

# Predictive Biosimulation and Virtual Patients in Pharmaceutical R&D

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**Abstract.** In the automotive, telecommunication, and aerospace industries, modeling and simulation are used to understand the behavior and outcomes of a new design well before production begins, thereby avoiding costly failures. In the pharmaceutical industry, failures are not typically identified until a compound reaches the clinic. This fact has created a productivity crisis due to the high failure rate of compounds late in the development process. Modeling and simulation are now being adopted by the pharmaceutical industry to understand the complexity of human physiology and predict human response to therapies. Additionally, virtual patients are being used to understand the impact of patient variability on these predictions. Several case studies are provided to illustrate the technology's application to pharmaceutical R&D and healthcare.

## 1. Introduction

The pharmaceutical industry is facing a productivity crisis. Many current blockbuster drugs are coming off patent and new drugs are not being introduced at a fast enough pace to meet investor expectations [1]. It currently costs over \$800M and takes an average of 14 years to develop a new drug [2]. The Food and Drug Administration recently announced the Critical Path Initiative, which attempts to address the issues of cost and time in the drug development process, and outlined the need for the industry to adopt technologies that may help [3].

A key challenge for the pharmaceutical industry is the high failure rate of drugs, particularly those in late in late phase development. In the automotive, aerospace, and telecommunication industry, modeling and simulation are used to design and test new products well before they are commercially produced. For example, the Boeing 777 flew many times in a computer before it was constructed [4]. Modeling and simulation have been used in some aspects of drug development, notably for molecular modeling and drug pharmacokinetics, but have not been widely applied in industry to modeling biological systems and in particular human physiology. The technology and methods now exist to build large-scale biosimulation models for pharmaceutical R&D. In fact, such models have already been built and applied, resulting in saving in terms of time and money, and lowered risk of drug failures.

## 2. Predictive Biosimulation Models

A number of approaches are being taken to understand complex biological systems [5]. Many of these approaches focus on analyzing data from high throughput technologies, such as gene expression arrays. These approaches seek possible correlations to behaviors that

may indicate relationships not previously identified or understood. Other approaches are focused on automatically or manually constructing relationship models based on information in the scientific literature. In most of these cases, the result is a static model of biological relationships. Missing from these approaches is the ability to understand the dynamics of the system (*e.g.*, what the quantities and signals are at any point in time, the relative effects of those quantities and signals, how feedback affects the system) and how they translate into therapeutic efficacy. In order to achieve this capability, a more quantitative approach is required.

A biosimulation model quantitatively captures biological elements (*e.g.*, proteins, cytokines, cell populations) and their relationships. The relationships between elements are represented using differential equations, allowing simulation techniques to predict the behavior of the system and the quantities of the biological elements over time. The model may be configured with parameter changes to predict new outcomes for different scenarios, *e.g.*, for new drug targets or new clinical trial protocols.

Constructing such models requires a significant amount of data about the biological elements, their states, and their relationships. Historically, much of the biosimulation work has been accomplished using “bottom-up” techniques, *i.e.*, building models of biochemical pathways or subcellular systems based on the data gathered on these systems. Another technique focuses on a “top down” approach to modeling biological systems [6].

The goal of the top-down approach is to build a model that can simulate a pathology or behavior in the context of a particular disease. This approach starts by defining a model scope, which is based on the disease characteristics and their related physiological systems, as well as the anticipated uses of the model. For example, a model of obesity may need to include the gastrointestinal tract, organ systems for processing and storing macronutrients (*e.g.*, the liver and adipose tissue), and brain regulation of appetite. Given the disease focus, the model does not need to include details of bone structure or lung tissue function. The underlying philosophy of the top-down approach is Einstein’s maxim that things should be made “as simple as possible, but no simpler.”

If the model is to be used for evaluating drug targets, the physiological systems where those targets play a role must be included in sufficient detail so that the target effects can be modeled. This does not require that every subcellular biochemical pathway in the body be included. Instead, many of these systems are modeled with the functional effects of the underlying biological pathways aggregated and represented at a higher level of detail. For example, rather than include all the dynamics of a cell type’s intracellular pathways, it may be sufficient to include enough dynamics of intercellular behavior that, under specific conditions, the cell produces cytokines at specified rates. Where necessary, the models include a deeper representation of the biological pathways to capture dynamics of interest at a lower level (*e.g.*, around a protein target of interest).

