Preface

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This special issue of the *Journal of Biological Physics* presents nine different facets of the research which is presently being conducted by the participants of the BioSim Network. BioSim (www.biosim-network.net) is a Network of Excellence under the Life Sciences, Genomics and Biotechnology for Health Thematic Priority Area of the 6th European Framework Programme. The Network was initiated on December 1, 2005 through a grant from the European Commission. The immediate goal of the Network is to develop a modelling and simulation approach that can help the pharmaceutical industry achieve a more rational drug development process. In a broader perspective, the Network aims at contributing in an essential manner to the development of an integrated and quantitative understanding of biological processes.

The BioSim Network includes a total of 40 partners, out of which 26 are academic research groups from various universities throughout Europe and nine are small and medium sized enterprises (SMEs). Novo Nordisk is the only large industrial partner, but many of the academic research groups and the SMEs individually maintain strong collaborations with the pharmaceutical industry. The Network also includes the regulatory agencies from Denmark, Holland, Sweden and Spain.

The SMEs are involved in a variety of different activities from the development of new simulation software for testing candidate drugs. One particular project aims at developing a ‘virtual population’ that can serve as a useful representation of the variability of human responses to various drugs. Half of the academic groups are primarily experimentally oriented, and the other half cover many forms of modelling expertise. The biological groups provide insights into genetics, biochemistry, cellular biology, pharmacology, endocrinology, neurology and physiology, and the Network also involves hospital departments that perform experimental treatments of depression, various forms of tremor, and cancer. Among the theoretical areas of expertise that the Network commands are bioinformatics, systems biology, network

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theory, statistical physics, nonlinear dynamics and complex systems theory, as well as pharmacokinetics and trial planning. In this way the Network has tried to establish the platform for a fruitful interdisciplinary collaboration.

BioSim has defined its efforts in relation to six main activity areas. One area covers communication with the public and simulation for the regulatory agencies. The purpose of our activities in this area is to create a broader understanding of the perspectives that biosimulation offers and the difficulties that the approach involves. Another area emphasizes different methodological issues while the remaining four areas focus on diabetes, cardiovascular diseases, mental disorders and cancer. The idea is to model the underlying physiological, pathological and pharmacological processes at different time scales and different biological levels. The activity area for diabetes, for instance, involves cellular metabolic aspects of the development of the disease, the electrophysiological activity of pancreatic α - and β -cells, interactions between fat and glucose metabolism, effects of exercise and prenatal nutrition, test procedures for new insulin variants, and disease lifecycle modelling.

In total we have defined 19 projects (workpackages) to cover the different aspects of the six activity areas. In the area of mental diseases, for instance, the Network activities encompass the treatments of depressive disorders as well as various forms of tremor, and in the area of hypertension our activities include the development of integrated heart models as well as studies of interacting nephrons in the kidney. Our methodological activities include the development of new techniques for analyzing nonlinear phenomena in nonstationary time series, studies of the effect of noise on cellular function, methods to identify genetic feedback networks, and investigations of synchronization in coupled oscillator systems. The papers published in this special issue provide examples of these different activities.

The pharmaceutical industry is obviously one of the best performing industries. At the same time, there are enormous needs for new and better treatments of a large variety of different diseases. However, a major problem that faces the industry is the significant financial risk associated with the development of a new drug. The development costs often run as high as 800 million Euro, and the development time may be as long as 10–12 years. To make the situation even worse, two out of three drugs fail in the final test because of toxicity or lack of efficacy. In spite of significant increases in the industry's R&D budget, the last decade has shown clear signs of stagnation or even decrease in the number of new molecular entities approved. The conclusion is that a more rational approach to the development of new drugs must be found, and *in silico* modelling clearly presents itself as one of the most obvious candidates.

As mentioned above, the BioSim Network aims at developing insights, concepts and illustrative examples that can help the industry replace its classical trial-and-error approach by an approach in which mathematical modelling and simulation are used as essential tools throughout the drug discovery and development process. The goal is not necessarily to develop large and 'complete' models, neither of the human body as such, nor of specific diseases or organs. Rather, the goal is to introduce modelling and simulation as natural tools in the initial selection of new drug candidates, in the planning of *in vitro* and *in vivo* trials, and in the interpretation of the obtained results. Correctly applied, this approach should allow pointless lines of research to be exposed – and ineffective or toxic drug candidates to be 'killed' – at an early stage of the process.

