Biological Systems Modeling: Powerful Discipline for Biomedical *e*-R&D

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Chemical engineers have been remarkably successful in incorporating mathematical rigor into various branches of the discipline. A solid quantitative foundation with predictive power now underlies chemical reaction engineering, control, plant design, and transport phenomena. Mathematical models of chemical reactors, complex kinetics, separations processes, materials properties and even entire plants have become standard tools for analyzing and understanding processes and systems, as well as predicting and designing desired material properties and functionality. Today, mathematical modeling is poised to emerge as a major approach for R&D within the pharmaceutical, biotechnology and health care industries.

Emergence of biological systems modeling

Over the past decade, the biomedical community has taken advantage of computers and mathematics extensively to expand its R&D capabilities, with bioinformatics and protein structural analysis emerging as major disciplines. Not surprisingly, computer-aided biomedical research disciplines have been termed *e*-R&D. The newest component of *e*-R&D is *biological systems modeling*, i.e., the application of engineering analysis to physiological systems. By creating mathematical models of complex biological systems, encompassing genes to organ systems, modelers can construct virtual laboratories for simulated experiments.

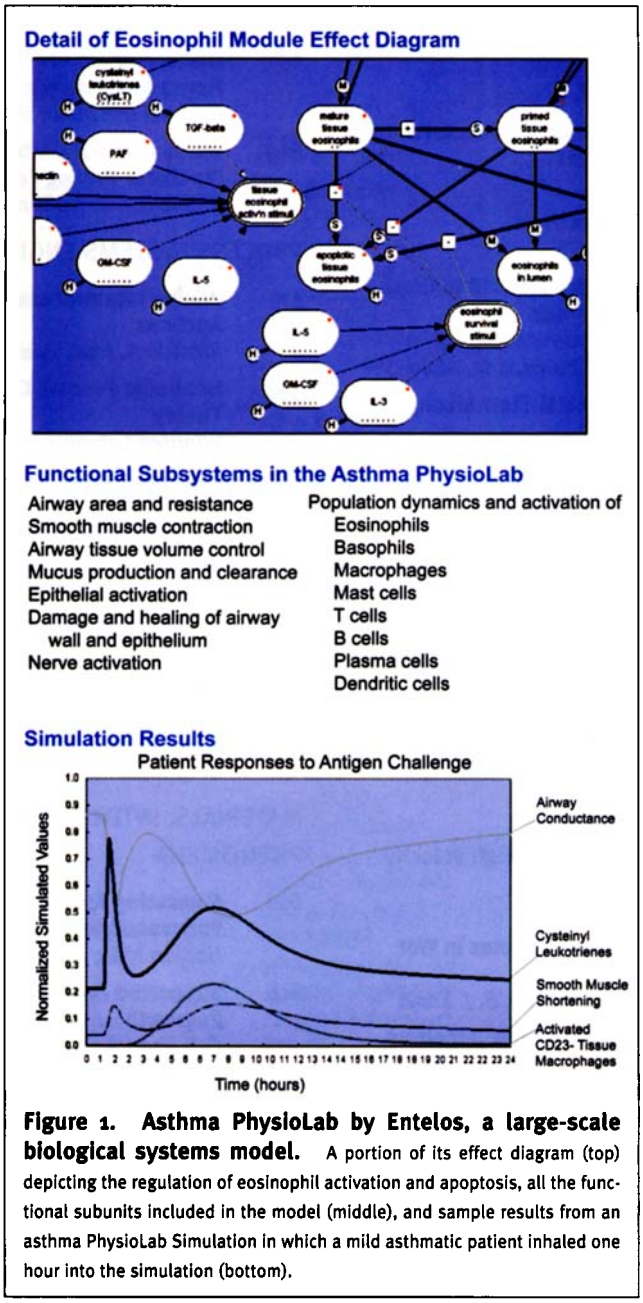

Figure 1. Asthma PhysioLab by Entelos, a large-scale biological systems model. A portion of its effect diagram (top) depicting the regulation of eosinophil activation and apoptosis, all the functional subunits included in the model (middle), and sample results from an asthma PhysioLab Simulation in which a mild asthmatic patient inhaled one hour into the simulation (bottom).

