can predict that.