From a scientific point of view, the challenge of biosimulation lies in the fantastic structural and functional complexity of the living systems. This complexity is partly associated with the large number of competing, reinforcing and mutually substituting feedback regulations, that operate over a broad range of temporal and spatial scales. This is again associated with the large number of hierarchical levels involved in the functioning of the human body, from the level of molecular processes and cellular metabolic networks, over intracellular transport processes, endocrine and neural regulations, to the control of functional units. Each time the description passes from one level to the next, new phenomena tend to arise from interactions of the units of the lower level, and it is presumably correct to say that we have neither the physical concepts nor the mathematical and computational tools to describe this complexity in detail. Moreover, from a thermodynamic point of view, living systems operate under far-from-equilibrium conditions. As a result, many feedback regulations are unstable and produce self-sustained oscillatory dynamics. Interaction between such oscillations can lead to an enormous variety of complex dynamic phenomena, including different forms of bifurcations, synchronization, wave propagation, transitions to chaos, and unusual responses to noise.

The papers published in this issue of *Journal of Biological Physics* illustrate many of these phenomena. At the same time, we have tried to maintain a close relation to experimental and clinical work. To us, the term biosimulation denotes the practical use of the concepts and ideas of systems biology.

In the first paper, Brazhe *et al.* (Unraveling Cell Processes: Interference Imaging Interwoven with Data Analysis) show how application of the newly developed technique of interference microscopy combined with wavelet analyses of the measured time series can be used to unravel cellular processes. Applied to erythrocytes, this approach can reveal reorganization of the cytoskeleton and inhomogeneities in the distribution of hemoglobin. Applied to neurons, the approach can reveal intercellular compartmentalization and submembrane structures as well as dynamical phenomena associated with changes in membrane fluidity, binding of submembrane Ca^{2+} , vesicle transport processes, etc. By studying different cell types, the authors have been able to deduce the mechanisms underlying some of the oscillatory processes, and the applied double-wavelet analysis can be used to detect how one oscillatory component modulates the frequency and amplitude of the other components.

In the second paper, Diderichsen and Göpel (Modelling the Electrical Activity of Pancreatic α -Cells Based on Experimental Data from Intact Mouse Islets) develop what appears to be the first model of the glucagons-releasing pancreatic α -cell. In contrast to the well-known bursting dynamics of insulin-secreting β -cells, α -cells do not display electrical activity in their normal state. On the basis of data from detailed patch clamp experiments on cells in intact mouse islets, the α -cell model describes the regulation of two different types of Ca^{2+} -currents, three K^{+} -currents, a voltage-gated Na^{+} -current, and an unspecific leak current. For each of these currents, the variation in the open probability is measured as a function of the relevant gating variable, and the time constants associated with the opening and closing of the ion channels are determined.

The model of Diderichsen and Göpel is tested by its ability to reproduce experimental results obtained in the presence of different concentrations of the anti-diabetic drug tolbutamide. This drug causes the ATP-gated K^{+} -channels to close and the α -cell to depolarize. In an intermediate range, both the model and the α -cell

itself display fairly irregular spiking dynamics. At larger depolarization, the spiking behavior ceases, and this change is also reproduced by the model. By substituting relevant parameter values, the model is finally applied to simulate the behavior of somatostatin releasing δ -cells.

To maintain cellular homeostasis, intracellular proteins must be degraded once their function is completed. Assuming that the lifetime of a typical protein in the cell is about 5 min, one can estimate that on the order of 10^{19} protein molecules must be degraded every minute in the human body. This function is performed by specialized enzymes, the proteasomes, of which each cell contains something like 500,000. The proteasomes also serve to destroy abnormal or misfolded proteins, and they produce the antigenic peptides presented at the surface of T4-lymphocytes and macrophages in order to stimulate other components of the immune system in response to infection by a foreign pathogen. Proteasome malfunctioning may be related to the development of type-I diabetes as well as to various neurodegenerative disorders and ageing.

The cleavage pattern and the length distribution of the produced peptides are considered as important characteristics of the degradation process. In the third paper, Zaikin and Kurths (Optimal Length Transportation Hypothesis to Model Proteasome Product Size Distribution) consider the translocation features of the 20S proteasome in order to explain typical length distributions for the produced protein fragments. A basic assumption is that transport through the proteasome depends on the length of the fragment such that there is an optimal length at which transport is most efficient. By means of a simple one-channel representation of the proteasome, the authors show how this transportation hypothesis can explain both the one-peak and the three-peak length distributions observed experimentally. As a possible mechanism for the protein translocation they suggest a fluctuation driven transport.