Mathematical biology has long been used to explore such areas as cell function, biochemical reaction cascades, and pharmacokinetics. Limitations (primarily in computer power), however, meant that typical models were small (fewer than a dozen state variables), and the questions any one model could address were very specific. Undoubtedly, such mathematical models have contributed important insights into many biological problems. Examples include the classic Hodgkin-Huxley model of ion channel function (Hodgkin and Huxley, 1952) and models of receptor binding and trafficking and their regulation of cell behavior, some of which are summarized by Lauffenburger and Linderman (1993). Nevertheless, limitations on model size and scope have kept mathematical biology primarily in the realm of academia and basic science.

Today, powerful computers and graphical user interfaces (GUIs) allow the creation of extensive mathematical models that span taxonomic levels (genes, biochemicals, cells, tissues, organs, and/or organ systems) and incorporate feedback across levels in an integrated system. These models can connect fine details of the biology to a larger functional context and *vice versa*, revealing the effects that manipulating one part, such as a biochemical pathway, has on the behavior of the entire system. In addition, integrative systems models allow us to investigate the effects of feedback, the sensitivity of system-level outcomes to manipulation of various subsystems, and the compen-

satory mechanisms within a system. These phenomena are very difficult to understand or predict when studying isolated subsystems, where a vast majority of biological experimental research is done (e.g., using cell culture or biochemical assays) and to which most mathematical models have been applied in the past.

Academic and industrial efforts

Both academia and industry are pursuing large-scale modeling of complex biological systems. Probably the broadest academic effort is the Physiome Project (www.physiome.org), a loose collaboration of international researchers that aims to summarize the functional behavior of organelles, cells, tissues, organs and organisms in integrative mathematical models. The Physiome Project's most extensive efforts so far are on the heart and microcirculation. Dr. James Bassingthwaighte of the University of Washington is a major organizing force behind this movement that already involves a few hundred researchers at more than 30 institutions worldwide. Other public large-scale modeling efforts include the Virtual Cell project at the National Resource for Cell Analysis and Modeling at the University of Connecticut, led by Dr. Leslie Leow (www.nrcam.uchc.edu), and the models being added to the extensive enzyme database based at the Argonne National Laboratory, developed by Dr. Evgeni Selkov (http://www-unix.mcs.anl.gov/compbio/compbio.html). A recently announced project, the Alliance for Cellular Signalling (afcs.swmed.edu) led by Dr. Alfred Gilman at the University of Texas Southwestern Medical Center, has been joined by 40 scientists with the objective of identifying all the proteins that make up the signaling pathways in certain cells and creating theoretical models to describe those pathways.

In contrast to efforts to integrate the work of many independent investigators, several companies are independently creating large-scale biological models that can be used in drug discovery and development, as well as education of life scientists and bioengineers. They include Physiome Sciences in Princeton, NJ (unrelated to the Physiome Project), and Entelos, Inc., in Menlo Park, CA. Several large-scale models are presently available from these companies. The models created by Physiome Sciences concentrate on particular organs—to date they have modeled the heart. The models created at Entelos encompass multiple organ systems to address the physiology and pathology involved in specific, complex diseases.

Since my familiarity is with Entelos' models, which I have helped build, I will use these as examples to comment on the scale and uses of biological systems models that are possible today. Entelos Asthma PhysioLab and Entelos Obesity PhysioLab are examples of large-scale biological systems models that span multiple taxonomic levels, from basic biochemical mechanisms to system physiology. A PhysioLab consists of a graphical user interface called an effect diagram that visually depicts the biological system's components and their interconnections, and a mathematical model and knowledge database that are embedded within that effect diagram. Figure 1 shows a small part of the effect diagram of the asthma PhysioLab, the major biological areas represented in the PhysioLab model, and a chart of simulation results. They illustrate the range of components included in the asthma model, including biochemicals, cells, tissues, and airway function. The entire asthma PhysioLab model comprises nearly 500 state variables, making the effect diagram about 100 times the area shown here. Simulations using PhysioLabs quantitatively relate dynamic changes at the biochemical level (e.g., leukotriene production) to functional outcomes at the patient level (e.g., the patient with compromised breathing).

