Preface

This edited volume contains a selection of chapters that are an outgrowth of the European Conference on Mathematical and Theoretical Biology (ECMTB05, Dresden, Germany, July 2005). The peer-reviewed contributions show that mathematical and computational approaches are absolutely essential for solving central problems in the life sciences, ranging from the organizational level of individual cells to the dynamics of whole populations.

The contributions indicate that theoretical and mathematical biology is a diverse and interdisciplinary field, ranging from experimental research linked to mathematical modeling to the development of more abstract mathematical frameworks in which observations about the real world can be interpreted, and with which new hypotheses for testing can be generated. Today, much attention is also paid to the development of efficient algorithms for complex computation and visualisation, notably in molecular biology and genetics. The field of theoretical and mathematical biology and medicine has profound connections to many current problems of great relevance to society. The medical, industrial, and social interests in its development are in fact indisputable. Insights and predictions from mathematical modeling are used increasingly in decision support in medicine (e.g., immunology and spread of infectious diseases, cancer research, cardiovascular research, neurological research, optimisation of medical treatments, imaging), environmental and nature management, climate problems, agriculture, and management of natural resources. Rapid developments in areas such as biotechnology (e.g., genome projects, genetic modification, tissue engineering) continue to add new focal points of activity to the field. The contributions of this volume capture some of these developments.

The volume is divided into five parts—cellular biophysics, regulatory networks, development, biomedical applications, and data analysis and model validation.

Part I deals with cellular biophysics and contains six chapters.

Kovalenko and Riznichenko consider multiparticle simulations of photosynthetic electron transport processes. In particular, a 3D model of cyclic electron transport is developed and applied to a study of fast and slow components of the reaction center of a photosystem 1 pigment-protein complex. It is demonstrated that the slow phase of

this process is diffusion-controlled and determined by the diffusion of reduced plastoquinone and plastocyanin molecules from the granal to stromal areas of the thylakoid membrane.

Knoke, et al. study the selective regulation of protein activity by complex Ca^{2+} oscillations. Calcium oscillations play an essential role in intracellular signal transduction. A particular question is how two or more classes of proteins can be specifically regulated at the same time. The question is general and concerns the problem of how one second messenger can transmit more than one signal simultaneously (bow-tie structure of signalling). To investigate whether a complex Ca^{2+} signal like bursting, a succession of low-peak and high-peak oscillatory phases, could selectively activate different proteins, several bursting patterns with simplified square pulses were applied in a theoretical model. The results indicate that bursting Ca^{2+} oscillations allow a differential regulation of two different calcium-binding proteins, and hence, perform the desired function.

Gamba, et al. focus on phase separation in eukaryotic directional sensing. Many eukaryotic cell types share the ability to migrate directionally in response to external chemoattractant gradients. The binding of chemoattractants to specific receptors leads to a wide range of biochemical responses that become highly localized as cells polarize and migrate by chemotaxis. This ability is central in the development of complex organisms, and is the result of millions of years of evolution. Cells exposed to shallow gradients in chemoattractant concentration respond with strongly asymmetric accumulation of several factors, including the phosphoinositides PIP_3 and PIP_2, the PI 3-kinase PI3K and phosphatase PTEN. An early symmetry-breaking stage is believed to trigger effector pathways leading to cell movement. Although many signaling factors implied in directional sensing have been recently discovered, the physical mechanism of signal amplification is not yet well understood. The authors propose that directional sensing is the consequence of a phase ordering process mediated by phosphoinositide diffusion and driven by the distribution of chemotactic signals. By studying a realistic reaction-diffusion lattice model that describes PI3K and PTEN enzymatic activity, recruitment to the plasmamembrane, and diffusion of their phosphoinositide products, it is shown that the effective enzyme-enzyme interaction induced by catalysis and diffusion introduces an instability of the system towards phase separation for realistic values of physical parameters. In this framework, large reversible amplification of shallow chemotactic gradients, selective localization of chemical factors, macroscopic response timescales, and spontaneous polarization arise naturally.