Understanding the side effects of a drug is one of the most challenging problems in pharmacology. This requires significant insights into the functioning of the drug at many different levels of biological systems, particularly if the purpose is to predict the side effects of a new molecular entity. Aspirin (or acetyl salicylate) is a commonly used painkiller that is particularly effective for rheumatic pains and which can be bought without prescription in drugstores as well as in supermarkets. The drug is also known to have beneficial effects in relation to development of thromboses. Unfortunately, salicylate interferes with the metabolic processes of the cell, and overusage can lead to toxic effects, particularly in liver cells.

In the fourth paper, Mogilevskaya *et al.* (Kinetic Model of Mitochondrial Krebs Cycle: Unraveling the Mechanism of Salicylate Hepatotoxic Effects) use *in silico* simulation to study the effect of salicylate on cellular energy metabolism. Based on available knowledge about the enzymatic processes and the relevant kinetic parameters, the authors identify the crucial points of influence on the mitochondrial Krebs cycle, and they show how the flux in the salicylate-inhibited Krebs cycle can be partly reestablished through external supply of glutamate and malate and through reduction of the external concentration of α -ketoglutarate and the internal concentration of glycine. Hence, the model shows that it may be possible to avoid the adverse side effects of high doses of aspirin.

Bruggeman and Westerhoff (Approaches to Biosimulation of Cellular Processes) present an overview of some of the different model types, simulation methods, and

theoretical approaches that are presently in use in the quantitative description of cellular processes. The paper first describes how molecular interaction networks can be represented by means of stoichiometric, topological, or kinetic models. Formulation of kinetic models using either mesoscopic (stochastic) or macroscopic (deterministic) equations is discussed. Situations can also occur in which most of the processes in a system can be discussed macroscopically, but a few rare events require a stochastic approach. The paper continues to describe how detailed models of molecular interaction networks (silicon cells) can be established on the basis of kinetic parameters for the cellular processes. The analysis of the response of the mitochondrial Krebs cycle to salicylate (Mogilevskaya *et al.*) is an excellent example of this approach.

Bruggerman and Westerhoff review some of the theoretical methods available to analyse kinetic models and determine the appropriate parameter values from experimental observations. Cell biology deals with a broad range of different problems, including metabolic and electrophysiological processes, protein degradation and immunological processes, hormone production and secretion processes, cell-division processes, etc. The type of model to be used in each particular case must depend on the problem at hand and on the information available about the involved processes and the associated parameters. A biological model is never complete in the sense that it can reproduce all the processes in the considered system. However, the model may still be useful to the extent that it answers relevant questions. The pancreatic α -cell model (Diderichsen and Göpel), for instance, provides a useful representation of electrophysiological processes. However, it does not describe how the α -cell detects variations in the extracellular glucose concentration (or in other external variables) and how glucagon secretion takes place.

In their paper on β -cell glucose sensing, Korsgaard and Colding-Joergensen (Time-Dependent Mechanisms in Beta-Cell Glucose Sensing) address precisely this type of problem. In contrast to the assumption of many models in the field, the relation between plasma glucose concentration and insulin release according to this study is not simple, but a number of time-dependent mechanisms appear to modify insulin release, both at a short and a longer time scale.

The paper describes glucose sensing in terms of the dynamics of glucokinase, the key enzyme which controls the first step in the glucose metabolism, the phosphorylation of glucose to glucose-6-phosphate. Three time-dependent phenomena are involved. The fastest, corresponding to the initial pulse of insulin release, is a delayed negative feedback that regulates the glucokinase activity. Due to this delay, a rapid increase in plasma glucose concentration will cause a burst of activity in the glucose sensing system until, after about 10 min, the glucokinase is down-regulated. The second mechanism involves the transformation of glucokinase from an inactive to an active form. As this transformation is controlled by the products of the glucokinase reaction, rather than by the substrate (glucose), the mechanism produces a positive, but saturable, feedback. Finally, the release of insulin granules is assumed to be enhanced by previous glucose response, giving a so-called glucose memory to the β -cells. This effect depends on the insulin release of the cells and produces a second positive, saturable feedback system.

Taken together, the three phenomena describe most of the characteristics of the glucose sensing and insulin releasing behavior of the β -cells. The model shows that the release of insulin is not a unique function of the plasma glucose concentration. It

is a consequence of the model assumptions that the β -cells will continue to increase the release of insulin until the plasma glucose is back to its normal level. This type of integral control has the advantage that the precise value of the glucose sensitivity of the β -cells is less important. By virtue of the somewhat unusual assumptions of this model, the authors are very careful in presenting the model building and the underlying assumptions step by step.

