# BIOSIMULATION: ADVANCEMENT IN THE PATHWAY OF DRUG DISCOVERY AND DEVELOPMENT

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**ABSTRACT**

The process of drug discovery from discovering a new drug molecule to registering it for marketing and commercialization are very complex and lengthy. The huge amount, a long period of time, and the clinical trials are required before a drug to be registered for human use. Nowadays there is development of various new and very promising notion to the drug development which can modified the traditionally drug development process, biosimulation are one of them. Biosimulation represent simulation the dynamics of biological systems and thereby analyze and predict system behavior in terms of mathematical expression with the help of modern computers. The key value of biosimulation comes from understanding clinical outcomes in discovery or development well before any human trial occurs. Modeling and simulation are now being adopted by the pharmaceutical industry to understand the complexity of human physiology and predict human response to therapies.

**Keywords:** Biosimulation, Bottom-up & Top-down modeling, Small scale & Large scale biosimulation.

## INTRODUCTION

Most of the time and money of the R & D section of pharmaceutical industry will be spent on the discovery and proper evaluation of new drug. A normal drug discovery and development cycle, which is the time between the discovery of a new drug and its delivery to the market, can easily take up to 10-15 years. Taking into consideration the expenses in all the phases, the average cost of a pharmaceutical product goes up to $800 million[1]. But recently it was found that decline in drug approvals and the increase in late-stage failures indicate that the ability to generate and screen large numbers of molecules has not improved the drug pipeline. According to the Tufts Centre for the Study of Drug Development, in Medford, Massachusetts, only one in 1,000 compounds tested makes it into human trials, and only one in five of those emerges as a 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].

In order to avoid all such hurdle in discovery and development of new drug, a most promising technology was developed known as 'biosimulation'. The biosimulation is relatively new tool in the pharmaceutical drug development and healthcare that promising tremendous benefits, saving both time and money and improving the predictability in early stage of drug development. Biosimulation refers to the simulation of biological systems. Any living system consisting of biological processes - whether a kidney, a liver, a heart, the body as a whole - can be defined as a biological system and by the use of advanced computer models, makes it possible to simulate the behaviour of biological systems in terms of their components and the interactions involved.

Biosimulation is a distinct part of the emerging field termed *systems biology*. Systems biology combines concepts from many scientific disciplines to obtain an integral understanding of complex biological systems in disease and health[4]. The biosimulation is often associated with the term *'in silico'* biology, which is used to represent the biological experiments carried out entirely by means of computer. 'In silico' biology appeared earlier than biosimulation, it was first used as an official term in 1989. The biosimulation itself is a relatively new field in drug development and healthcare industry. It emerged in the beginning of the 21st century, after the first draft of human genome was unveiled in 2000[5].

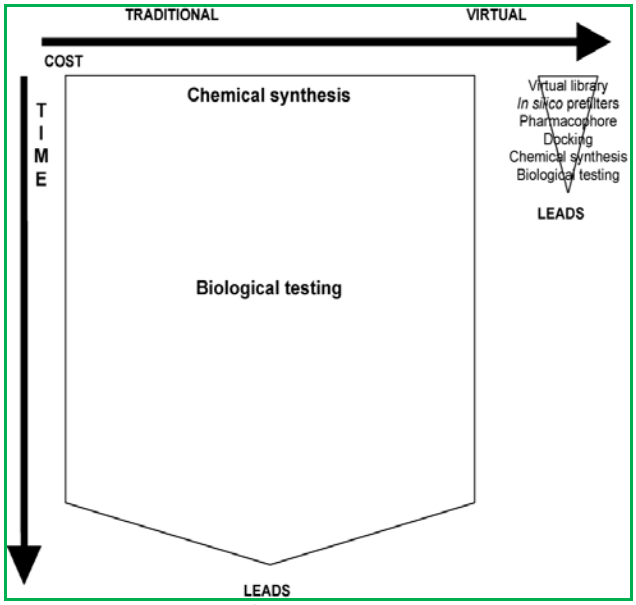



**Figure 1:** Comparison of traditional and virtual (biosimulation) screening in terms of expected cost and time requirements.