Brusch, et al. consider the formation of spatial protein domains of small guanosine triphosphatases (GTPases) on membranes. In particular, several mechanisms for spatial domain formation of GTPases on cellular membranes are discussed. Furthermore, a kinetic model of the basic guanine-nucleotide cycle common to all GTPases is developed and coupled along a one-dimensional axis by diffusion of inactive and activated GTPases. It is asked, whether a parameter set exists such that domain formation is possible by Turing's mechanism, i.e., purely by reactions and diffusion, and shown that the Turing instability does not occur in this model for any parameter combination. But as revealed by stability and bifurcation analysis, domain formation is reproduced after augmenting the model with combinations of two spatial interaction mechanisms:

(1) attraction; and (2) adhesion among active GTPases. These interactions can be mediated by effector proteins that bind active GTPases. The model predicts domains to disintegrate if effector binding is inhibited.

Tracqui, et al. discuss in vitro tubulogenesis of endothelial cells. The formation of new blood vessels *in vivo* is a multistep process in which sprouting endothelial cells (ECs) form tubes with lumen, these tubes being additionally organized as capillary networks. In vitro models of tubulogenesis have been developed to investigate this highly regulated multifactorial process, with special attention paid to the determinant role of mechanical interactions between ECs and the extracellular matrix (ECM). In agreement with experimental results obtained when culturing endothelial EAhy926 cells on fibrin gels, the authors define theoretical thresholds between cellular traction and active cell migration along ECM strain fields above which tubulogenesis is induced. In addition, it is illustrated how mechanical factors may provide long-range positional information signals leading to localized network formation. This provides an alternative view to the classical approach of morphogenesis based on gradients of diffusible morphogens.

Time distributions in biocatalytic systems are considered by *Kühl and Jobmann*. Formal kinetic methods to analyze biocatalytic systems are traditionally based on the law of mass action. This law involves the assumption that each molecular state has an exponentially distributed lifetime. The authors regard this assumption as unduly restrictive and propose a more general, service theory-based approach (termed mass service kinetics or briefly service kinetics). In service-theoretic terms, biocatalysts are servers and their ligands are customers. The time intervals between arrivals of ligand molecules at special service loci (active or binding sites) as well as the service periods at these loci need not be exponentially distributed; rather, they may adopt any distribution (e.g., Erlangian, hyperexponential, variomorphic). The authors exemplify the impact of nonexponential time distributions on a performance measure of wide interest: the steady-state throughput. Specifically, it is shown that nonexponential interarrival times convert hyperbolic mass action systems (whose characteristic is a hyperbolic velocity-concentration or dose-response curve) into nonhyperbolic mass service systems, and that type and extent of their nonhyperbolicity are determined by type and parameters of the interarrival time distribution. A major conclusion is that it is a questionable practice to routinely and exclusively use mass action kinetics for the interpretation and performance evaluation of biocatalytic systems.

Part II deals with regulatory networks and comprises five chapters.

Booth, et al. analyze a stochastic model of gene regulation using the chemical master equation. This equation in combination with chemical rate equations is employed as a tool to study Markovian models of genetic regulatory networks in prokaryotes. States of the master equation represent the binding and unbinding of protein complexes to DNA, resulting in a gene being expressed in a cell or not, while protein and substrate concentrations are represented by continuum variables which evolve via differential equations. The model is applied to a moderately complex biological system, the switching mechanism of the bacteriophage λ driven by competition between production of CI and Cro proteins. Numerical simulations of the model successfully move

between lysogenic and lytic states as the host bacterium is stressed by the application of ultraviolet light.

Ropers, et al. consider piecewise-linear models of genetic regulatory networks and analyze the carbon starvation response in *Escherichia coli*. The growth adaptation of *Escherichia coli* to the availability of the carbon source is controlled by a complex genetic regulatory network whose functioning is still very little understood. Using a qualitative method based on piecewise-linear differential equations, which is able to overcome the current lack of quantitative data on kinetic parameters and molecular concentrations, the authors model the carbon starvation response network and simulate the response of *E. coli* cells to carbon deprivation. This allows one to identify essential features of the transition between the exponential and the stationary phase and to make new predictions on the qualitative system behavior, following a carbon upshift.

