

Interdisciplinary Applied Mathematics

Volume 20

Editors

S.S. Antman J.E. Marsden

L. Sirovich S. Wiggins

Mathematical Biology

L. Glass, J.D. Murray

Mechanics and Materials

R.V. Kohn

Systems and Control

S.S. Sastry, P.S. Krishnaprasad

Problems in engineering, computational science, and the physical and biological sciences are using increasingly sophisticated mathematical techniques. Thus, the bridge between the mathematical sciences and other disciplines is heavily traveled. The correspondingly increased dialog between the disciplines has led to the establishment of the series: *Interdisciplinary Applied Mathematics*.

The purpose of this series is to meet the current and future needs for the interaction between various science and technology areas on the one hand and mathematics on the other. This is done, firstly, by encouraging the ways that mathematics may be applied in traditional areas, as well as point towards new and innovative areas of applications; and, secondly, by encouraging other scientific disciplines to engage in a dialog with mathematicians outlining their problems to both access new methods and suggest innovative developments within mathematics itself.

The series will consist of monographs and high-level texts from researchers working on the interplay between mathematics and other fields of science and technology.

Interdisciplinary Applied Mathematics

Volumes published are listed at the end of this book.

Springer

New York

Berlin

Heidelberg

Barcelona

Hong Kong

London

Milan

Paris

Singapore

Tokyo

Christopher P. Fall Eric S. Marland John M. Wagner
John J. Tyson
Editors

Computational Cell Biology

With 210 Illustrations



Springer

Christopher P. Fall
Center for Neural Science
New York University
New York, NY 10003
USA
fall@cns.nyu.edu

Eric S. Marland
Department of Mathematical Sciences
Appalachian State University
Boone, NC 28608
USA
marlandes@appstate.edu

John M. Wagner
Center for Biomedical Imaging
Technology
University of Connecticut Health
Center
Farmington, CT 06030
USA
jwagner@nso.uchc.edu

John J. Tyson
Department of Biology
Virginia Polytechnic Institute
Blacksburg, VA 24061
USA
tyson@vt.edu

Editors

S.S. Antman
Department of Mathematics
and
Institute for Physical Science and Technology
University of Maryland
College Park, MD 20742
USA

J.E. Marsden
Control and Dynamical Systems
Mail Code 107-81
California Institute of Technology
Pasadena, CA 91125
USA

L. Sirovich
Division of
Applied Mathematics
Brown University
Providence, RI 02912
USA

S. Wiggins
Control and Dynamical Systems
Mail Code 107-81
California Institute of Technology
Pasadena, CA 91125
USA

Mathematics Subject Classification (2000): 92-01, 92BXX, 92C30, 92C20

Library of Congress Cataloging-in-Publication Data
Computational cell biology / editors, Christopher P. Fall . . . [et al.].

p. cm. — (Interdisciplinary applied mathematics)

Includes bibliographical references and index.

ISBN 0-387-95369-8 (alk. paper)

1. Cytology—Computer simulation. 2. Cytology—Mathematical models. I. Fall, Christopher P.

II. Series.

QH585.5.D38 C65 2002

571.6'01'13—dc21

2001054912

ISBN 0-387-95369-8

Printed on acid-free paper.

© 2002 Springer-Verlag New York, Inc.

All rights reserved. This work may not be translated or copied in whole or in part without the written permission of the publisher (Springer-Verlag New York, Inc., 175 Fifth Avenue, New York, NY 10010, USA), except for brief excerpts in connection with reviews or scholarly analysis. Use in connection with any form of information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed is forbidden.

The use in this publication of trade names, trademarks, service marks and similar terms, even if they are not identified as such, is not to be taken as an expression of opinion as to whether or not they are subject to proprietary rights.

Printed in the United States of America.