## WHAT IS BIOSIMULATION

Biosimulation is new notion in drug development industry, which is based on expressing the biological systems in mathematical expressions, thus, capturing biological elements and their relationships, and simulating the behaviour of a certain system in different situations[5].

The relationships between elements are represented using differential equations, allowing simulation techniques to predict the behaviour 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[6].

Biosimulation uses mathematical representation of the real-life processes inside the human body, which is expressed in interconnected sets of differential equations. Using differential equations for the simulation of the biology systems allows tracking the response of the systems to different factors, their behaviour and quantitative change over time. These mathematical models are built based on a huge amount of information about the biology systems, sub cellular pathways and human genome. Such information can be obtained from laboratory studies, researches and investigations. Validation of the model can be done by means of clinical data, ensuring that the model reflects the behaviour of a given patient under the same clinical protocol.

Models obtained on the previous stage are loaded into the computer or computer network, processed and prepared for simulation. Starting the simulation invokes the calculation of complicated processes inside the human body. Every model has to be checked by the scientists and experts for feasibility and it should be ensured that the calculation done by the computer reflects the real life behaviour of the investigated organism.

## BIOSIMULATION MODEL DEVELOPMENT APPROACHES

A biosimulation model quantitatively captures biological elements 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. Although current best practices in biosimulation modeling include adherence to some annotation standards[7], integrating models remains a daunting task which is further hampered by conflicting computational languages, differences in implicit assumptions, and pervasive coding errors[7,8]. Over the past decade, physiology-based mathematical models and biosimulation systems have been applied to both target identification and validation[9-13]. For example, physiological models of cancer growth and therapy have been used to suggest optimal chemotherapeutic regimens in breast cancer[14-16]. Similarly, a model of the heart was developed to characterize the pathophysiology underlying electrocardiographic dysfunction[17,18]. A number of approaches are being taken to understand complex biological systems[19]. There are two main approaches in biosimulation that are being extensively used at the moment. Those are top-down and bottom-up techniques.

### 1. Bottom-up approaches:

Bottom-up approach aims at building models of biochemical pathways, then cells, then tissues and organs, and finally a virtual human that can reproduce a clinical trial or be applied to address many other medical problems (such as environmental pollutants, blunt force trauma effects, etc).

Ultimately, such a system would have great value for drug discovery and development. A bottom-up approach focuses on the measurement and description of complex systems using the building blocks – their interactions and dynamic properties, such as kinetic parameters.

### 2. Top-down approaches:

This approach starts with the clinical manifestations of a disease, then drives down deeper to focus on the subsystems required to represent that disease's pathophysiology. These top-down models are built with enough detail to simulate human behavior for use in focused research efforts (e.g. for characterizing specific targets of interest) and are validated against data sets of clinical, animal and *in vitro* data. Given the top-level starting point of a disease (i.e. symptoms and clinical presentations), clinical data can thus be used as part of the modeling process, providing a powerful constraint that is not available when modeling at lower levels using a bottom-up approach.

When testing a specific pharmaceutical product on a designed simulation model it is enough if only physiological systems that are affected by the drug, i.e. "drug targets", are included and described in detail, and the rest of the sub cellular biochemical pathways are mentioned on a high level. This gives the scientists an opportunity to focus and concentrate all efforts on the main areas of interest.

### *3. Hybrid models*

Bottom-up models serve as scaffolds for top-down models by providing information of possible and potential interactions and sub processes, how these sub processes respond to drugs and infection and how matter and information is passed between sub processes and through different scales. Such hybrid approaches benefit from bottom-up molecular measurements and knowledge as well as top down predictive modeling. A 'post genomic physiology' could span many different levels of biology, from molecules to whole organisms, moving away from 'naïve reductionism' towards a discipline that fosters integration and synthesis [20].

## CLASSIFICATION OF BIOSIMULATION

Biosimulation can be categorized into two general classes viz small scale biosimulation and large scale biosimulation depending upon mathematically equation and various parameters involves.

