

Executive Summary

Pharma's current innovation deficit issues can be traced in part to today's rational drug discovery paradigm, which evolved from classical reductionist biochemistry and molecular biology. The emerging systems biology paradigm aims to view life not only in terms of interaction networks at multiple levels, from the molecular to the whole organism, but through interactions among these networks. From the systems biology perspective, it is not surprising, in light of pathway redundancy and gene ubiquity among body systems, that many drug candidates end up falling short in safety or efficacy, or both. Incorporation of systems biology perspectives and methods promises not only to pinpoint optimal individual targets, but also combinations of targets, modulation of which may overcome pathway redundancy.

Although the origins of systems biology date back to the first half of the 20th century, the field experienced a renaissance in the new millennium triggered by the Human Genome Project, the "omic" technologies revolution, and dramatic increases in computational capability. Furthermore, pharma's productivity problems have stimulated a dramatic acceleration in basic systems biology research, which promises to revolutionize our understanding of disease processes, how to treat them, and, ideally, how to prevent them.

Current systems biology research in pharma and biotechnology tries mainly to make sense of omic data through application of pathway and network analysis. However, radically new concepts will have to emerge from basic research before applied systems biology can begin to approach anywhere near its full potential. The emerging paradigm centers on concepts such as modeling, simulation, networks, emergent properties, and complexity, and applied research has much to gain from their application. Still, major steps forward may have to await what one pioneer calls the first real theory of biology.

This report starts with a brief survey on the origins of systems biology, together with consideration of its varying definitions in use today. Chapter 2 focuses on the technologies that enable systems biology research today, both the bioanalytical- and bioinformatics-based varieties. Chapter 3 delves into the nature of and results from basic research in systems biology today. Chapter 4 covers results from applied systems biology research viewed both from the perspective of gaining deeper understanding of disease mechanisms and of deriving benefits for the expedited discovery of drugs with improved safety and efficacy.

Most big pharmas and a number of biotechnology companies currently sponsor some level of systems biology research. Additionally, several drug discovery startups feature strong systems biology leanings. A number of small technology-based companies have been formed, initially as service providers and more recently with discovery-based augmentation. Chapter 5 considers the nature and dynamics of this systems biology market, its business models, deals, scope, and prospects. Chapter 6 focuses on conclusions from this report and future expectations for systems biology. Finally, Chapter 7 contains transcripts of interviews with scientists and managers who are deeply engaged in this dynamic and vitally important endeavor.

Definitions of systems biology vary, depending largely on the main discipline practiced by the definer. As summarized by Genstruct's (Cambridge, MA) Keith Elliston, definitions include the application of engineering perspectives to biology, the application of systems and dynamics analysis to biology, and the use of an integrative approach versus the classical reductionist one [Lieu CA, Elliston KO. *Ernst Schering Res Found Workshop*. 2007;61;139-152]. At a recent conference, Pfizer's Bruce Gomes took a pragmatic stance in claiming that present-day systems biology in pharma reflects the integration of biological measurements with computational models to study how molecular interactions lead to healthy versus disease states.

Technological Aspects of Systems Biology

Systems biology as practiced at the iconic Institute for Systems Biology (ISB) requires dynamic quantitative measurements across all molecular species (genes, proteins, etc.), computational and mathematical integration of data types, measurements across selected systems perturbations, and integration of discovery-driven and hypothesis-driven measurements [Russell J. www.bio-itworld.com/newsitems/2007/sept/sbnl-sidebar2/].

Technologies relevant to systems biology divide into bioanalytical and computational categories. Omic technologies, key elements in the former category, have been covered in depth elsewhere and are not described in this report beyond observing that DNA microarrays generate large data sets that reflect gene expression and genetic variation; mass spectrometry and gel electrophoresis generate protein expression data sets; nuclear magnetic resonance (NMR) and mass spectrometry enable metabolomics; and yeast two-hybrid technology and mass spectrometry help define protein-protein interactions.

In the future, nanosystems capable of performing global molecular studies on single cells may become available to facilitate data gathering. A groundbreaking paper published recently by researchers from the ISB and other institutions employs the aforementioned strategy and technologies to construct a predictive model for transcription control in a bacterium under a range of environmental conditions, and provides a template for others to conduct similar studies [Bonneau R et al. *Cell*. 2007;131:1354-1365].

In addition to the now-classical omic technologies, studies of biological control are increasingly aided by ChIP-on-chip technology for global transcription factor identification and methylation-specific polymerase chain reaction (PCR) for global DNA methylation detection as an entry point to epigenetics. As if the cell regulatory control picture were not already complicated enough, microRNAs (miRNAs) entered the picture during the early 1990s, and have since come to play increasingly important roles both in basic and applied systems biology research. Methods have been developed to isolate, detect, and identify miRNAs.