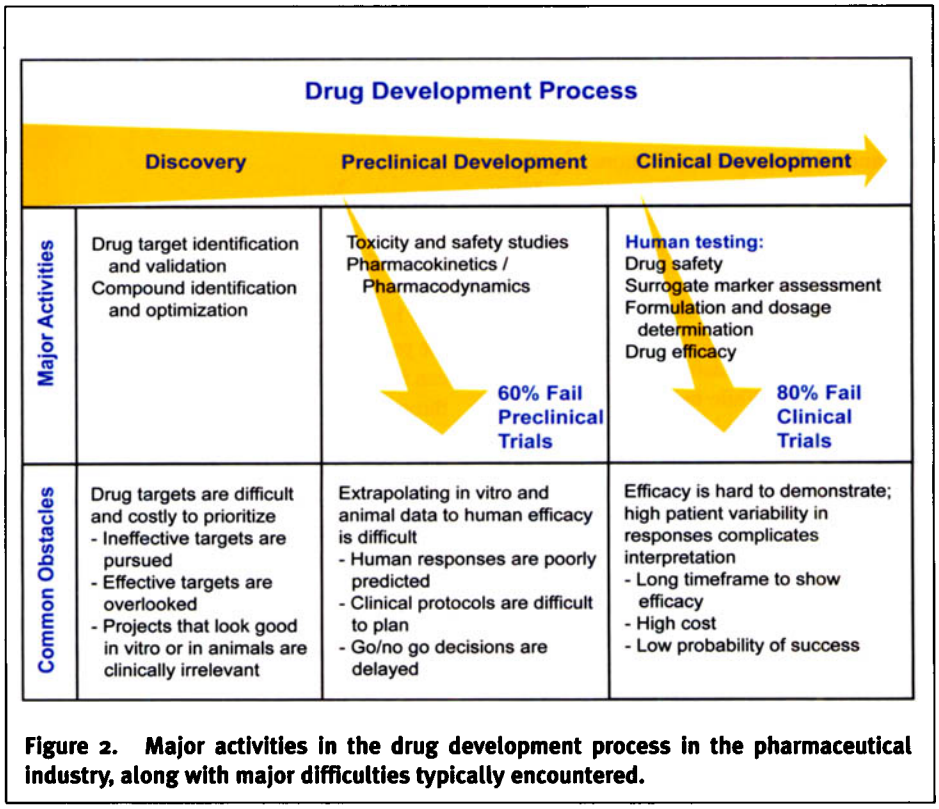

Figure 2. Major activities in the drug development process in the pharmaceutical industry, along with major difficulties typically encountered.

Biological systems models such as PhysioLabs are powerful research tools because they put the function of system elements in context, they help identify and bridge gaps in data, and they can be predictive, not just summaries of known data. Because they explicitly detail the dynamic connections among diverse system elements, these models can reveal why the manipulation of subsystem components affects the function of a larger system. Such explicitness also helps to identify gaps in known data, suggesting experimental investigation needed. Testing of alternate mechanisms in a model to bridge such gaps enhances understanding of those areas by showing what types of mechanisms can reproduce known system behaviors. Finally, because biological systems models must incorporate the feedback and nonlinear properties inherent to many physiological systems, they can generate system behaviors that were not designed into them, making them powerful predictive tools.

Opportunities

The timing is right for mathematical biology to emerge from its academic base to become a powerful component of *e*-R&D because our ability to create useful models matches an urgent need. Innovative methods for biomedical R&D are being sought to manage increasing costs and a flood of data created by two decades of technological innovation. Although I use the pharmaceutical industry to illustrate the pressing need for such a tool, many of my observations also apply to biomedical research in academic and government laboratories.

The drug development process is costly and uncertain (Studt, 1999). Figure 2 illustrates the major activities undertaken and difficulties encountered at each stage of the process. Development of a single new drug takes 10–15 years and costs approximately $500 million (Mathieu and Foster, 1999). Drug failure is a major contributor to this cost, because less than 1% of all drug candidates that emerge from discovery research ever reach the market—60% or more fail in the preclinical stage and another 80% fail in clinical trials. The reasons are many and varied. They range from difficulty in validating drug targets to difficulty in predicting human efficacy using *in vitro* and animal data and complications of patient variability in clinical trials. Many of these challenges stem from the same core problem: current technologies do not address how to evaluate the effects of modulating individual biochemical pathways within the integrated biological system.

