Preface

The life of multicellular organisms, such as humans and animals, is a complex dynamic process requiring the constant interaction of various molecules, cells, organs and other factors within the organism itself, and in exchange with the environment. In the human body, each cell has its specific task that is necessary to enable us to walk, breath, produce energy or fight infections. Only the tight regulation of multiple processes on various scales, be it on the genetic, molecular or cell population level, leads to the proper functioning of the complete system. Each cell on its own also represents a complex, multi-scale system that receives, processes and transmits information by cellular signalling, the production of enzymes and proteins, or by adapting their mechanical properties or cell cycle dynamics. While, step by step, we learn more and more about individual elements and processes of cellular dynamics and interactions, how these parts are connected within the complete system still remains an area of active research. Currently, some major topics of interest are the investigation of interacting processes across different spatio-temporal scales (i.e. the genetic or chemical regulation of complex cell behaviours like division, motility or ageing), the importance and effects of the inherent stochasticity in biological systems, and the integration of complex interactions of many cellular components to a stimulus or new environment leading to a single, well-defined cellular behaviour.

To better understand the processes regulating the functioning of single cells, or the interaction between cells, mathematical models provide help to formulate hypotheses in an abstract way and represent a means to make predictions. Mathematical models formalise physical and chemical laws underlying biological systems, for instance chemical reaction kinetics or diffusion. They allow the integration of elements and processes from various sources and scales in a systematic and quantitative framework, i.e. studying the interdependency of individual processes. Using these models, we are also able to quantify elements that are not directly observable in lab experiments and to identify key processes that shape the behaviour of the system.

The development of mathematical models as a tool to generate understanding of biological processes has always been driven by the progress of experimental

techniques. Novel experimental data and observations usually also require the development of appropriate mathematical methods in order to analyse and interpret these data in a meaningful way. The theoretical considerations on particle diffusion followed the development of microscopy. Similarly, one of the most famous mathematical models in biology—the Hodgkin–Huxley model describing the molecular basis of action potentials in nerves—was guided by observations based on voltage clamp, a new experimental technique that allowed to measure ion currents of neuronal membranes and control the membrane potential.

In recent years, biological sciences have experienced enormous advances in experimental techniques that allow the quantification of biological processes in more and more detail. In particular imaging technologies have improved substantially in terms of spatial and temporal resolution, also driven by the development of novel fluorescent dyes and techniques. Single molecule spectroscopy allows the visualisation and quantification of single molecules within individual cells. With life cell and two-photon imaging, as well as 3-D microscopy we are able to observe and track the behaviour of single cells within particular organs over time, or even across an entire organism. Further experimental techniques, such as high-throughput -omics technologies quantifying entire chemical subsystems of a cell (e.g. proteins, metabolic compounds or gene expression), cellular barcoding, which enables us to follow the fate of individual cells during differentiation and migration, or traction force microscopy, generate tremendous amounts and various types of quantitative data. We strongly expect that inspired by the data generated by these technologies novel mathematical models and methods have to be developed, in order to formalise and test newly generated hypotheses about biological processes, and to provide a systematic and quantitative understanding of the often complex structures and interactions across multiple scales. Without the help of mathematical models a proper quantification and interpretation of these novel types of data and observations is practically impossible. Mathematical models are essential to describe the underlying mechanistic processes spanning different spatio-temporal scales and the interaction of many biological components. They provide a more thorough understanding of the observed data than purely statistical approaches, as they go beyond simple quantitative and qualitative comparisons.

The process of mathematical model building is thereby challenging and often tedious, as many different requirements have to be considered:

1. Does the model correctly describe the experimental data?
2. Are the assumptions on the underlying biological processes plausible and how sensitive are our conclusions with regard to these assumptions?
3. Does the model comprise the minimum complexity necessary to explain all observed behaviours, or is a further reduction sensible?
4. Does the model allow predictions that can be tested experimentally and, thus, allow model validation?
5. Is a rigorous mathematical analysis of the model possible? If not, can the model be analysed numerically?

The chapters of this book contain examples of mathematical modelling approaches describing and analysing cellular systems on different scales. The different models and technical approaches depend on the biological system being investigated, and the particular question addressed. An important role plays the consideration of stochasticity within the modelling procedures.