These models are constructed using a wide range of data. For example, data from laboratory studies is used to confirm the existence of biological relationships, and where possible, determine their dynamics. At the top level, clinical data is used to validate the model, ensuring that the full system behaves as a patient would under the same clinical protocol. The result is a model that simulates a patient with the disease of interest.

### **3. Virtual Patients**

The diseases being studied in pharmaceutical research today are highly complex. It is typical to hear a scientist refer to a disease such as asthma as being not one but rather many different diseases clustered together. Complex diseases do not result from a single gene defect, but rather, an interaction of multiple genetic and environmental factors. Therefore,

a model needs to represent not just “the disease,” but also the range of patients that may present with the disease, as well as the unique set of genetic and environmental variations they incorporate.

In addition, while building a model, there will be knowledge gaps. These may include a lack of specific information about the rate of a particular biological process, or the quantities of various biological elements at specific times. In some cases, these may be reverse engineered, which may be time consuming or even impossible given technical limitations. The first question in attempting to bridge any knowledge gap is therefore “Is this unknown significant?”— will the predictions of the model change based on changes in this unknown? Therefore, a system to explicitly represent these gaps, and the possible variations of their solutions, can help us identify the key knowledge gaps. With this information, experiments can be defined to resolve them.

The concept of a *virtual patient* was developed to encompass the variations required to study the broad range of patients and the underlying uncertainties about patient biology [7]. The modeling platform supports the representation of virtual patients, along with the tests required to validate them as being “real” in terms of their physiological readouts. Once virtual patients are constructed, “what if” experiments are performed to validate, for example, whether manipulating a particular drug target has the desired effect in a diverse set of potential patients.

#### 4. Case Studies

Entelos has developed a modeling approach and technology platform to construct large-scale physiological models of human disease. These platforms, called PhysioLab<sup>®</sup> systems, facilitate pharmaceutical R&D in a number of immune/inflammatory diseases, including asthma and rheumatoid arthritis, and in diseases related to metabolism, including obesity and diabetes. These models have been applied to a wide variety of R&D problems (Figure 1). To illustrate their use, a selection of case studies is included below.

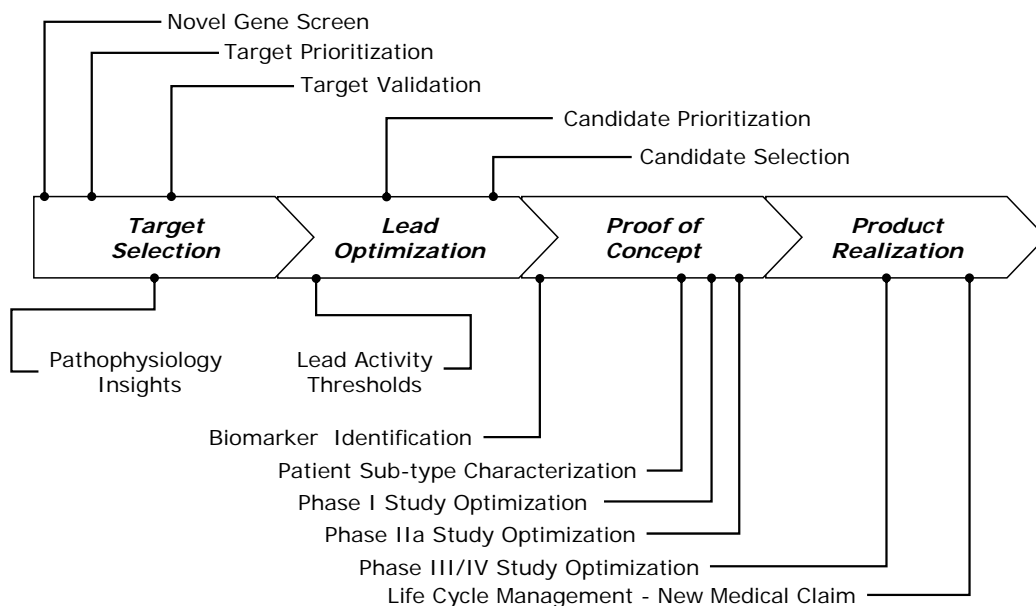


Figure 1: Applications of PhysioLab technology in pharmaceutical R&D

#### 4.1 Drug Target Validation

Entelos collaborated with Pfizer to evaluate phosphodiesterase 4 (PDE4) as a drug target in asthma [8]. The process started with defining all of the known functions of PDE4 based on the scientific literature. Additional hypothesized functions were added where PDE4 was thought to have an effect, but for which it had not been explicitly measured. These functions and hypotheses were then represented in the model, allowing the mathematical effect of inhibiting PDE4 to be simulated. In addition, a set of moderate asthmatic virtual patients were constructed with different mediator expression profiles.

