Computer-Based Models and Virtual Patients: The Newest Biomedical Research Laboratory

Cynthia L. Stokes
Entelos, Inc.

The pharmaceutical industry has recently entered an era of large-scale mechanistic mathematical models capable of simulating and predicting human response. Most research intensive industries have long utilized these models and simulation to design and understand complex systems, such as cars, airplanes, chemical plants, and petroleum recovery. For the last several decades however, the like effort within the life sciences has been limited to a small, mainly academic, research community using relatively small mathematical models of biological systems to develop and disseminate insights into biological function. The pharmaceutical industry has traditionally used modeling to interpret pharmacokinetic data and to scale from animals to humans. In the 1980s and 90s, mathematical modeling of molecular structure-function relationships gained a foothold in the rational drug design movement, although the impact on drug development has been modest. Recently, bioinformatics has become a core competency in the industry to recognize correlations in and, hopefully, gain mechanistic understanding from the enormous data sets derived from genomics, proteomics, and metabolomics. The recent development of technologies and approaches to building large-scale mathematical models of complex biological systems combined with the biological modeling expertise and successes within academia have provided the foundation upon which the pharmaceutical industry can embrace modeling and simulation. These are fast becoming an accepted research effort complementing in vitro, animal model, and human clinical studies.

For the last five years at Entelos, I have been involved in the development of large-scale quantitative models of biological systems, called PhysioLab® platforms, and have used these platforms for basic and applied pharmaceutical research. I have lead several immunologic modeling efforts at Entelos including the development of the asthma PhysioLab platform. I will use these experiences and other, smaller-scale modeling work to describe how such models provide a new laboratory for understanding the complexity of large biological systems of interconnected components functioning on multiple time and spatial scales, and managing and exploiting that complexity in drug development.

The PhysioLab platforms we've developed at Entelos are computer-based embodiments of the biology related to diseases. Each platform includes a set of nonlinear, coupled, ordinary differential equations that describe the networked functions of biological components relevant to a disease, a graphical effect diagram coupled to the equations, a reference and rationale documentation set, and a research architecture for conducting experiments *in silico* and managing the results. The research architecture includes structure to manage parameter changes, run simulated experiments, and store, view and analyze simulation results. The platforms are developed with a top-down, behavior-driven approach, where the clinical level behaviors are modeled first, and the specifics of biological components and functions are included in more and

more detail as needed to reproduce those higher level behaviors and address specific research problems. Where data are missing, scientists use related data and general physiological and physical principles to reverse engineer system structure in the models. In addition to the asthma PhysioLab platform, Entelos has platforms in rheumatoid arthritis, obesity, and type 2 diabetes.

To use these platforms for research, we represent specific patient phenotypes by specifying genotypic and environmental factors that would give rise to a disease state. We call these representations Virtual Patients. Mathematically, a Virtual Patient is the model equations with a given set of parameter values that represent biological characteristics, e.g., rates, concentrations, and dose-response relationships. Alternate sets of parameters can be selected to represent different biological features, such as increased or decreased expression of a receptor, rate of cytokine production, tissue mass or organ geometry, thereby specifying alternate virtual patients. The specifications of these Virtual Patients are stored in the platform and the patients are used in many types of investigations, including target identification, prioritization and validation, chemical lead development, and clinical trial design.

One focus of using the platforms is to predict human response to support critical pharma R&D decisions (Is this a good drug target? Will this drug dosing regimen work in these patients?). More importantly, however, we identify the reasons behind the results, identify gaps in our knowledge of the biological system or chemical compound under study, identify those gaps that are material to decisions at hand, and define experiments needed to reduce material uncertainties and provide improved rational for decisions. Two projects using the asthma PhysioLab platform are useful to illustrate these principles. In the first, we were asked by Merck to simulate a protocol for a Phase IV clinical trial, the results of which were not public. Simulations done in two weeks predicted that a rescue medication for asthma attacks lost its efficacy in patients taking a competitor's drug while it continued to provide relief in patients taking Merck's drug. When compared, these results were nearly identical to the actual clinical trial results, which took a year and approximately a million dollars to obtain. In addition to accurately predicting human outcomes,,we identified the mechanisms in the model responsible for the results. Had the platform been used before the trial, the rationale for the trial would have been clearer, the prediction and identified reasons for likely success would have added confidence in the investment, and the effects of patient variations could have been explored before enrolling real patients at significant expense.