This issue is compounded by difficulty in translating the enormous volumes of data from genomics, proteomics, high-throughput screening, and combinatorial chemistry, into knowledge applicable to treating human disease. While methods for connecting these data to actual biological function in an organism are progressing, they cannot keep up with our capacity to generate raw data. For example, in the field of genomics, biomedical researchers need better methods to identify how gene products are *functionally* connected to a state or disease and when a potential therapeutic would have beneficial effect.

Biological systems modeling addresses many of the difficulties in the drug development process that make it so uncertain and costly. Models with a broad scope and a substantial degree of biological and mechanistic detail can be used to address problems ranging from drug target identification (the first step in the drug development process) to patient care. Several examples follow.

Target Identification and Prioritization. In drug discovery, models can be used to identify and prioritize drug targets. Targets are the specific biological components that can be functionally manipulated by a drug, such as an enzyme in a biochemical pathway. Varying parameter values in a systems model to find if the overall diseased system reacts well (indicating alleviation of disease state) could show whether various biochemical pathways might be good drug targets. Comparing variations of several pathways within the same system provides a means of prioritizing drug targets.

Experiment Design. Models can help define many aspects of experiment protocols, such as appropriate drug concentrations, experiment duration, and which variables to measure and how often.

Surrogate Marker Selection. Another potential use is the identification of potential surrogate markers, which are variables correlating with drug efficacy but whose measurement may yield results sooner, more easily, or with less expense.

Patient Selection. Patient variability can be a major obstacle in clinical trials; certain patients may respond well to a drug while others may not, obscuring the true efficacy of the drug. With appropriate biological systems models, one can represent different patient types parametrically and simulate a drug's effects to investigate how each patient responds. Identification of responding and nonresponding types, and combining of this information with known prevalence of patient types in the general population, could guide patient selection for clinical trials.

Testing Combination Therapies. Testing drug combinations is difficult, costly, and time-consuming. Models should be beneficial in predicting efficacy and illustrating why a combination is likely to work.

Understanding Biological Systems. One of the best uses of large-scale biological systems models is to increase understanding of normal and diseased biological systems. Anyone who has created a model with nonlinearity and feedback has undoubtedly gained valuable insight into the system through exploration, above and beyond knowledge of the data used to create or validate the model.

Challenges

While the promise of biological systems modeling is substantial, there remain significant challenges to successfully integrating it into biomedical R&D. The first major challenge is to demonstrate the predictive and instructive capability of the models to those who can invest in further development. The fastest route for this may be through industrial applications, as pharmaceutical companies have a great incentive to invest in technologies that can decrease the time and cost of drug development. To take this route, we must make the use of mathematical models accessible to a user group (life scientists) that has little experience with them. This will include making the concepts of mathematical models and dynamics understandable, using the biologists' language while avoiding math and engineering jargon, and creating user interfaces that allow easy manipulation and interpretation of the models, all while maintaining the model integrity and robustness.

The second major challenge is to justify the expense of building biological systems models. The development cost is high, including the time of engineers and life scientists who create the models and build software platforms (GUIs and simulation engines) on which the models are run. Since an investment in systems models may save hundreds of millions of dollars in drug development costs, such expense should be justifiable to pharmaceutical companies.

A third major challenge is the time sensitivity of biomedical research. Our knowledge of biological systems is expanding very rapidly. Therefore, we must find ways to create relevant biological systems models that can be validated and predictive within 6 to 24 months. Otherwise, the models may be obsolete even before they are available.

With our training in systems, dynamics, control theory with its consideration of feedback, and modeling, engineers are well qualified to investigate biological systems mathematically. Engineers who are solidly trained in the basics and some advanced topics, such as nonlinear dynamics, can make excellent contributions to biological systems modeling. Exposure to biology is helpful, although I find that the necessary biological background can be

acquired as needed, and collaboration with life scientists speeds the model-building process considerably.

The opportunity now exists for mathematical modeling to take a prominent place in biology and medicine as it already has in so many other subjects involving complex systems. Oddly, after dwelling for so long in academia, its broad acceptance may come through industrial applications such as pharmaceutical *e*-R&D. Ideally, this should also lead to increased activities in the academic community, including increased grant availability and establishment of more training programs. Biological research needs additional methods for understanding the mechanisms underlying system function. Engineers know from experience that mathematical models and analysis are powerful tools for achieving this.

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