Elo and Aittokallio present an attempt to predict gene expression by combining information from expression and promoter profiles. Gene expression microarrays have become a popular high-throughput technique in functional genomics. By enabling the monitoring of thousands of genes simultaneously, this technique holds enormous potential to extend our understanding of various biological processes. The large amount of data poses, however, a challenge when interpreting the results. Moreover, microarray data often contain frequent missing values, which may drastically affect the performance of different data analysis methods. Therefore, it is essential to effectively exploit additional biological information when analyzing and interpreting the data. In the present study, the authors investigate the relationship between gene expression profile and promoter sequence profile in the context of missing value imputation. In particular, it is demonstrated that the selection of predictive genes for expression value estimation can be considerably improved by the incorporation of transcription factor binding information.

Centler, et al. focus on chemical organization in the central sugar metabolism of *Escherichia coli*. The theory of chemical organizations is employed as a novel method to analyze biological network models. The method allows one to decompose a chemical reaction network into subnetworks that are (algebraically) closed and self-maintaining. Such subnetworks are termed *organizations*. Although only stoichiometry is considered to compute organizations, the analysis allows one to narrow down the potential dynamic behavior of the network: organizations represent potential steady-state compositions of the system. When applied to a model of sugar metabolism in *E. coli* including gene expression, signal transduction, and enzymatic activities, some organizations are found to coincide with inducible biochemical pathways.

Noé and Smith present transition networks. A transition network (TN) is a graph-theoretical concept describing the transitions between (meta)stable states of dynamical systems. The authors review methods to generate and analyze TNs for molecular systems. The appropriate identification of states and transitions from the potential energy surface of the molecule is discussed. Furthermore, a formalism transforming a TN on a static energy surface into a time-dependent dynamic TN is described that yields the population probabilities for each system state and the inter-state transition rates. Three analysis methods that help in understanding the dynamics of the molecular system based on the TN are discussed: (1) Disconnectivity graphs allow important features

of the energy surface captured in a static TN to be visualized; (2) Graph-theoretical methods enable the computation of the best transition paths between two predefined states of the TN; and (3) Statistical methods from complex network analysis identify important features of the TN topology.

Part III focuses on development and consists of five chapters.

Sekimura, et al. consider pigmentation pattern formation in butterfly wings, one of the most spectacular and vivid examples of pattern formation in biology. The authors devote their attention to the mechanisms for generating global patterns with a focus on the relationship between pattern forming mechanisms for the fore- and hind-wing patterns. Through mathematical modeling and computational analysis of *Papilio dardanus* and *polytes*, the results indicate that the patterns formed on the fore-wing need not correlate to those of hind-wing patterns in the sense that the formation mechanism is the same for both patterns. The independence of pattern formation mechanisms means that the coordination of unified patterns of fore- and hind-wing is accidental. This is remarkable, because owing to Oudemans's principle, patterns appearing on the exposed surface of fore- and hind-wing at the natural resting position are often integrated to form a composite and unified adaptive pattern with their surrounding environment.

Christley, et al. introduce an agent-based model for developmental pattern formation with multiscale dynamics and varying cell geometry. Cells of the embryonic vertebrate limb in high-density culture undergo chondrogenic pattern formation, which results in the formation of regularly-spaced "islands" of cartilage analogous to the cartilage primordia of the developing limb skeleton. The authors describe a discrete, multiscale agent-based stochastic model, which is based on an extended cell representation coupled with biologically motivated reaction-diffusion processes and cell-matrix adhesion, for studying the behavior of limb bud precartilage mesenchymal cells. The model is calibrated using experimental data and the sensitivity of key parameters is studied.