Pathway analysis, cell modeling, and disease modeling technologies today dominate the bioinformatics branch of systems biology. Database-mediated pathway analysis studies, which are particularly popular today, help to discover meaning in global biological data for drug discovery and diagnostics. A number of public databases and software programs facilitate such studies, but commercial entries from companies such as Ingenuity Systems (Redwood City, CA), GeneGo (St. Joseph, MI), and Ariadne Genomics (Rockville, MD) provide enhanced usability and comprehensiveness. Alternative approaches have proved useful as well. Genstruct's Knowledge Assembly platform enables "knowledge-driven systems biology;" Gene Network Sciences' (Cambridge, MA) REFS (Reverse Engineering and Forward Simulation) systems permit reverse engineering and hypothesis generation from omic data; and Entelos' (Foster City, CA) PhysioLab biosimulation models, which incorporate both molecular and higher-order disease data, permit construction of "virtual patients."

Basic Research in Systems

Although this report stresses systems biology applications, the recent explosion of academic activity merits consideration of basic research progress and its future implications for the field. Pharma and diagnostics are already starting to benefit from such research, and forthcoming work may well provide highly novel approaches to drug discovery and diagnostics, which cannot even be envisioned today.

Networks representing interactions among biological entities are central elements in the emerging systems biology paradigm. Networks exist at multiple levels (some systems have as many as 12) in organisms ranging from the molecular up through whole organisms and possibly beyond to groups of them. Most current studies recognize cells as the basic units of life and focus on their structure and function. Networks studied to date center on metabolites, transcriptional regulatory elements, the signaling systems, protein-protein interactions, the cytoskeletal elements, and membrane-organelle systems. Key concepts derived from network analysis include complexity, emergence, modularity, clique structures, the diseaseome, and genetic variation-guided transcriptomics. Already, some of these leading-edge subjects have begun to yield fresh insights into the nature and vulnerabilities of disease networks.

Applied Research in Systems Biology

Although applied systems biology has far to go, researchers are already applying available knowledge to facilitate drug and biomarker discovery. Much of this activity centers on cancer, a disease whose origins and essential nature remain rather obscure and controversial. The methods and perspectives of systems biology have triggered new thinking, and the recent literature reflects fresh and promising approaches to the subject. For example, a systems biology approach played a key role in explaining why AstraZeneca's Iressa (gefitinib) was effective as an anticancer agent in some people who lack ErbB1 mutations and ineffective in some individuals who had them, contrary to expectation. Further research on the epidermal growth factor receptor (EGFR) network revealed that drug responders were characterized not by mutations but by receptor internalization rate. This groundbreaking study arguably laid the groundwork for the initial acceptance of systems biology at AstraZeneca and for big pharma in general.

In another example, Pfizer was able to provide and validate a mechanism for liver abnormalities resulting from treatment with a kinase inhibitor series. Earlier, the systems biology group was able to help biotherapeutic groups decide whether they needed to mature antibodies further, and whether extending a binding peptide's half-life would be useful, thus permitting early decision-making in situations that would previously have required waiting for the results of late animal or early clinical studies. Gene Network Sciences reports a case in which it was able to use computational biology to help Johnson & Johnson determine the mechanism of an anticancer receptor kinase inhibitor and to stratify patients according to drug response.

Other cancer systems biology studies point to the significance of tissue heterogeneity in aiding tumor survival, to the possibility that cancers beget mutations rather than the reverse, to the possible role of a particular set of dysregulated transcription factors in acute myelocytic leukemia, to the possible role of embryonic attractors in epigenetic landscapes, to the role of "stem-ness" cell signatures in predicting patient outcomes, to the role of mutations in highly connected network hub genes, and to the interplay of robustness and fragility in tumors.

Regarding neurological diseases, a great deal of research has been conducted in the last century on electrical signal transduction in the nervous system. In the past few years, neuroscientists have come to

realize that greater understanding of neuronal signaling requires greater knowledge of biochemical signaling. Little has been done so far to link biochemical signaling pathways with electrical dynamics and ionic diffusion. Differences in time scales for these processes together with associated difficulties in building model systems mean that electrical and biochemical aspects of neuronal physiology have been, for the most part, studied separately. Omic technologies open the possibility of devising studies to bridge the two perspectives, and work directed along these lines can be expected to increase in the near-term future. Recent studies suggest that a particular gene contributes both to Alzheimer's disease and normal aging, and that another gene plays a key role in Huntington's disease.

