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# Biosimulation in Biomedical Research, Health Care and Drug Development

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# Preface

Growing funding for research in biomolecular and other forms of biological research during the last decades has provided us with a fantastic insight into many aspects of biological function. The aim of most studies has been to penetrate ever more deeply into the world of molecular and sub-cellular processes, and many important results have been achieved in studies of the structures, functions and regulatory mechanisms of the genes and their immediate products. One should not forget, however, that the single most characteristic feature of the living organism is its system's nature, i.e. its dependence on the complicated network of mutually interacting control mechanisms that regulate the biological processes over an enormous range of different time and space scales.

The genes provide a prescription for the proteins that the cells can produce, but the activity of the various genes is subject to a range of different controls, from other genes as well as from their RNA and proteins products and, to properly describe the genetic processes, the biological sciences need to apply a systems-oriented approach that can account for interactions among the various controls and for the time-dependent phenomena they generate.

Chronic progressive disorders such as cancer, depression and diabetes may be related to genetic factors but are also associated with risk factors such as smoking, alcohol consumption, lack of physical activity, and stress. One can try to find explanations in the genetic factors, or one can investigate the significance of the various risk factors. However, diseases of this type can seldom be ascribed to a single cause. More likely, they develop through shifts in essential biological balances, leading to the gradual disruption of one protective mechanism after the other. To follow up on this perspective the biomedical sciences again need to adopt a systems-oriented approach that will allow the flow of data to be structured into a consistent pattern and the causal relations to be traced from genes to cells to organs and to the organism's response to varying external conditions.

The pharmaceutical industry is clearly one of the most research intensive and best performing industries. There is an enormous demand for new and more effective drugs to treat both a variety of new infectious diseases and the many

age related diseases in the industrialized countries. So far, however, the expectation that the rapidly growing biological insight would lead to new and more effective drugs at lower costs has not materialized. The enormous costs associated with the development of a new drug are primarily related to the large number of tests that a drug candidate must undergo to demonstrate its efficacy and prove its lack of adverse side effects. If the cost of drug development could be significantly reduced it would become economically feasible to develop drugs for rare diseases, and new possibilities would open up for the development of drugs against many of the serious diseases that plague the less developed countries.

As emphasized by the European Federation of Pharmaceutical Sciences (EUFEPS) in its report on "New Medicines Faster", the pharmaceutical industry is in need of new predictive approaches that can utilize the information available in the individual test more effectively and thus reduce the number of animal and human tests required to prove efficacy and lack of toxicity. The use of mechanism-based computer models will allow the results of each new test to be interpreted directly in the context of already existing knowledge. *In silico* modeling also provides an effective means to reveal theoretical misconceptions or data inconsistencies. By adjusting parameter values, computer models can provide us with valuable information about the function of a new drug under situations that have not previously been experienced, and models can be designed to identify adverse effects that are linked, for instance, to particular groups of patients. This is also important in connection with the development of drugs for pregnant women and small children where experimentation is excluded for ethical reasons. At the same time, there is a strong wish in the industry, as well as in the broader society, to reduce the need for animal experiments in the drug development process.

By developing detailed dynamic and quantitative models of the biological processes and regulatory mechanisms, Systems Biology aims at providing the insights needed to establish an integrated understanding of life and living organisms. Such models will allow us to accumulate information from experiment to experiment and to start to make extrapolations and quantitative predictions under conditions where measurements have not yet been performed. How far and how fast we can proceed with the development of biological models is heavily debated amongst leading scientists in the field. Serious attempts are made to establish a so-called "Virtual Physiological Human", i.e., a large scale computer model that integrates mathematical descriptions of the (main) physiological (and biochemical) processes across the hierarchical levels of the human organism. This is clearly a fantastic project that will require contributions from a broad range of different disciplines.

The aim of the present book is to illustrate how *in silico* modeling can be used as a platform for the development of personalized and more effective treatments of patients in the healthcare sector and of new and safer drugs in the pharmaceutical industry. As used in the book, the term "Biosimulation" is largely synonymous with "Systems Biology", perhaps with a somewhat stronger emphasis on applications to concrete problems in health care and drug development. At the same time, the book gives significant attention to the unusual problems arising from the complexity in the behavior of living systems.