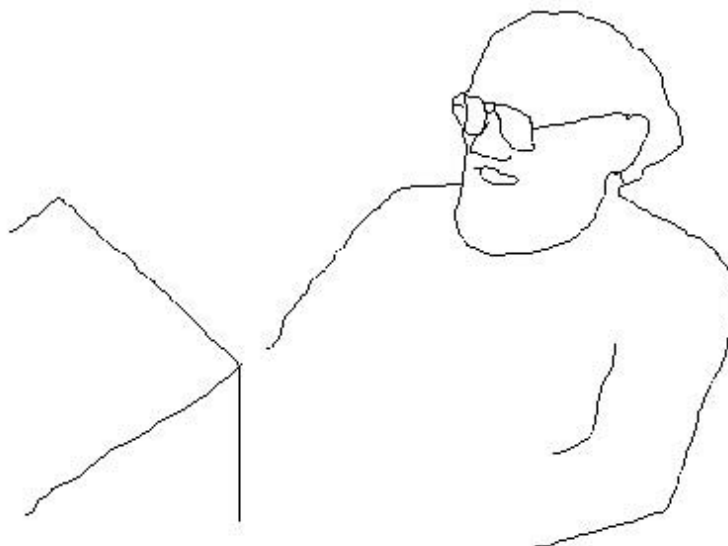
9 8 7 6 5 4 3 2 1

SPIN 10853277

www.springer-ny.com

Springer-Verlag New York Berlin Heidelberg

A member of BertelsmannSpringer Science+Business Media GmbH



Joel Edward Keizer 1942–1999

Joel Keizer's thirty years of scientific work set a standard for collaborative research in theoretical chemistry and biology. Joel served the University of California at Davis for 28 years, as a Professor in the Departments of Chemistry and of Neurobiology, Physiology and Behavior, and as founder and Director of the Institute for Theoretical Dynamics. Working at the boundary between experiment and theory, Joel built networks of collaborations and friendships that continue to grow and produce results. This book evolved from a textbook that Joel began but was not able to finish. The general outline and goals of the book were laid out by Joel, on the basis of his many years of teaching and research in computational cell biology. Those of us who helped to finish the project—as authors and editors—are happy to dedicate our labors to the memory of our friend and colleague, Joel Edward Keizer. All royalties from this book are to be directed to the Joel E. Keizer Memorial Fund for collaborative interdisciplinary research in the life sciences.



Preface

This text is an introduction to dynamical modeling in cell biology. It is not meant as a complete overview of modeling or of particular models in cell biology. Rather, we use selected biological examples to motivate the concepts and techniques used in computational cell biology. This is done through a progression of increasingly more complex cellular functions modeled with increasingly complex mathematical and computational techniques. There are other excellent sources for material on mathematical cell biology, and so the focus here truly is computer modeling. This does not mean that there are no mathematical techniques introduced, because some of them are absolutely vital, but it does mean that much of the mathematics is explained in a more intuitive fashion, while we allow the computer to do most of the work.

The target audience for this text is mathematically sophisticated cell biology or neuroscience students or mathematics students who wish to learn about modeling in cell biology. The ideal class would comprise both biology and applied math students, who might be encouraged to collaborate on exercises or class projects. We assume as little mathematical and biological background as we feel we can get away with, and we proceed fairly slowly. The techniques and approaches covered in the first half of the book will form a basis for some elementary modeling or as a lead in to more advanced topics covered in the second half of the book. Our goal for this text is to encourage mathematics students to consider collaboration with experimentalists and to provide students in cell biology and neuroscience with the tools necessary to access the modeling literature and appreciate the value of theoretical approaches.

The core of this book is a set of notes for a textbook written by Joel Keizer before his death in 1999. In addition to many other accomplishments as a scientist, Joel founded and directed the Institute of Theoretical Dynamics at the University of California, Davis. It is currently the home of a training program for young scientists studying nonlinear

dynamics in biology. As a part of this training program Joel taught a course entitled “Computational Models of Cellular Signaling,” which covered much of the material in the first half of this book.