### 1. Small-scale biosimulations:

Small-scale biosimulations, consisting of a few equations and parameters that are designed to address a specific, well-defined problem and have been useful tools in the drug development process and clinical management of disease. Small-scale biosimulations have been particularly useful for interpreting clinical data and developing novel biomarkers. Some of the example small-scale

biosimulations that have been used to help collect and interpret clinical data are summarized as below:

***Case 1 : HIV-1 replication biosimulation***

Acquired immunodeficiency syndrome (AIDS) is a chronic disease that begins with HIV infection and in adults progresses over a median period of ten years. Measurement of the plasma concentration of HIV RNA, known as the viral load, is considered the best predictor of disease progression in untreated HIV-infection[21].

To investigate HIV replication dynamics, Perelson *et al.* developed a biosimulation of HIV and T-cell dynamics following administration of a potent HIV protease inhibitor[22]. By assuming that the system was in a quasi-steady state prior to therapy, and that the number of uninfected T cells would not appreciably change over the first week of therapy, the authors were able to analytically solve the three ordinary differential equations of their model and express the viral load as a function of time. Clinical measurements of viral load were made several times over the course of one week of therapy, and model parameter values were adjusted to best match these data. This provided *in vivo* parameter estimates of HIV clearance and the rate of loss of HIV-producing T cells for each patient. From these parameter estimates, Perelson *et al*. computed the infected T-cell lifespan, the HIV production rate prior to therapy, and the average viral generation time.

The numerical parameter estimates suggested that HIV replication and turnover were much larger than previous estimates. Based on these new estimates, Perelson *et al.* made three conclusions that are important for the development of HIV treatments. First, effective anti-viral therapies will act within a few days to detectably lower the plasma viral load. Thus, clinical efficacy of an anti-viral compound can be determined rapidly. Second, the risk of developing drug-resistant viruses is high given the estimated replication rate and the previously measured rapid mutation rate of HIV. Thus, treatments should consist of a combination of anti-retroviral agents, requiring the virus to mutate simultaneously at multiple positions before acquiring drug resistance. Third, although only two to three weeks of anti-viral treatment is necessary to decrease viral load by approximately 99%, treatment regimens must be continued for a sufficient time to deplete other viral compartments, such as latently infected cell populations and sanctuary sites, which may spark a high rate of viral replication if therapy is withdrawn. These insights have 'transformed thinking about HIV disease and have had a major impact on clinical management'[21]. Further development and use of HIV biosimulations continue to provide a better understanding of disease processes[23].

***Case 2: Minimal-model glucose biosimulation***

Insulin is a polypeptide harmone produced by the beta cell of islet of langerhans of pancreas. It has profound influences on many physiological process including hepatic glucose production and skeletal muscle glucose uptake. Decreased sensitivity of various organs to insulin is associated with diabetes, cardiovascular disease, hypertension and obesity. Because many present and future therapies are aimed at improving insulin sensitivity, it is important to have a clinical measure of insulin sensitivity to assess therapeutic efficacy. However, the 'gold standard' for measuring insulin sensitivity, the euglycaemic hyperinsulinaemic clamp, is labor-intensive, time-consuming and expensive[24,25], making it inappropriate for use in large-scale clinical trials.

Bergman *et al.* developed an alternative clinical measure of insulin sensitivity using a biosimulation of the plasma glucose response to an intravenous bolus infusion of glucose[26, 27]. Their 'minimal-model' consisted of a pair of nonlinear ordinary differential equations describing the plasma glucose kinetics and the kinetics of insulin in an interstitial fluid compartment. By using the measured plasma insulin profile as a forcing function, Bergman *et al.* determined a unique set of model parameters for each patient, such that the simulated plasma glucose response best matched the measured glucose data. The insulin sensitivity index for each patient was then determined as a simple function of the optimal parameters.