The book is based on work performed by partners of the Network of Excellence in "Biosimulation – A New Tool in Drug Development" (or "BioSim"). The BioSim Network grew out of the above mentioned realization by the European pharmaceutical industry that, in spite of rapidly increasing investments in research and development, the fantastic breakthroughs in gene technology and other areas of biological research failed to materialize in the form of new effective drugs at the expected rate. The Network was established under the Life Sciences, Genomics and Biotechnology for Health Thematic Priority Area of the 6th European Framework Programme on December 1, 2004 and, after a four month extension, the activities ended on March 31, 2010. During the five years of EU-sponsored activities, Network partners published nine books on different aspects of "Systems Biology", "Biomedical Modeling", "Pharmacology" and "Complex Systems Theory". The Network also edited five special issues of different international journals and published close to 800 scientific papers.

With its 29 academic partners, 5 small and medium-sized enterprises, Novo Nordisk, and the Medicines Agencies of Spain, the Netherlands, Sweden and Denmark, BioSim represented an unusual combination of expertise from a broad range of biomedical fields, including genetics, biochemistry, cell biology, physiology, and pharmacology. Several of the participating groups had more than 20 years of experience in biomedical modeling, and much of Europe's expertise in the area of complex systems theory was associated with the Network. BioSim also involved partners with expertise in pharmacokinetics, bioinformatics and drug development as well as hospital departments that performed experimental, model-based treatments of patients with cancer and Parkinson's disease. The regulatory agencies took part in simulation studies of bioavailability and bioequivalence of different drug formulations, particularly drugs with active metabolites. The Danish Medicines Agency, in particular, was involved in a study of subcutaneous insulin absorption [1].

Some of the Network's most impressive results were achieved in the areas of model-based treatment of cancer and Parkinson's disease. Chronotherapy of cancer, for instance, is an approach in which the anti-cancer drugs are administered according to a well-defined schedule that follows the biological rhythms of the patient, e.g., the 24-h circadian cycle. The potential benefits of this approach arise from the tendency of both the cell division rate and the toxicity of many anti-cancer drugs to vary in step with specific phases of the circadian rhythm. The BioSim group at Hôpital Paul Brousse in Paris has demonstrated, for instance, that an 8 h shift in dosing time may cause an eight-fold increase in tolerability for more than 30 different anti-cancer drugs, and the group successfully exploits this insight to design personalized treatments of patients with intestinal cancer.

Mechanism-based modeling and simulation is used successfully in practically all other industries, and the potential benefits that can be achieved through the application of similar approaches in both the health care sector and the pharmaceutical industry seem enormous. The difficulties that face the development of biomedical models typically stem from the extreme complexity of living systems. The first significant problem is the fantastic interconnectedness of biological processes and

the huge number of processes that take place in each individual cell, as well as among the cells and at higher levels of the physiological system. The human genome, for instance, codes for about 90,000 different proteins, and the number of possible interactions that can take place between the genome and its RNA and protein products goes beyond our wildest imagination. At the same time the biological regulatory mechanisms involve enormous ranges in time and space, ranges that by far exceed the capacity of even the fastest computer.

The way the book proposes to deal with these problems is through a careful definition of the system boundary and time horizon for the study. In many cases this implies that a new model has to be formulated if the time scale or other essential aspects of the problem change. The response of the pancreatic insulin secretion to a meal is not the same problem as the metabolic regulation considered over a couple of days, and these problems are not the same as the development of type-II diabetes through insulin resistance of the muscle and fat cells, or the appearance of late complications of diabetes. It is essential that a modeler realizes the difficulties associated with these problems, and the initial chapters of the book provide detailed discussions of how to distinguish between what to include and what not to include in a particular model.