In the following contribution, Majtanik *et al.* (Desynchronization in Networks of Globally Coupled Neurons with Dendritic Dynamics) consider the desynchronization process in a network of globally coupled neuron models with dendritic dynamics. This type of analysis is essential for the development of an effective treatment of Parkinsonian (and other forms of) tremor by means of deep brain electrical stimulation. The authors show that the pulse-based desynchronization techniques, originally developed for networks of globally coupled phase oscillators (the Kuramoto model), can be adapted to networks of neurons with dendritic dynamics. Compared to the predictions of the Kuramoto model, however, the dendritic dynamics significantly alter the neuronal response. With intermediate stimulation amplitudes, the individual neurons displays bistability. For certain initial phases of the stimulation signal, the neuron only modulates its firing dynamics, while for other initial phases it stops oscillating all together.

Significant changes are also observed in the stimulation-induced transients. These transients, which continue after the end of the stimulation, cause maximum desynchronization to occur with some delay after the stimulation has been turned off. To account for this effect the authors have previously designed a calibration procedure for finding the stimulation parameters that produce optimal desynchronization, and they have also developed a new desynchronization technique based on low frequency entrainment. With proper modifications, both the calibration procedure and the low frequency stimulation technique can be adapted to systems of nerve cells with dendritic dynamics. In the coming years we are likely to see a development where the modelling of interacting nerve cells becomes more and more realistic. It is extremely impressive, however, to see how much progress analyses of the simple Kuramoto model have allowed.

Over the past decade, bioinformatics has developed a number of tools by which one can predict to what part of a microbe (the epitope) the immune system will react. Many such epitopes have subsequently been identified experimentally. At the same time, simulation models have increasingly been used to describe the dynamics of different immune cell populations and their interactions with various microbes. Simulation models are particularly useful when temporal phenomena are of significance, e.g., the initial response and subsequent phases of the immune reaction to an infection or, in the case of an HIV-infection, the response to a secondary (opportunistic) infection.

In their contribution, Rapin *et al.* (Integrating Bioinformatics and Systems Biology for Modelling of the Immune System) outline a framework for integration of the two approaches. As an example, the authors develop a model in which the dynamics of the immune system in response to an HIV-infection is correlated with genomic data. For the first time, the characteristics of wild type and mutated virus are assessed by means of a sequence-dependent scoring matrix (derived from a BLOSUM matrix) that links protein sequences to growth rates of the virus in the mathematical model. The authors conclude that an approach that combines the strengths of bioinformatics

and systems biology can lead to a better understanding of immune system-related diseases.

In the last contribution to this issue, Holden *et al.* (The Virtual Ventricular Wall: A Tool for Exploring Cardiac Propagation and Arrhythmogenesis) develop a model of the ventricular wall as a tool for exploring signal propagation and the development of arrhythmias in the hearts of individual patients. Methods for experimental and clinical investigations of cardiac arrhythmias are limited to inferring propagation within the myocardium from surface measurements or from a few electrodes within the cardiac wall. Biophysically and anatomically detailed computational models of cardiac tissues offer a powerful way of studying electrical propagation processes and arrhythmias within the virtual heart.

In their contribution, Holden *et al.* use virtual tissues to study and visualize the effects of normal and pathophysiological conditions as well as of pharmacological interventions on transmural propagation in virtual ventricular walls. The authors illustrate the automated construction of a virtual anisotropic ventricle from Diffusion Tensor Magnetic Resonance Imaging for individual hearts and use it to explore mechanisms leading to ventricular fibrillation. They conclude that the virtual ventricular wall provides an effective tool for exploring, evaluating and visualising processes during the onset and further development of ventricular arrhythmias.

As editors of this special issue of *Journal of Biological Physics*, we would like to thank all the contributors for the professional manner in which they have demonstrated the usefulness of biological modelling and simulation. The first six papers were mainly concerned with problems at the cellular level, i.e., the formulation of silicon cell models, interactions between intracellular oscillations, protein degradation, the electrical activity of pancreatic α -cells, the glucose sensing of pancreatic β -cells, and the mechanisms of salicylate hepatotoxic effects. The last three papers have illustrated the phenomena that can arise through cellular interaction and through the interaction of immune cells with external pathogens. It is interesting to note how the different coupling schemes assumed for brain cells and heart cells lead to very different dynamic phenomena at the tissue level.