Joel took palpable joy from interaction with his colleagues, and in addition to his truly notable accomplishments as a theorist in both chemistry and biology, perhaps his greatest skill was his ability to bring diverse people together in successful collaboration. It is in recognition of this gift that Joel’s friends and colleagues have brought this text to completion. We have expanded the scope, but at the core, you will still find Joel’s hand in the approach, methodology, and commitment to the interdisciplinary and collaborative nature of the field. The royalties from the book will be donated to the Joel E. Keizer foundation at the University of California at Davis, which promotes interdisciplinary collaboration between mathematics, the physical sciences, and biology.

Audience: We have aimed this text at an advanced undergraduate or beginning graduate audience in either mathematics or biology.

Prerequisites: We assume that students have taken full-year courses in calculus and biology. Introductory courses in differential equations and molecular cell biology are desirable but not absolutely necessary. Students with more substantial background in either biology or mathematics will benefit all the more from this text, especially the second half. No former programming experience is needed, but a working knowledge of using computers will make the learning curve much more pleasant. Note that we often point students to other textbooks and monographs, both because they are important references for later use and because they might be a better source for the material. Instructors may want to have these sources available for students to borrow or consult.

Organization: We consider the first six chapters, through intercellular communication, to be the core of the text. They cover the basic elements of compartmental modeling, and they should be accessible to anyone with a minimum background in cell biology and calculus. The remainder of the chapters cover more specialized topics that can be selected from, based on the focus of the course. Chapters 7 and 8 introduce spatial modeling, Chapters 9 and 10 discuss biochemical oscillations and the cell cycle, and Chapters 11–13 cover stochastic methods and models. These chapters are of varying degrees of difficulty.

Finally, in the first appendix, some of the mathematical and computational concepts brought up throughout the book are covered in more detail. This appendix is meant to be a reference and a learning tool. Sections of it may be integrated into the chapters as the topics are introduced. The second appendix contains an introduction to the XPPAUT ODE package discussed below. The final appendix contains pseudocode versions of the code used to create some of the data figures in the text.

Internet Resources: This book will have its own web page which will contain a variety of resources. We will maintain a list of the inevitable mistakes and typos and will make available actual code for the figures in the book. The web address is <http://www.compcell.appstate.edu>.

Software: We designed the text to be independent of any particular software, but have included appendices in support of the XPPAUT package. XPPAUT has been developed by Bard Ermentrout at the University of Pittsburgh, and it is currently available free of charge. XPPAUT numerically solves and plots the solutions of ordinary differential equations. It also incorporates a numerical bifurcation software and some methods for stochastic equations. Versions are currently available for Windows, Linux, and Unix systems. Recent changes in the Macintosh platform (OSX) make it possible to use XPP there as well. Ermentrout has recently published an excellent user's manual available through SIAM (Ermentrout 2002).

There are a large number of other software packages available that can accomplish many of the same things as XPPAUT can, such as MATLAB, MapleV, Mathematica, and Berkeley Madonna. Programming in C or Fortran is also possible. However XPPAUT is easy to use, requires minimal programming skills, has an excellent online tutorial, and is distributed without charge. The aspect of XPPAUT which is available in very few other places is the bifurcation software AUTO, originally developed by E.J. Doedel. The bifurcation tools in XPPAUT are necessary only for selected problems, so many of the other packages will suffice for most of the book. The the book and web site contain code that will reproduce many of the figures in the book. As students solve the exercises and replicate the simulations using other packages, we would encourage the submission of the code to the editors. We will incorporate this code into the web site and possibly into future editions of the book.

There are many people to thank for their help with this project. Of course, we are deeply indebted to the contributors, who first completed or wrote from scratch the chapters and then dealt with the numerous revisions necessary to homogenize the book to a reasonable level. Carla Wofsy and Byron Goldstein, as well as Albert Goldbeter, encouraged us to go forward with the project and provided valuable suggestions. We thank Chris Dugaw and David Quinonez for their assistance with typesetting several of the chapters, and Randy Szeto for his work with the graphic design of the book. We thank James Sneyd for many helpful comments on the manuscript, and also Tim Lewis for commenting on several of the chapters. Carol Lucas generously provided many corrections for the first half of the text. C.F., J.W., and E.M. were supported in part by the Institute of Theoretical Dynamics at UC Davis during some of the preparation of the manuscript.

