Preface

Systems techniques are integral to current research in molecular cell biology. These systems approaches stand in contrast to the historically reductionist paradigm of molecular biology. The shift toward a systems perspective was gradual: it passed a turning point at the end of the twentieth century, when newly developed experimental techniques provided system-level observations of cellular networks. These observations revealed the full complexity of these networks and made it clear that traditional (largely qualitative) molecular biology techniques are ill-equipped for the investigation of these systems, which often exhibit nonintuitive behavior. This point was illustrated in a thought experiment proposed by Yuri Lazebnik (Lazebnik, 2002). He described a (failed) attempt to reverse engineer a transistor radio using qualitative methods analogous to those used in traditional molecular biology. Lazebnik's exercise demonstrates that without a quantitative framework to describe large networks of interacting components, the functioning of cellular networks cannot be resolved. A quantitative approach to molecular biology allows traditional interaction diagrams to be extended to mechanistic mathematical models. These models serve as working hypotheses: they help us to understand and predict the behavior of complex systems.

The application of mathematical modeling to molecular cell biology is not a new endeavor: there is a long history of mathematical descriptions of biochemical and genetic networks. Successful applications include Alan Turing's description of patterning in development (discussed by Murray, 2003), the models of neuronal signaling developed by Alan Hodgkin and Andrew Huxley (reviewed by Rinzel, 1990), and Denis Noble's mechanistic modeling of the heart (Noble, 2004). Despite these successes, this sort of mathematical work has not been considered central to (most of) molecular cell biology. That attitude is changing: system-level investigations are now frequently accompanied by mathematical models, and such models may soon become requisites for describing the behavior of cellular networks.

What This Book Aims to Achieve

Mathematical modeling is becoming an increasingly valuable tool for molecular cell biology. Consequently, it is important for life scientists to have a background in the relevant mathematical techniques so that they can participate in the construction, analysis, and critique of published models. Also, those with mathematical training—mathematicians, engineers, and physicists—now have increased opportunity to participate in molecular cell biology research. This book aims to provide both of these groups—readers with backgrounds in cell biology or mathematics—with an introduction to the key concepts that are needed for the construction and investigation of mathematical models in molecular systems biology.

I hope that after studying this book, the reader will be prepared to engage with published models of cellular networks. By "engage," I mean not only to understand these models but also to analyze them critically (both their construction and their interpretation). Readers should also be in a position to construct and analyze their own models, given appropriate experimental data.

Who This Book Was Written For

This book evolved from a course I teach to upper-level (junior/senior) undergraduate students. In my experience, the material is accessible to students in any science or engineering program, provided they have some background in calculus and are comfortable with mathematics. I also teach this material as a half-semester graduate course for students in math and engineering. The text could easily be adapted to a graduate course for life science students. Additionally, I hope that interested researchers at all levels will find the book useful for self-study.

The mathematical prerequisite for this text is a working knowledge of the derivative: this is usually reached after a first course in calculus, which should also bring a level of comfort with mathematical concepts and manipulations. A brief review of some fundamental mathematical notions is included as appendix B. The models in this text are based on differential equations, but traditional solution techniques are not covered. Models are developed directly from chemical and genetic principles, and most of the model analysis is carried out via computational software. To encourage interaction with the mathematical techniques, exercises are included throughout the text. The reader is urged to take the time to complete these exercises as they appear: the exercises will confirm that the concepts and techniques have been properly understood. (All of the in-text exercises can be completed with pen-and-paper calculations; none are especially time-consuming. Complete

solutions to these exercises are posted at the book's Web site.[1]) More involved problems—mostly involving computational software—are included in the end-of-chapter problem sets.

An introduction to computational software is included as appendix C. Two packages are described: XPPAUT, a freely available program that that was written specifically for dynamic modeling; and MATLAB, which is a more comprehensive computational tool. Readers with no background in computation will find XPPAUT more accessible.

I have found that most students can grasp the necessary cell and molecular biology without a prior university-level course. The required background is briefly reviewed in appendix A: more specialized topics are introduced throughout the text. The starting point for this material is a basic knowledge of (high school) chemistry, which is needed for a discussion of molecular phenomena, such as chemical bonds.

How This Book Is Organized

The first four chapters cover the basics of mathematical modeling in molecular systems biology. These should be read sequentially. The last four chapters address specific biological domains. The material in these latter chapters is not cumulative: they can be studied in any order. After chapter 2, each chapter ends with an optional section, which is marked with an asterisk (*). These optional sections address specialized modeling topics, some of which demand additional mathematical background (reviewed in appendix B).

Chapter 1 introduces molecular systems biology and describes some basic notions of mathematical modeling, concluding with four short case-studies. Chapter 2 introduces dynamic mathematical models of chemical reaction networks. These are differential equation models based on mass-action rate laws. Some basic methods for analysis and simulation are described. Chapter 3 covers biochemical kinetics and describes rate laws for biochemical processes (i.e., enzyme-catalyzed reactions and cooperative binding). An optional section treats common approximation methods. Chapter 4 introduces techniques for analysis of differential equation models, including phase plane analysis, stability, bifurcations, and sensitivity analysis. The presentation in this chapter emphasizes the use of these techniques in model investigation; very little theory is covered. A final optional section briefly introduces the calibration of models to experimental data.

Chapter 5 covers modeling of metabolic networks. Sensitivity analysis plays a central role in the investigation of these models. The optional section introduces stoichiometric modeling, which is often applied to large-scale metabolic networks.

1. www.math.uwaterloo.ca/~bingalls/MMSB.

Chapter 6 addresses modeling of signal transduction pathways. The examples taken up in this chapter survey a range of information-processing tasks performed by these pathways. An optional section introduces the use of frequency response analysis for the study of cellular input–output systems.

Chapter 7 introduces modeling of gene regulatory networks. The chapter starts with a treatment of gene expression, then presents examples illustrating a range of gene-circuit functions. The final optional section introduces stochastic modeling in molecular systems biology.

Chapter 8 covers modeling of electrophysiology and neuronal action potentials. An optional section contains a brief introduction to spatial modeling using partial differential equations.

The book closes with three appendices. Appendix A reviews basic concepts from molecular cell biology. Appendix B reviews mathematical concepts. Appendix C contains tutorials for two computational software packages—XPPAUT and MATLAB—that can be used for model simulation and analysis.

The Web site www.math.uwaterloo.ca/~bingalls/MMSB contains solutions to the in-text exercises, along with XPPAUT and MATLAB code for the models presented in the text and the end-of-chapter problem sets.

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