Despite the massive lethality of cardiovascular diseases, relatively little has been done to apply systems biology methodologies and perspectives to new therapeutic approaches. One recent study revealed a network of eight cholesterol-responsive genes that may be of interest for the development of new atherosclerosis therapies. Although relatively little omic work has been done in the cardiovascular field, Oxford University's Professor Denis Noble has spearheaded an international effort to create a multilevel virtual heart, the world's first such organ. Initial models made in the 1980s dealt with calcium balance and electrical signaling. The current model includes elements of protein function to link with cellular and higher-level functions. Further incorporation of molecular perspectives is planned, but already the current model has proved useful in drug discovery.

The recent growth of interest in metabolic syndrome has naturally drawn intense interest from drug discoverers, and the complexity of its manifestations suggests the need for systems biology approaches to identify promising points for intervention. Findings to date include the observation that the development of new therapies requires identifying fragilities in acquired robustness mechanisms, that a type 1 diabetes biosimulation predicts emergent behaviors including disease progression and therapy responses consistent with published results, and that network analysis could identify key obesity genes.

Market Dynamics

Commercial activities of systems biology companies center on fee-for-service, biomarker discovery, and drug discovery models, along with various mixtures of the three. Some companies have dual identities. Bioinformatics-oriented companies tend to find it difficult to grow their businesses based strictly on service-based models, and increasingly augment them either with drug or biomarker discovery. Entelos, Compugen (Richmond Hill, Ontario, Canada), BG Medicine (Waltham, MA), Optimata (Ramat Gan, Israel), BioSeek (Burlingame, CA), and Genstruct are cases in point. Others, such as Gene Network Sciences and Ingenuity Systems have chosen for the present to remain service-based organizations. Still others, such as Ariadne and GeneGo, mainly provide software to client companies. Companies that employ systems biology methods and perspectives for drug discovery and development include Merrimack Pharmaceuticals (Cambridge, MA), CombinatoRx (Cambridge, MA), and Connexios Life Sciences (Bangalore, India).

Brief profiles of companies that are active in systems biology are provided in this report. Of the 18 small systems biology companies considered, two-thirds (12) provide systems biology services, primarily in the form of computational modeling and biosimulation. Four of the 18 sell software to drug and biomarker developers, and 2 of these are also service providers. Nearly half (8) of the 18 engage, or intend to engage, in drug development. Three of these companies also provide client services. Finally, three companies engage in biomarker development, and all provide services as well.

Deal activity among systems biology companies remains comparatively light. Much activity takes the form of license agreements with big pharma that facilitate R&D access to systems biology services. A few deals represent higher potential value. For example, BG Medicine exclusively licensed a cardiovascular biomarker from a research institute for possible development. CombinatoRx is offering licenses to a subset of its lead candidates, and Angiotech Pharmaceuticals (Vancouver, BC, Canada) has taken a royalty-bearing license permitting it access to as many as 10 CombinatoRx compounds for further development, with an option to license 5 more. Fovea Pharmaceuticals (Paris, France) has taken a license to CombinatoRx compounds for development in the ophthalmology area. Health Discovery Corporation (Savannah, GA) has granted a royalty-bearing license to its prostate cancer biomarker.

Conclusions and Future Prospects

For the most part, provision of systems biology products and services has not generated much in the way of high-growth business opportunities. A number of participant companies have accordingly expanded into drug or biomarker discovery, or both. Furthermore, systems biology has not yet made major headway toward influencing R&D in big pharma. What it has done, quite convincingly, is to suggest that combination drug therapies may be required to enable pharmacological progress in some of the biologically complex “money” diseases.

Nonetheless, systems biology groups have been established in several big pharmas, their influence is spreading beyond their immediate confines, and at least some manifestations of systems biology have infiltrated essentially all of big pharma R&D. One can certainly make a convincing argument that pharma needs systems biology to stimulate innovation. However, most pharmas have been less than impressed with past benefits from large investments in postgenomic technologies and are proceeding with caution.

From another perspective, organizational factors may militate against adopting systems biology perspectives—thus, the subtitle of this report, *Systems Biology: A Disruptive Technology*. One can argue that the way that pharmaceutical companies are typically organized and the current industrialized drug discovery paradigm are more consistent with a reductionist, compartmentalized approach to the subject than with the more interdisciplinary, holistic tendencies of systems biology. Reconsideration of organization and reward criteria for pharma may accelerate adoption of systems biology and conversion to a more productive paradigm.