We suspect that Joel, for a start, would have thanked Lee Segel, Jim Murray, Leah Edelstein-Keshet and others whose pioneering textbooks in mathematical biology certainly informed this one. We *know* that Joel would have thanked many friends and colleagues for contributing to the true excitement he felt in his "second career" studying biology. While we have dedicated this work to the memory of Joel, Joel's dedication might well have been to his wife, Susan; his daughter, Sarah; his son and daughter-in-law, Sidney and Noelle; and his grandson, Justin Joel.

We hope you enjoy this text, and we look forward to your comments and suggestions. We strongly believe that a textbook such as this might serve to help to develop the field of computational cell biology by introducing students to the subject. This textbook

will be more successful in helping to forge a community if it represents what most of us agree is necessary to teach beginning students. This is only a first step, and we truly look forward both to input about the material already presented and to suggestions and contributions of additional material and topics for future editions.

Contributors

Timothy C. Elston
North Carolina State University
Department of Statistics

G. Bard Ermentrout
University of Pittsburgh
Department of Mathematics

Christopher P. Fall
New York University
Center for Neural Science

James P. Keener
University of Utah
Department of Mathematics

Joel E. Keizer
University of California at Davis
Institute of Theoretical Dynamics

Yue-Xian Li
University of British Columbia
Department of Mathematics

Eric S. Marland
Appalachian State University
Department of Mathematical Sciences

Alexander Mogilner
University of California at Davis
Department of Mathematics

Béla Novák
Budapest University of Technology and
Economics
Department of Agricultural Chemical
Technology

George Oster
University of California at Berkeley
Departments of Molecular and Cellular Biology
and ESPM

John E. Pearson
Los Alamos National Laboratory
Applied Theoretical and Computational Physics

John Rinzel
New York University
Center for Neural Science and
Courant Institute of Mathematical Sciences

Arthur S. Sherman
National Institutes of Health
Mathematical Research Branch
National Institute of Diabetes and
Digestive and Kidney Diseases

Gregory D. Smith
College of William and Mary
Department of Applied Science

John J. Tyson
Virginia Polytechnic Institute
and State University
Department of Biology

John M. Wagner
University of Connecticut Health Center
Center for Biomedical Imaging Technology

Hongyun Wang
University of California at Santa Cruz
Department of Applied Mathematics
and Statistics

Graphic design by
Randy Szeto



Contents

| | |
|---|------------|
| Preface | vii |
| I Introductory Course | 1 |
| 1 Dynamic Phenomena in Cells | 3 |
| 1.1 Scope of Cellular Dynamics | 3 |
| 1.2 Computational Modeling in Biology | 8 |
| 1.2.1 Cartoons, Mechanisms, and Models | 8 |
| 1.2.2 The Role of Computation | 9 |
| 1.2.3 The Role of Mathematics | 10 |
| 1.3 A Simple Molecular Switch | 11 |
| 1.4 Solving and Analyzing Differential Equations | 13 |
| 1.4.1 Numerical Integration of Differential Equations | 15 |
| 1.4.2 Introduction to Numerical Packages | 18 |
| 1.5 Exercises | 20 |
| 2 Voltage Gated Ionic Currents | 21 |
| 2.1 Basis of the Ionic Battery | 23 |
| 2.1.1 The Nernst Potential: Charge Balances Concentration | 24 |
| 2.1.2 The Resting Membrane Potential | 26 |
| 2.2 The Membrane Model | 27 |
| 2.2.1 Equations for Membrane Electrical Behavior | 28 |
| 2.3 Activation and Inactivation Gates | 29 |
| 2.3.1 Models of Voltage-Dependent Gating | 29 |