Starruß, et al. address bacterial swarming driven by rod shape. Swarming pattern formation of self-propelled entities is a prominent example of collective behavior in biology. The authors show that the rod shape of self-propelled individuals is able to drive swarm formation without any kind of signaling. The proposed mechanism is purely mechanical and is evidenced through two different mathematical approaches: an on-lattice and an off-lattice individual-based model. The intensities of swarm formation obtained in both approaches uncover that the length-width aspect ratio controls swarm formation, and that there is an optimal aspect ratio that favors swarming.

King and Franks consider stability properties of some tissue-growth models. In particular, free-boundary problems associated with biological tissue growing under conditions of nutrient limitation are formulated. Analysis by linear-stability methods, clarifying the models' stability properties, is then described.

Madzvamuse introduces a modified first-order backward Euler finite difference scheme to solve advection-reaction-diffusion systems on fixed and continuously deforming domains. This scheme is compared to the second-order semi-implicit backward finite differentiation formula, and it is concluded that for the type of equations considered, the first-order scheme has a larger region of stability for the time-step than

that of the second-order scheme (at least by a factor of ten), and therefore the first-order scheme becomes a natural choice when solving advection-reaction-diffusion systems on growing domains.

Part IV deals with biomedical applications and consists of twelve chapters.

Iomin considers fractional transport of cancer cells due to self-entrapping by fission. In particular, a simple mathematical model is proposed to study the influence of cell fission on transport. The model describes fractional tumor development, which is a one-dimensional continuous-time random walk (CTRW). Furthermore, an answer to the question of how malignant neoplasm cells can appear at an arbitrary distance from the primary tumor is proposed. The model may provide a possible explanation for diffusive cancers as well. In addition, a chemotherapy influence on the CTRW is studied by an observation of stationary solutions.

Panovska, et al. address mathematical modeling of vascular tumor growth and implications for therapy. The authors discuss the results of a mathematical model that incorporates many processes associated with tumor growth. The deterministic model, a system of coupled nonlinear partial differential equations, is a combination of two previous models that describe the tumor-host interactions in the initial stages of growth and the tumor angiogenic process. Numerical simulations show that the model captures both the avascular and vascular growth phases. Furthermore, a number of characteristic features of vascular tumor growth are recovered, such as the rate of tumor growth and the invasion speed. It is also shown how the model can be used to investigate the effects of different anti-cancer therapies.

Stein, et al. present a stochastic model of glioblastoma invasion. Glioblastoma is the most malignant form of brain cancer. It is extremely invasive; the mechanisms that govern invasion are not well understood. To better understand the process of invasion, the authors conducted an *in vitro* experiment in which a 3D tumor spheroid is implanted into a collagen gel. The paths of individual invasive cells were tracked. These cells were modeled as radially biased, persistent random walkers. The radial velocity bias was found to be 19.6 μm/hr.

A model for the morphology of the tumor vasculature is introduced by *Bartha and Rieger*. The model is based on the molecular interactions between a growing tumor and a dynamically evolving blood vessel network, and describes the transformation of the regular vasculature in normal tissues into a highly inhomogeneous tumor specific capillary network. The emerging morphology, characterized by the compartmentalization of the tumor into several regions differing in vessel density, diameter, and degree of tumor necrosis, is in accordance with experimental data for human melanoma. Vessel collapse, due to a combination of severely reduced blood flow and solid stress exerted by the tumor, leads to a correlated percolation process that is driven towards criticality by the mechanism of hydrodynamic vessel stabilization.

Clairambault, et al. present a mathematical model of the cell cycle and its circadian control. The following question is addressed: Can one sustain, on the basis of mathematical models, that for cancer cells, the loss of control by a circadian rhythm favors a faster population growth? This question, which comes from the observation that tumor growth in mice is enhanced by experimental disruption of the circadian

rhythm, may be tackled by mathematical modeling of the cell cycle. For this purpose an age-structured population model is considered with control of death (apoptosis) rates and phase transitions, and two eigenvalues: one for periodic control coefficients (via a variant of Floquet theory in infinite dimension) and one for constant coefficients (taken as the time average of the periodic case). It is shown by a direct proof that, surprisingly enough considering the above-mentioned observation, the periodic eigenvalue is always greater than the steady-state eigenvalue when the sole apoptosis rate is considered. It is also demonstrated by numerical simulations when transition rates between the phases of the cell cycle are taken into account, that, without further hypotheses, no natural hierarchy between the two eigenvalues exists. This at least shows that, if such models are to take account the above-mentioned observation, control of death rates inside phases is not sufficient, and that transition rates between phases are a key target in proliferation control.