Another and presumably less recognized factor contributing to the biological complexity derives from the fact that living systems from the point of view of physics operate under far-from-equilibrium conditions. This implies that many of the regulatory feedback mechanisms are unstable and generate self-sustained oscillatory dynamics or even more complicated behavior. As described in this book, instabilities and nonlinear dynamic phenomena are in many ways the very signature of life. Rhythmic signals are essential to allow the cells to organize their internal functions and to communicate with neighboring cells. Besides neurons, which are known to sustain electrical pulses that travel over macroscopic distances, many other cells exhibit complicated patterns of spikes and bursts in their membrane potential, and these variations are again coupled to the intracellular calcium dynamics and to metabolic oscillations.

The book on "Biosimulation in Biomedical Research, Health Care and Drug Development" attempts to provide the reader with a feel for the enormous potential for *in silico* modeling in the biomedical sciences and their applications. The book provides a variety of different models of cellular systems, including systems of interacting smooth muscle cells, nerve and heart cells. The book also discusses both intra-cellular signaling through localized bursts in the calcium concentration and the response of fat cells to a rising insulin concentration in the blood. Synchronization of the spiking activity for clusters of brain cells in patients with Parkinson's disease represents an example of the emergence of a phenomenon that leads to mal-functioning of the organism while synchronization of the oscillations of the incoming blood flow to neighboring nephrons of the kidney may be considered an element of normal physiological regulation.

In time we hope that *in silico* modeling, as a clear supplement to laboratory experiments, will help us reduce the number of laboratory animals in medical research by providing the same and additional information with fewer and more

well-designed experiments. In the US the FDA advocates the use of computer simulation models, however there is still a need to conduct experiments on animals and humans in order to provide safe medicines. In Europe the regulatory process of approving new drugs does not yet provide the opportunity to include models in the documental material. However, we follow the developments of the use of simulation models in the drug development process with interest.

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# Chapter 1
# Modeling in Biomedical Research and Health Care

**Steen G. Dawids, Jakob L. Laugesen, and Erik Mosekilde**

*Modeling is a means to make better experiments, and to learn more from the individual experiment.*

## 1.1 Efficiency, Safety and Money, and the Challenge to Science

The fantastic development that the biomedical sciences and technologies continue to undergo makes it possible to offer treatments for an ever growing range of diseases and conditions. With the costs of health care in most countries rising faster than the National Product, the limits to this process in many cases will be set by the available resources. From an economic point of view, the efficiency of the health care sector is often linked to standardization of treatments and increased specialization of hospitals and hospital departments. From a medical point of view it is obviously linked to the development of new and more effective treatments and of faster and more accurate diagnostic tools. However, the cost associated with this process clearly depends on our ability to make effective use of the information available from experimental and clinical work.

The pharmaceutical industry also plays a role in this picture. Economically, the pharmaceutical industry is one of the best performing industries in the World.

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Compared to many other industries, the pharmaceutical industry is very research intensive, and there is an obvious need for new, effective drugs to treat both the serious diseases that plague the populations in many less-developed countries and the lifestyle and age-related diseases that become increasingly common in most industrialized countries. Yet, the pharmaceutical industry experiences significant pressures associated with the rapidly growing costs and enormous risks of drug development. Estimates of the typical costs of developing a new drug run as high as 1 billion Euro, and a major part of these costs derives from the large number of tests that a drug must undergo to prove its efficacy and demonstrate its lack of adverse side effects. Again, a more active use of modeling could presumably cut the costs significantly.

At an early stage in the model development process, i.e., as long as the available information is relatively scarce, data-driven modeling is often the most efficient approach. With this modeling technique one extracts information about the system by fitting one or more parameterized curves to the available data. However as knowledge about the system accumulates a state will be reached at which it becomes more efficient to interpret the experimental results directly in a framework of already existing information.

The so-called mechanism-based modeling approach allows information from different sources to be integrated into a consistent structure. Moreover, since the parameters of mechanism-based models have clearly defined biological interpretations, the models can continuously be improved and expanded as new information becomes available. The main idea of this approach is to represent the biological mechanisms underlying a given phenomenon as directly as possible. At the same time, the modeling process should enter into a continuous feedback process with experimental and clinical work so that the predictions of the models are continuously tested through new experiments, and the results of such experiments are used to correct the models. As we shall try to demonstrate in the different chapters of this book, the use of *in silico* models represents an obvious means to develop effective treatments that respect both the biological parameters and conditions of the individual patient. At the same time the book will try to illustrate how the use of modeling and simulation can lead to a more rational approach to drug development, hence allowing the development costs and times for new drugs to be reduced.