The minimal-model insulin sensitivity index was found to be repeatable and in good agreement with the index obtained using the euglycaemic hyperinsulinaemic clamp [28-30]. Because the minimal-model analysis is straight forward and economical[31], it has been widely used to assess insulin sensitivity in large-scale clinical trials[32]. The minimal model methodology continues to be improved and extended to provide novel clinical measures of glucose and insulin dynamics.[33-35]

**2. Large-scale biosimulations:**

Large-scale biosimulations are designed to comprehensively represent physiologic mechanisms responsible for health and disease. It typically integrate a wide variety of data and can provide insights into how complex biological systems are regulated in both health and disease. Such models are designed to address a wide variety of problems, predict overall system behavior and help design experiments and interpret their results. These models are generally relatively large, consisting of tens to hundreds of equations and parameters. Some of the example large-scale biosimulations are listed below:

***Case 1: Asthma biosimulation***

Asthma is a chronic inflammatory disease of the lower airways. To better understand asthma pathophysiology in the context of the complex interactions between airway tissues and the allergen induced immune response, Stokes *et al.* created an asthma biosimulation that encompasses airway physiology and the inflammatory effectors system [36]. This model accurately simulated the acute and chronic characteristics of asthma, including both early- and late-phase airway obstruction following allergen challenge, airway hyper-responsiveness and chronic eosinophilic inflammation. The asthma biosimulation also exhibited characteristic responses to known therapeutics. To evaluate the predictive capability of the asthma biosimulation at the clinical level, Stokes *et al.* investigated the ability of a leukotriene receptor antagonist and a long-acting β2-agonist to reduce the severity of exercise-induced asthma (EIA)[37]. The biosimulation accurately predicted the efficacy of each therapy when

subsequently compared with clinical data from Merck and Co., Inc (Whitehouse Station, NJ, USA). Both the biosimulation and the clinical results showed greater protection in EIA with the leukotriene receptor antagonist than with the long-acting β2-agonist. In addition, administration of a short acting β2-agonist, an acute rescue therapy for EIA, was more effective in combination with the leukotriene receptor antagonist than when combined with the long-acting β2-agonist. The biosimulation was further used to elucidate the mechanisms underlying these clinical observations. Perhaps the most compelling result of the asthma biosimulation was the prediction that a therapeutic in clinical trials, an interleukin-5 (IL-5) antagonist, would not be effective for treating acute airway obstruction in asthma[38]. IL-5 increases eosinophil number in the airways – a hallmark characteristic of asthma. Based on animal studies, anti-IL-5 therapy should decrease airway eosinophil number and thereby reduce airway obstruction[39-41]. Surprisingly, although anti-IL-5 effectively reduced eosinophil number, the asthma biosimulation predicted that this therapy would have little effect on improving airflow obstruction. This prediction was confirmed by the results from an anti-IL-5 clinical trial[42]. The biosimulation further showed that ongoing airway obstruction was because of the continued presence of other resident and infiltrating cells in the airway, highlighting the significant redundancy in the system.

***Case 2: Cardiac electrophysiology biosimulation***

Detailed, quantitative biosimulations of cardiac cell electrophysiology have been used to better understand the pathophysiology of heart disease[43]. For example, Winslow *et al.* investigated whether the observed altered gene expression of ion channels, pumps and exchangers could account for the known electrophysiological properties of congestive heart failure[44]. Beginning with a detailed biosimulation of a normal canine ventricular cell, the authors adjusted model parameters to simulate altered protein levels based on observed gene expression from failing ventricular cells. They found that simulations of the diseased action potentials and calcium dynamics accurately matched experimental measurements. With this model, Winslow *et al.* determined the relative contribution of each of the altered protein levels to the observed cellular electrophysiological behavior. Although these results gave insight into the cellular defects associated with heart failure, it is necessary to understand how spatial propagation of the cardiac action potential is altered to predict clinical outcome. By incorporating the cellular electrophysiology biosimulation into a realistic, three-dimensional model of the canine ventricle, Kohl *et al.* were able to predict disrupted spatial propagation of cardiac action potentials in heart failure[45]. They showed that the altered protein levels caused the electrical activation pattern to change from a normal, coordinated pattern to a dangerous, abnormal pattern of irregular circulating waves of electrical activity. To predict how pharmacological modulation of cellular electrophysiology affects clinical outcome, the authors simulated the effect of adding an ATP-sensitive potassium channel opener and showed that such an intervention returns the heart to a more normal activation pattern. These cardiac biosimulations have led to a better electrophysiological understanding of the clinical manifestations of heart failure and have predicted potentially effective targets for therapeutic development.