The second example is an evaluation of PDE4 as a target for asthma, conducted in a research collaboration between Entelos and Pfizer. PDE4 is involved in many cellular functions such as smooth muscle relaxation. From a thorough examination of available public and proprietary data, the team quantified 20 known functions of PDE4 in human cells in the airways, and another 26 hypothesized functions based on data in nonhuman cells and on related biological functions. We implemented the effects of modulating these functions and simulations indicated that inhibition could be effective at certain doses in a variety of moderate patients. Further, the team identified the four functions out of the 46 that, when inhibited, were primarily responsible for the clinical level effects. These four were not commonly understood to be important drivers beforehand. Based on the study, we provided a plan for experiments that should be done to confirm important hypothesized functions in human cells, a target validation plan, and a specification of screening assays. In subsequent research, we compared efficacy and potency of five PDE4 inhibitor compounds, prioritized them based on efficacy and recommended one for

advancement to first-into-man. Pfizer estimated that together these studies saved a number of years and millions of dollars from several go and no-go decisions on them.

Although the industry has seen tremendous success and advancement in modeling and simulation technologies exemplified by these two studies, challenges continue to face the computational systems biology field. One is how to mathematically and computationally represent biology that has multiple important time and spatial scales. Appropriately matching up subsystems of different scales, such as the intracellular signaling networks that drive a single cell to the function of a population of such cells in a tissue and that tissue in an innervated organ perfused with blood bearing hormones, is not straightforward. In addition, stochastic elements are critical in certain problems, and deterministic descriptions will be oversimplified. Numerous efforts in both academics and industry are underway to define and address these issues, including, for instance, the development of new numerical solutions algorithms that better address multi-scale models. Another challenge is how to utilize the rich arrays of genomic, proteomic, and metabolomic data in mechanistic models. To meet this challenge, Entelos is collaborating with researchers at MIT to develop joint experimental and modeling methodologies for interpreting such data and linking it to larger system function. Finally, biological data is frequently not available in the forms needed to specify parameter values for mechanistic models and against which to validate such models. Much closer integration of modeling and data acquisition is needed to allow for even greater contributions of modeling to biomedical research.

These challenges notwithstanding, the examples above illustrate that research with mechanistic mathematical models is complementing the experimental lab to gain new understanding beyond what we glean from examining empirical data, and beyond the specific data used to create such models. Clearly, modeling can bring valuable insight and understanding today, and we do not have to wait until all genes and proteins (and their various functions) have been identified. These models are being used already to complement experimental work and bring new insight to drug development decisions.

Keywords:

Mechanistic mathematical model: Set of equations that represent mechanisms that underly known system behaviors and can reproduce those behaviors. Compare to *phenomenologic models* that quantitatively describe phenomena (system behaviors) but whose equations don't represent specific mechanisms.

Biosimulation: Calculating the solution of a mathematical model (numerically or analytically) of a biological system to obtain the evolution of the modeled system through time.

Top-down (or behavior-driven) approach to modeling: Identifying system level behaviors that must be reproduced by a model and writing equations that do so, starting with high-level mathematical descriptions and iteratively including more and more detail on biological components and their functions as needed to reproduce the desired behaviors as well as address the research problems of interest.

Virtual Patient: A mathematical specification of a patient phenotype, including genotypic and environmental factors that would give rise to a disease state. A Virtual Patient can be defined in a mathematical model that links basic biological function to clinical-level outcome, and consists of a model's equations along with a given set of parameter values that represent biological characteristics, e.g., rates, concentrations, and dose-response relationships.

Systems biology: Multidisciplinary field that concentrates on understanding biology in terms of functional integrated systems, typically utilizing mathematical modeling in concert with experimental observation.