Besides their system's nature, by which we refer to the enormous number of interacting feedback mechanisms that control the biological processes over time scales from fractions of a second to years, living organisms are characterized by their self-generated and sustained activity in the form, for instance, of genetic clocks, of the complex spiking and bursting dynamics by which the cells organize their internal processes and communicate with one another, and of the waves and pacemaker activities in the brain. The multitude of functional levels in the hierarchical physiological system and the structural heterogeneity of many tissues represent other sources of complexity, and it is probably correct to say that we dispose of neither the physical concepts nor the mathematical tools to cope with biological complexity in a proper manner.

Formulation of a mechanism-based and systems-oriented description of the human organism in this way becomes one of the most challenging areas of science, and one can easily imagine that the study of living systems becomes a major source of inspiration for both mathematics and physics. We should not forget, however, that modeling is a way to learn and understand, and that there are many problems in biomedical research, health care and drug development where application of formal modeling approaches already has made significant contributions. To illustrate the scope of such contributions, the following sections of this chapter will present a few examples.

## 1.2 Optimization of Dialysis

Early examples of biomedical simulation models were applied already in the mid 1970s in connection, for instance, with the treatment of patients with kidney failure [5, 6]. It is well-known that the kidneys play an important role in maintaining a proper environment for the cells in the body. In particular, the kidneys control the plasma osmolality (i.e. the total concentration of solutes in the blood), the proportions of the various solutes, and the extracellular volume. The kidneys also play a role in the regulation of the blood pressure, both through the excretion of surplus water and via the production of hormones that, together with hormones produced by other organs, regulate the peripheral resistance of the vascular system.

Degradation of proteins by the cellular machinery leads to waste products that, in higher concentrations, are poisonous to the body and, hence, must be removed. For patients with impaired kidney function, the metabolic end products accumulate in the blood and, together with other compounds (potassium, phosphate, drug metabolites, etc.) that are normally excreted with the urine they will lead to the death of the untreated patient.

Hemodialysis is one of three possible treatments that, besides kidney transplantation, also include so-called peritonealdialysis. In hemodialysis blood from the patient flows through a filtering device (an artificial kidney) where waste products are filtered out and surplus fluid removed before the blood is returned to the patient. Peritonealdialysis does not require an artificial kidney, but exploits one of the organisms own membranes (the peritoneum) as the filtering membrane.

Hemodialysis typically requires that the patient comes to a hospital department 2–3 times a week. Each treatment takes of the order of 4–5 h, during which time the patient's blood passes 10–15 times through the artificial kidney. The treatment has a number of side effects, such as nausea, vomiting, spasms, and drop in blood pressure, side effects that typically occur $\frac{1}{2} - 1$ h after the treatment is started. These side effects are likely to arise from osmotic unbalances between the blood plasma and the extracellular fluid volumes of the body induced by the treatment. The faster the dialysis is performed, the larger the unbalances will be, and the more severe the side effects are. On the other hand, both the patient and the hospital department are obviously interested in performing the dialysis as fast as possible.

Today the treatment has been standardized but it is still associated with the above side effects. However during the early years of hemodialysis, computer simulation models were helpful tools to examine the diffusion of the various compounds across the boundaries of the relevant compartments and to identify the critical processes and parameters in the system [5, 6]. Besides the initial concentrations of the various compounds in different spaces, the main parameters of such models are the volumes of the different compartments and the diffusion capacities that determine the rate of flow from one compartment to another. An obvious problem that we often meet in the modeling of biological systems is that the compartments themselves change in size during the treatment. As we shall see, this has specific ramifications for the choise of variables.

As mentioned above, application of a mechanism-based approach in general implies that the parameters have a direct biological interpretation and can be determined experimentally independently of the model. At the same time the presence of the same feedback regulations in the model as in the biological system implies that the parameters in general do not need to be known with a very high precision. It is therefore likely that many of the parameters required for a personalized dialysis can be obtained simply by adjusting standard parameters in accordance with biological indicators such as gender, weight, lifestyle, etc.