The first chapter by Ádám M. Halász, Meghan McCabe Pryor, Bridget S. Wilson and Jeremy S. Edwards on "Spatiotemporal Modeling of Membrane Receptors" provides a detailed overview of mathematical modelling approaches for cellular processes with a specific focus on the processes involved in early signalling of membrane receptors. Mathematical modelling of chemical reactions and reaction networks is being discussed, as well as the necessity for stochastic approaches when the copy numbers of the involved compounds are small. The chapter introduces models of increasing complexity starting from simple approaches based on reaction–diffusion models up to models including specific spatial aspects such as agent-based modelling systems accounting for Brownian and non-Brownian motion or anomalous diffusion. This chapter describes and discusses classical modelling principles and approaches also used in the following chapters. It provides an introduction to the field of mathematical modelling in biology, also accessible to non-experts in the field. Elaborating on the topic of stochasticity of chemical reactions, Chapter "Distribution Approximations for the Chemical Master Equation: Comparison of the Method of Moments and the System Size Expansion"—contributed by Alexander Andreychenko, Luca Bortolussi, Ramon Grima, Philipp Thomas, and Verena Wolf—focuses on stochastic chemical kinetics. The chapter presents and compares two different approaches to estimate the probability distribution associated with the amounts of different chemical species: the indirect estimation via moment closure techniques and the direct approach using system size expansion. The two approximation methods analysed represent useful tools for the analysis of large-scale models.

The authors of Chapter "Sampling from T Cell Receptor Repertoires", Marco Ferrarini, Carmen Molina-París and Grant Lythe, address a related problem by trying to predict the complete repertoire of T-cell clonotypes, a specific type of immune cells, from a sample of a few hundred T-cells. The estimation of the size and the distribution of these T-cell clonotypes is challenging due to the total population size, which is distributed heterogeneously across the whole organism, and the immense natural variability of clonotype construction. Therefore, a large probability space needs to be estimated from extremely sparse experimental data. Using various assumptions on the underlying distribution of clone sizes, they investigate the possibility and challenges to infer the total population structure based on small individual samples.

Chapters "IL-2 Stimulation of Regulatory T Cells: A Stochastic and Algorithmic Approach" and "Understanding the Role of Mitochondria Distribution in Calcium Dynamics and Secretionin Bovine Chromaffin Cells" couple stochastic modelling of signalling processes determining cell–cell interactions and higher order cell functions, respectively. In Chapter "IL-2 Stimulation of Regulatory T Cells: A Stochastic and Algorithmic Approach" an algorithmic approach is presented by Luis de la Higuera, Martín López-García, Grant Lythe, and Carmen Molina-París to solve and analyse a

stochastic model of receptor-mediated cell–cell interactions. In the underlying biological scenario looking at the IL-2 dependency of regulatory T-cells, one cell type, i.e. effector T-cells, provides the chemical substance needed by the second cell type, i.e. the regulatory T-cells for survival. The authors provide an algorithmic approach to determine the rates at which receptor–ligand interactions are formed and thereby define cell fate. Chapter "Understanding the Role of Mitochondria Distribution in Calcium Dynamics and Secretion in Bovine Chromaffin Cells", contributed by Amparo Gil, Virginia González-Vélez, José Villanueva and Luis M. Gutiérrez, couples a stochastic description of intracellular calcium signalling with cell function, i.e. exocytosis. The regulatory relationship between signalling and function is hereby affected by the spatial distribution of cell organelles, in particular mitochondria, since they limit the diffusion of the involved components. The authors present a spatially explicit modelling scheme analysing the dynamics of intracellular components.

The book concludes with Chapters "Dynamical Features of the MAP Kinase Cascade" and "Numerical Treatment of the Filament-Based Lamellipodium Model (FBLM)", which comprise two different deterministic modelling approaches at two different scales. In Chapter "Dynamical Features of the MAP Kinase Cascade", Juliette Hell and Alan D. Rendall use a deterministic modelling approach to describe the dynamics of the MAPK signalling cascade, a widespread intracellular signalling pathway within eukaryotes. They perform a mathematical analysis of the system described by ordinary differential equations showing its qualitative behaviour under different conditions. Finally, Chapter "Numerical Treatment of the Filament-Based Lamellipodium Model (FBLM)", authored by Angelika Manhart, Dietmar Oelz, Christian Schmeiser and Nikolaos Sfakianakis, introduces a continuous model coupling cell mechanics with the dynamics of cytoskeleton components, discussing its mathematical analysis and showing corresponding numerical simulations based on a finite-element method.

In summary, the different chapters in this book address various types of mathematical models and methods to describe and analyse biological systems and processes on different cellular scales. They cover a variety of biological topics reaching from the analysis of intracellular signalling pathways to the level of cell mechanics and cytoskeleton structuring, up to the regulation of cell populations within immune responses. The different approaches demonstrate how challenging mathematical problems arise from the mechanistic description of cellular processes and interactions. The importance of the development of such models, as well as their rigorous mathematical and numerical analysis is steadily increasing in line with the progress of measurement techniques in quantitative biology. The combination of detailed quantitative measurements of increasing resolution in time and space with novel mathematical models will help us to get a systems level understanding of individual processes, and might finally lead us to a better understanding of the dynamics and regulation of cellular processes that shape life.

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