The PDE4 inhibitory effect was then simulated against the set of virtual asthma patients. First, all the functions were inhibited simultaneously to evaluate the potential efficacy of target inhibition. Under these conditions, the model predicted the target would have a significant clinical effect on all the patients, improving their ability to breathe as measured through forced expiratory volume in one second (FEV<sub>1</sub>) scores. Second, each of the functions was inhibited individually. This analysis showed that of the 50+ pathways where PDE4 was thought to play a role, only four had a significant effect on the clinical outcome. Based on this information, Entelos provided recommendations for wet lab confirmation of the simulation results, including advice on the development of predictive, *in vitro* assays. Following this initial target validation analysis, a set of PDE4 inhibitor compounds were simulated to show the effects of different dosing strategies on the efficacy of PDE4 inhibition.

This approach provides unique value in target validation, providing new information on drug target effects, reducing the time for target validation and predicting human results well before a drug enters clinical trials. Additionally, the positive prediction of PDE4 efficacy increased the company's confidence in moving the target forward in the research pipeline.

#### 4.2 Clinical Trial Design

Entelos collaborated with Johnson & Johnson Pharmaceutical Research and Development (J&JPRD) on designing a Phase 1 clinical trial for a new diabetes drug [10]. With new glucose-lowering drugs, there is a concern about patients becoming hypoglycemic. To ensure that this would not be an issue with the new drug, J&JPRD had planned to run a trial in healthy patients with escalating doses to see if there was any risk of hypoglycemia. Entelos simulated the trial using healthy virtual patients, and predicted that the hypoglycemic effects between the different doses would not be easily observable, and that there did not appear to be any adverse effects at the highest dose.

The trial was run with a smaller patient population and only the highest dose *versus* placebo was examined. The simulation results were confirmed by the trial results.

Overall the process resulted in cost and time savings. J&JPRD was able to run a shorter trial with fewer dosing arms, reducing patient recruitment. The result was a 40% reduction in time and 66% reduction in patients for the Phase 1 trial. Further simulations were performed in a population of virtual patients to provide additional information, including biomarkers and the optimization of a backup compound.

#### 4.3 Biomarker/Diagnostic Identification

With the complex, chronic diseases being studied today, it is important to be able to characterize patients and understand what therapeutic regimen would best fit each patient.

To achieve this, biomarkers (*e.g.*, patient measurements, diagnostic tests), are needed to differentiate and diagnose patients. Biomarkers are also used during clinical trials to identify which patients best respond to a drug or to identify whether the drug is having a desired effect.

Entelos collaborated with Roche Diagnostics to identify a new biomarker for insulin sensitivity [9]. A signal in a patient's progression to diabetes is their increased insensitivity to insulin. Early identification of this condition could have a significant impact on patient care, but existing markers were not very predictive. The goal was to identify a new, more predictive marker that would be based on simple tests using measurements from a single blood sample.

To perform this analysis, Entelos evaluated potential markers in 62 virtual patients with diverse phenotypes and pathophysiologies. In addition, a novel prevalence weighting methodology was developed that allowed the results from the virtual patients to be compared to a typical clinical population. The markers were further evaluated against a number of patient scenarios, including different diets.

The result was a new, more predictive biomarker of insulin sensitivity. The marker was defined faster and more easily than would be possible with regular patients. In the future, this technology may be used not only to create new diagnostics, but applied directly to patient care, helping to characterize patients and identify the best treatment regimen for an individual patient.

## 5. Conclusion

The pharmaceutical industry is starting to benefit from biological modeling and simulation – learning early which products will work in the marketplace and how best to bring them to market. The result will be cost and time savings, and ultimately, more effective products being brought to market. The technology can also be extended into the healthcare arena, identifying new tests to improve patient care, and eventually, applying it directly to individual patient care.

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