A few critical parameters should be measured for the individual patient, but as soon as the model has been developed and tested for a number of patients, one can start to make predictions for new patients. In the beginning, such "predictions" should, of course, only be accepted as guidelines for the optimization of the treatment. However, as the model is gradually improved through comparison of its predictions with the course of actual treatments, confidence in the model predictions will soon increase. In this way the main purpose of the modeling approach becomes to help identify the critical parameters.

Between the sessions, waste products such as urea, phosphate, urate and creatinine will accumulate in the patient's organism. Extended to account for the rates at which the different waste compounds are produced and perhaps also adjusted for the longer time horizon of the new problem (a week rather than 5 h), the model could be used to optimize the length of the individual session and the interval between sessions.

## 1.3 Safe Operation of Anesthetic Systems

As another example of a physiological model from approximately the same time we may mention the use of computer simulations to better understand the response of the human respiratory system to sudden changes in physical activity or to restrictions of the oxygen supply in connection, for instance, with gas anesthetics or with the use of diving and fireman's equipment (Fig. 1.1) [8].

Application of the anesthetic systems available in the 1970s could involve a variety of complications and potentially dangerous situations in connection, for

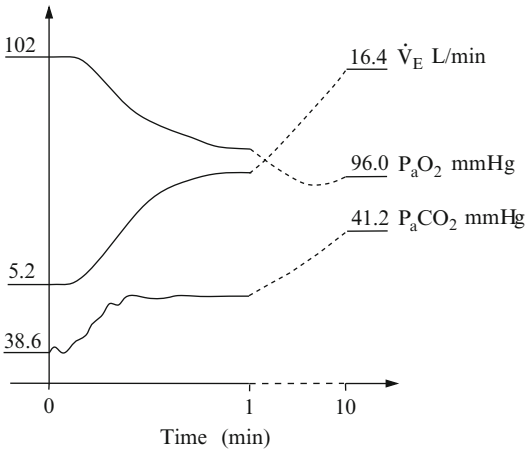


**Fig. 1.1** Dynamic responses of the ventilation $\dot{V}_E$, the arterial oxygen pressure $P_aO_2$, and the carbon dioxide pressure following a sudden reduction in the fresh gas flow from 30 to 6 l/min at time 0. Note particularly the dramatic increase in ventilation form 5.2 to 16.4 l/min. This increase is the result of a positive feedback caused by re-breathing. (In the medical terminology applied here, a dot over a variable identifies it as a flow)

instance, with incorrect adjustments of the fresh gas flow. For the so-called Hafnia A anesthetic system, removal of the expired gas (i.e., the mixture of surplus anesthetic gasses and expiration air) was controlled directly by the flow of fresh gas with a 4–6 l rubber bladder as a temporary storage to smoothen the respiratory flow and pressure variations. If the fresh gas flow fell below a certain threshold value, the patient would start to inspire his own expiration (a condition called "re-breathing"). The partial pressure of carbon dioxide in the patient's blood would then increase while the oxygen pressure would fall. As a result, the patient would breathe faster, thereby increasing re-breathing and starting a run-away phenomenon that might end with the $CO_2$ stifling of the patient. On the other hand there were obvious reasons to try to keep the fresh gas flow as low as possible, both to utilize the anesthetic gas effectively and to avoid unnecessary contamination of the operation theater.

This optimization problem is an example where clinical experiments must be kept at an absolute minimum as one cannot deliberately expose a test person to life-threatening situations. Moreover, since anesthesia seldom is applied repeatedly to the same person, it is not possible by trial and error to gradually optimize the fresh gas flow to the individual patient. Computer simulation of the interaction of the anesthetic system with the human respiratory system thus represents a valuable tool to understand the dynamics of the problem and determine the critical parameters that control the onset and temporal development of the run-away phenomenon (Fig. 1.2).

With this purpose, a simulation model was developed [8] to follow the flows of oxygen and carbon dioxide through the various compartments of the body, the air ways, and the anesthetic system. The model included detailed descriptions of the exchange of the two gasses both in the lungs and in the oxygen consuming