Preface

The discrete and random occurrence of chemical reactions, far from thermodynamic equilibrium, among less-abundant chemical species in single cells, necessitates stochastic approaches for modeling. Currently available texts on stochastic approaches relevant to systems biology can be classified into two categories. Books in the first category require the reader to have sufficient background of probability theory and focus directly on applications. Books in the second category take a two-step approach: first, they provide the necessary background in probability theory and then the concepts so developed are applied to model systems. We here follow the "introduce when needed" approach which is more natural and avoids distractions to the reader. While we still provide a review of probability and random variables, subsequent notions of biochemical reaction systems and the relevant concepts of probability theory are introduced side by side. This will hopefully lead to an intuitive presentation of the stochastic framework for modeling subcellular biochemical systems. In particular, we make an effort to show how the notion of propensity, the chemical master equation, and the stochastic simulation algorithm arise as consequences of the Markov property. The reader is encouraged to pay attention to this because it is not easy to see this connection when reading the relevant literature in systems biology. The nonobvious relationship between various stochastic approaches and our own struggle to find texts explaining them provided a motivation to write this book.

Throughout the text we use several examples to illustrate ideas and motivate stochastic modeling. It is shown how such systems can be studied with computer simulations, and the reader is encouraged to experiment with the programming code provided. Additionally, the cell cycle model is included as a more complex case study. Exercises in each chapter provide an opportunity to deepen one's understanding.

Another aspect of this work is a focus on analytical approaches. Most works concentrate on stochastic simulations: the exact stochastic simulation algorithm and its various improvements and approximations. This work is an attempt to complement those works on stochastic simulation approaches. The most common formulation of stochastic models for biochemical networks is the chemical master equation (CME). While stochastic simulations are a practical way to realize the CME, analytical approximations offer more insight into the influence of randomness. Toward that end, the two-moment approximation (2MA) is a promising addition to the established analytical

approaches including the chemical Langevin equation (CLE) and the related linear noise approximation (LNA). The 2MA approach directly tracks the mean and (co)variance, which are coupled in general. This coupling is not obvious in CME and CLE and ignored by LNA and conventional differential equation models.

For the advanced reader, we include a chapter at the end that deals with a general Markov process with both continuous and jump character.

Readership

The most frequently used conceptual framework to model and simulate biological systems is that of differential equations. Their widespread use is also reflected by the fact that any undergraduate course in the engineering and physical sciences, as well as many life science programs, will teach ordinary differential equations and the basics of dynamical systems theory. The book *Computational Cell Biology* by Fall et al. [42] provides an excellent treatment of modeling with differential equations, including a short introduction to stochastic modeling. As we shall argue in this book, there are natural systems for which stochastic modeling is more appropriate. We would thus hope that an advanced undergraduate student would find the material of this book accessible and helpful. As a complementary text we recommend *Branching Processes in Biology* by Kimmel and Axelrod [82] as a textbook for stochastic approaches in biology. The book focuses on branching processes, in which an entity (e.g., cell or molecule) exists for a time and then may be replaced by one, two, or more entities of a similar or different type. The book provides an excellent introduction to the theory but at the same time provides various examples that are relevant to experimentalists. Examples and application areas include the application of branching processes to polymerase chain reactions, DNA sequence analysis, cell cycle kinetics, drug resistance, and chemotherapy. With these examples and the combination of theory and practical examples it is a suitable complement for further reading to the present text.

We are well aware of the fact that stochastic modeling is less frequently, and less thoroughly covered by university courses. We admit that the material appears more abstract at first sight and takes some getting used to. We therefore encourage the reader of this book to experiment with the examples provided. To this end, we have included the code with which one can simulate these systems.

Computer Experiments

Stochastic modeling requires some of the more advanced material a graduate student encounters, and the notation alone can be daunting. To ease the pain, we have included a glossary and various examples, supported by the code

that can be used to reproduce the examples. There are numerous software tools available to model and simulate dynamical systems. For most of the examples in this book we use Matlab from MathWorks [96], including the SimBiology and Symbolic toolboxes. An alternative software, which we have also used, is Cains http://cain.sourceforge.net, a free tool that excels in computationally efficient stochastic simulations. Anyone looking for more examples of subcellular biochemical networks for modeling will find model databases such as BioModels http://www.ebi.ac.uk/biomodels-main/ and JWS Online http://jjj.biochem.sun.ac.za useful.

Supporting material for this book, including software and a list of corrections, will be provided on our website at www.sbi.uni-rostock.de

Acknowledgements

The book documents a friendship between the authors that began in 2003, when we both moved from England to Germany, forming the nucleus of the new systems biology research group at the University of Rostock. The first couple of years were stressful, and our regular scientific discussions provided a sanctuary and escape from things happening around us. Our discussions had no other purpose than to improve our understanding of a problem under consideration. The mixture of competing ideas and collaborative effort allowed us to derive pleasure from proving ourselves *wrong*. Although we were interested in a wide range of questions related to systems biology, the theme of "uncertainty" appeared in various disguises. This eventually culminated in Mukhtar's PhD thesis, which provided the starting point for this book. Stochastic modeling is a wide area with a long history in the natural sciences and physics in particular. Knowing our own limitations, we decided on a concise form, tracing our discussions over the last four years, rather than attempting the seemingly impossible task of writing a comprehensive account of existing stochastic approaches. We would very much appreciate feedback, corrections, and suggestions on the text.

During the writing of this book we received support from various sources, including the Deutsche Forschungsgemeinschaft (DFG), the German Federal Ministry for Education and Research (BMBF), the Helmholtz Gesellschaft, the European Commission, and the Stellenbosch Institute for Advanced Study (STIAS). We are grateful for the financial support and feel slightly embarrassed that our work has been such an enjoyable experience. We thank the following people for their willingness to discuss the work described in this book: Thomas Millat (University of Rostock), Hanspeter Herzel (Humboldt University, Berlin), Akos Sveiczer (Budapest University of Technology and Economics), Kevin Burrage (University of Queensland, Brisbane), Allan Muir (Llanfynwydd, Wales) and Johan Elf (Uppsala University, Sweden).

In October 2010, Allan Muir, a good friend and twice a visitor to the Department of Systems Biology & Bioinformatics at the University of Rostock, died of cancer. For most of his academic working life Allan Muir was associated with the Department of Mathematics at City University, London, where he worked mostly on game theory. He never retired from doing mathematics; his interest in math, science, and philosophy were inseparable from himself. His astonishing general knowledge, his unique style of approaching a problem through questions and thus reducing something complex to its essence, could connect seemingly unrelated things and communicate the result to the lucky ones who were allowed to tune in. He will be deeply missed.

Olaf Wolkenhauer (olaf.wolkenhauer@uni-rostock.de)
Mukhtar Ullah (mukhtar.ullah@uni-rostock.de)

Rostock, May 2011

http://www.springer.com/978-1-4614-0477-4

Stochastic Approaches for Systems Biology

Ullah, M.; Wolkenhauer, O.
2011, XXXII, 290 p., Hardcover
ISBN: 978-1-4614-0477-4