

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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