Moroz and Wimpenny consider a bone turnover cycle model with a torus-like steady state. A quantitative understanding of the bone remodeling process is of considerable biomedical and practical biotechnological interest to support the application of layer manufacturing techniques to produce scaffolds for surgical applications. Osteoclasts and osteoblasts play a principal role in different models of the bone multicellular unit operating in bone and display a rich spectrum of behaviors. The goal of the authors is to show that it is possible to capture the cyclic dynamics of operating cells. The central idea of the mathematical model is that the regulatory nature of osteocytes is the basis of the cyclic behavior associated with the system (remodeling process) as a whole. Simulations show that for a particular range of constants, the model exhibits a torus-like quasi-steady state. Further investigation of these simulations indicates the existence of a surface in the osteoclasts-osteoblasts-osteocytes-bone space, which could be interpreted as a conservative value confirming the substrate-energy regenerative capability of the bone remodeling system. It is suggested that the nature of this recovering potential is directed against both mechanical and biochemical damage to the bone.

Plank, et al. address the modeling of the early stages of atherosclerosis. Atherosclerotic lesions are predominantly localised to arterial bifurcations and bends, and are highly correlated with areas of low wall shear stress (WSS), but the underlying reason for this localisation is not fully understood. A key role is played by endothelial cells, which regulate the transport of materials from the bloodstream to the artery wall and secrete vasoactive agents that modulate vascular tone. A mathematical model is presented, exploring the link between arterial geometry, WSS, and factors related to atherogenesis. The model simulates the cellular response to the fluid shear stress on the cell membrane and the binding of ligands to cell surface receptors. This is used to calculate the rate of production of nitric oxide (NO), which is a potent vasodilator and anti-atherogenic factor. It is hypothesised that the section of endothelium adjacent to a region of recirculating flow is most at risk of developing atherosclerotic plaque, due to reduced bioavailability of NO.

Trenado and Strauss consider magnetic nanoparticles for in vivo applications. In particular, in vivo applications of biocompatible magnetic nanoparticles in a carrier liquid controlled by an external magnetic field from outside the body have recently

been proposed for specific drug delivery, such as in locoregional cancer therapies or occlusion aneurysms. Such particles can also be used as guided contrast agents in myocardial imaging after myocardial infarction. However, the choice of the optimal clinical setting still remains a challenge for each of the mentioned applications. The authors introduce a numerical heterogeneous multiscale model that can be used for the optimal a priori determination of the free parameters and might help to overcome this problem.

Cherniha, et al. address fluid transport in peritoneal dialysis. In particular, a mathematical model incorporating water flow between the dialysis fluid in the peritoneal cavity, blood flow through the capillary wall, and homogeneous interstitium driven by high hydrostatic and osmotic pressure of dialysis fluid is formulated. The model is based on nonlinear equations of reaction-diffusion-convection type. Numerical simulations provide the distribution profiles for hydrostatic pressure, glucose concentration, and water flux in the tissue for different times from the infusion of dialysis fluid into the peritoneal cavity for different transport parameters that represent clinical treatments of peritoneal dialysis.

Sibona, et al. discuss the relevance of intracellular replication to the evolution of Chagas' disease. In particular, a model is introduced for the interaction between the parasite *Trypanosoma cruzi* and the immune system in Chagas' disease by separately describing the intracellular and extracellular parasite stages. The solution of the case where two antibody species are active is worked out in detail, and a diagram showing the differents outcomes of the model is presented. The predictions accurately reproduce experimental data on the infection evolution during the acute phase of the disease and lead to an estimate of the damage generated by direct parasite action.