## BIOSIMULATION OBJECTIVES

The objective of biosimulation is to provide:

- ***Better insights*** into the behaviour of biological systems like the human body and the progression of diseases
- ***Better predictions*** of the function and effects of new medicine
- ***Better ways*** of conducting science by offering a versatile alternative to human and animal experimentation

## BIOSIMULATION CHALLENGES

**Industry:**

The industry has relatively few qualified experts in the field, and acquisition of the necessary expertise is impeded by the unusual combination of insights required. The complexity of biological systems combined with the traditional lack of mathematics in the life sciences and insufficient understanding of biological process from the part of engineers and computer scientist represent serious obstacles to the application of simulation models in the pharmaceutical industry.

**Academic:**

To make biosimulation work, integrating knowledge across disciplines is essential. Many academic institutions in Europe already dispose of a significant expertise in biomedical modeling, and several groups are individually at the research front in their specific areas. However, the efforts are strongly fragmented both because of the enormous diversity of the field and because of the absence of a common purpose and an organizing structure. The European tradition for collaboration between academic institutions and the pharmaceutical industry is also relatively weak.

**Regulatory Authorities:**

In the U.S., the simulation approach is already strongly recommended by the American Food and Drug Administration (FDA).

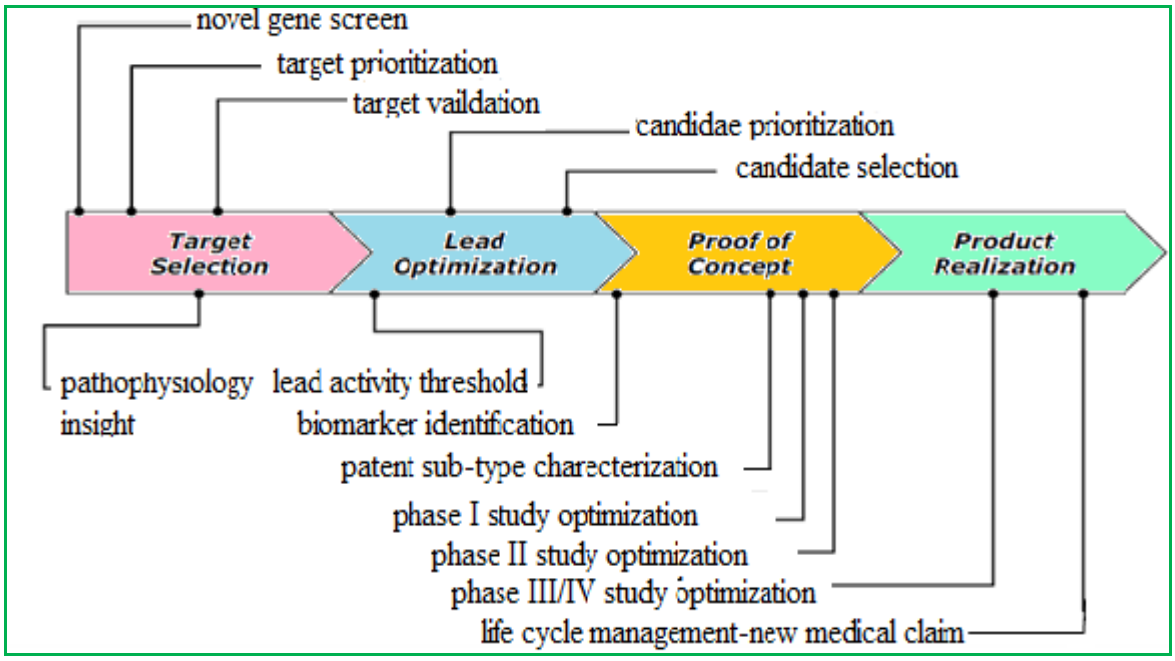
***To make biosimulation a success it is necessary to:***

- Encourage collaboration and communication among those in various academic disciplines ranging from the life sciences to physics and mathematics
- Invest in training and education programmes in biosimulation thereby providing an adequate cohort of professional staff with the necessary expertise in modeling of biological systems
- Foster stronger links between industry, academia, and regulatory authorities[46]

## APPLICATION OF BIOSIMULATION

Clinically relevant biosimulation models enable a broad set of application throughout the pharmaceuticals pipeline.