Gerisch and Geris introduce a finite-volume spatial discretisation scheme for taxis-diffusion-reaction systems with axi-symmetry. In particular, the numerical simulation of a time-dependent taxis-diffusion-reaction model of fracture healing in mice using the method of lines is considered. The partial differential equation problem has an axi-symmetric structure, and this is employed to properly reduce the model to an equivalent problem in 2D space leading subsequently to an efficient spatial discretisation. Special care is given to respect conservation of mass and the nonnegativity of the solution. The numerical simulation results are contrasted to those obtained from a simplistic reduction of the axi-symmetric model to 2D space (at the same computational cost). Quantitative and qualitative differences are observed.

The information content of clinical time series is analyzed towards the development of a neonatal disease severity score system by *Menconi, et al.* In particular, a score is introduced to classify the severity of patients by analysing the information content of clinical time series.

Part V focuses on data analysis and model validation and is comprised of four chapters.

The statistical analysis and physical modeling of oligonucleotide microarrays is introduced by *Burden, et al.* Inference of regulatory networks from microarray data relies on expression measures to identify gene activity patterns. However, currently existing expression measures are not the direct measurements of mRNA concentra-

tion one would ideally need for an accurate determination of gene regulation. If the development of expression measures is to advance to the point where absolute target concentrations can be estimated, it is essential to have an understanding of physical processes leading to observed microarray data. The authors survey here the performance of existing expression measures for oligonucleotide microarrays and describe recent progress in developing physical dynamic adsorption models relating measured fluorescent dye intensities to underlying target mRNA concentration.

Bortfeldt, et al. discuss the validation of human alternative splice forms using the EASED platform and multiple splice site discriminating features. The authors have shown for a data set of computationally predicted alternative splice sites how inherent information can be utilized to validate the predictions by applying statistics on different features typical for splice sites. As a promising splice-site feature, the frequencies of binding motifs in the context of exonic and intronic splice-site flanks and between the alternative and reference splice sites have been investigated. It is shown that both partitions of splice sites can statistically be separated, not only by their distance to the splice signal consensus, but also via frequencies of splice regulatory proteins (SRp) binding motifs in the splice-site environment.

Polańska, et al. consider the Gaussian mixture decomposition of time-course DNA microarray data. Especially, the decomposition approach to the analysis of large gene expression profile data sets is presented, and the problem of analysis of transient time-course data of expression profiles is addressed. The assumption that co-expression of genes can be related to their belonging to the same Gaussian component is accepted, and it is assumed that parameters of Gaussian components, means and variances, can differ between time instants. However, the gene composition of components is unchanged between time instants. For such problem formulation the appropriate version of the expectation maximization algorithm is derived as well as recursions for the estimation of model parameters. The derived method is applied to the data on gene expression profiles of human K562 erythroleukemic cells, and the obtained gene clustering is discussed.

Simek and Jarząb discuss SVD analysis of gene expression data. The analysis of gene expression profiles of cells and tissues, performed by DNA microarray technology, strongly relies on proper bioinformatical methods of data analysis. Due to a large number of analyzed variables (genes) and a usually low number of cases (arrays) in one experiment, limited by high cost of the technology, the biological reasoning is difficult without previous analysis, leading to the reduction of the problem's dimensionality. A wide variety of methods has been developed, with the most useful, from the biological point of view, methods of supervised gene selection with estimation of false discovery rate. However, supervised gene selection is not always satisfying for the user of microarray technology, as the complexity of biological systems analyzed by microarrays rarely can be explained by one variable. Among unsupervised methods of analysis, hierarchical clustering and PCA have gained wide biological application. In the authors' opinion, Singular Value Decomposition (SVD) analysis, which is similar to PCA, has additional advantages very essential for the interpretation of biological data. The authors show how to apply the SVD to unsupervised analysis of transcriptome data, obtained by oligonucleotide microarrays.

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Andreas Deutsch (on behalf of the volume editors)