**Figure 2:** Application of biosimulation technology in pharmaceutical R&D




## ADVANTAGES OF BIOSIMULATION

Biosimulation is becoming increasingly important for drug development[47]. Since on average only 11 % of all drug candidates are approved[48], it is anticipated that biosimulation may be the tool to predict whether a candidate drug will fail in the development process e.g. in clinical trials due to adverse side effects, bad pharmacokinetics or even toxicity. The early prediction if a drug will fail in animals or humans would be a key to reduce both drug development costs and the amount of required animal experiments and clinical trials. The latter is also in line with the so called "3Rs" which refer to the principle of **r**eduction and **r**eplacement of animal experiments as well as to the **r**efinement of the methodology in cases where animal tests are still necessary[49].

- The reduction, refinement and replacement of animal experimentation.
- The reduction, refinement and replacement of human experimentation.
- More ethically acceptable drug evaluation in particular at risk patient groups, such as children, pregnant women, and those with specific gene modifications.
- Contributing to the development of safer and more effective medicines better adapted to patients needs.
- Improving today's knowledge about how patients need to administer medicine.

## CURRENT SCENARIO OF BIOSIMULATION

There are several companies that proved themselves as professionals in simulation of biological systems and processes, such as Entelos, Gene Network Sciences (GNS), and Roseta Biosoftware. Some companies in this field, such as Spotfire, Simulations Plus, Select Biosciences and Lion Bioscience are more specialized in creating three-dimensional images from the results of the simulation. These companies have already conducted a number of successful projects in biosimulation, showing remarkable results.

Entelos, mentioned earlier, created a technology based on the mathematical model of the human metabolism, which simulates carbohydrate, lipid and amino-acid metabolism, and models the actions of the gut, the absorption of intestinal nutrients, insulin release, and nutrient cycles in muscle, connective tissue, liver and other tissues. They developed 125 unique virtual patients and ran a simulation to evaluate an experimental approach to asthma treatment for Pfizer. The results obtained from this simulation revealed the physiological processes and drug targets on which the company had to concentrate. It would have cost Pfizer several years and millions of dollars to get this answer using its standard techniques .

Entelos is also known for its simulation that helped Johnson & Johnson Pharmaceutical Research & Development (J&JPRD) to reduce the total number of recruited patients by 60% and to shorten the trial's duration by 40%. This was achieved by running a simulation on the virtual patients, determining the safety limits for a new treatment for type-2 diabetes, eliminating four-fifths of the trial.

Another company GNS, which is based in Ithaca, New York, serves such pharmaceutical companies as Novartis, Merck and Johnson & Johnson and combines the bottom-up simulation of physiological processes with a top-down "inference modeling" approach based on the analysis of clinical-trial data. They use machine-learning and data-mining techniques, which process enormous amount of data in order to reveal certain patterns, and it enables both to confirm known behaviors of biological systems, and to predict other, unknown behaviors.

Designing clinical trials could also benefit from the computational modeling and biosimulation. This was proved by Pharsight when they delivered the "computer-assisted trial design" system models to the market, which allowed simulating clinical trials and determining the optimal number of patients, dose amounts, and dosing frequency. Traditionally these data was obtained through time-consuming and costly trial and error. Pfizer and IBM Life Sciences are among clients of Pharsight.

In a future scenario biosimulation would change the way substances are tested, in which in vivo and in vitro tests are substituted by tests in silico[49].

## CONCLUSION

Biosimulation have emerged as an efficient means in the pathway of drug discovery & development which reduces the time, money and complexity of traditional system. The introduction of biosimulation can have a significant impact on prediction the response of drug therapy to human system in the early stage of drug development process that remain a major pharmaceutical bottleneck. Interest in adopting biological simulation and modeling in the pharmaceutical industry is high, but concerns remain over how soon the technology will pay off.

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