| | | |
|----------|--|------------|
| 2.3.2 | The Voltage Clamp | 31 |
| 2.4 | Interacting Ion Channels: The Morris–Lecar Model | 34 |
| 2.4.1 | Phase Plane Analysis | 36 |
| 2.4.2 | Stability Analysis | 38 |
| 2.4.3 | Why Do Oscillations Occur? | 40 |
| 2.4.4 | Excitability and Action Potentials | 43 |
| 2.4.5 | Type I and Type II Spiking | 44 |
| 2.5 | The Hodgkin–Huxley Model | 45 |
| 2.6 | FitzHugh–Nagumo Class Models | 47 |
| 2.7 | Summary | 49 |
| 2.8 | Exercises | 50 |
| 3 | Transporters and Pumps | 53 |
| 3.1 | Passive Transport | 54 |
| 3.2 | Transporter Rates | 57 |
| 3.2.1 | Algebraic Method | 59 |
| 3.2.2 | Diagrammatic Method | 60 |
| 3.2.3 | Rate of the GLUT Transporter | 62 |
| 3.3 | The Na ⁺ /Glucose Cotransporter | 65 |
| 3.4 | SERCA Pumps | 70 |
| 3.5 | Transport Cycles | 73 |
| 3.6 | Exercises | 76 |
| 4 | Fast and Slow Time Scales | 77 |
| 4.1 | The Rapid Equilibrium Approximation | 78 |
| 4.2 | Asymptotic Analysis of Time Scales | 82 |
| 4.3 | Glucose–Dependent Insulin Secretion | 83 |
| 4.4 | Ligand Gated Channels | 88 |
| 4.5 | The Neuromuscular Junction | 90 |
| 4.6 | The Inositol Trisphosphate (IP ₃) receptor | 91 |
| 4.7 | Michaelis–Menten Kinetics | 94 |
| 4.8 | Exercises | 98 |
| 5 | Whole–Cell Models | 101 |
| 5.1 | Models of ER and PM Calcium Handling | 102 |
| 5.1.1 | Flux Balance Equations with Rapid Buffering | 103 |
| 5.1.2 | Expressions for the Fluxes | 106 |
| 5.2 | Calcium Oscillations in the Bullfrog Sympathetic Ganglion Neuron | 107 |
| 5.2.1 | Ryanodine Receptor Kinetics: The Keizer–Levine Model | 108 |
| 5.2.2 | Bullfrog Sympathetic Ganglion Neuron Closed–Cell Model | 111 |
| 5.2.3 | Bullfrog Sympathetic Ganglion Neuron Open–Cell Model | 113 |
| 5.3 | The Pituitary Gonadotroph | 115 |
| 5.3.1 | The ER Oscillator in a Closed Cell | 116 |

| | | |
|-----------|---|------------|
| 5.3.2 | Open-Cell Model with Constant Calcium Influx | 122 |
| 5.3.3 | The Plasma Membrane Oscillator | 124 |
| 5.3.4 | Bursting Driven by the ER in the Full Model | 126 |
| 5.4 | The Pancreatic Beta Cell | 128 |
| 5.4.1 | Chay-Keizer Model | 129 |
| 5.4.2 | Chay-Keizer with an ER | 133 |
| 5.5 | Exercises | 136 |
| 6 | Intercellular Communication | 140 |
| 6.1 | Electrical Coupling and Gap Junctions | 141 |
| 6.1.1 | Synchronization of Two Oscillators | 142 |
| 6.1.2 | Asynchrony Between Oscillators | 143 |
| 6.1.3 | Cell Ensembles, Electrical Coupling Length Scale | 144 |
| 6.2 | Synaptic Transmission Between Neurons | 146 |
| 6.2.1 | Kinetics of Postsynaptic Current | 147 |
| 6.2.2 | Synapses: Excitatory and Inhibitory; Fast and Slow | 148 |
| 6.3 | When Synapses Might (or Might Not) Synchronize Active Cells | 150 |
| 6.4 | Neural Circuits as Computational Devices | 153 |
| 6.5 | Large-Scale Networks | 159 |
| 6.6 | Exercises | 165 |
| II | Advanced Material | 169 |
| 7 | Spatial Modeling | 171 |
| 7.1 | One-Dimensional Formulation | 173 |
| 7.1.1 | Conservation in One Dimension | 173 |
| 7.1.2 | Fick's Law of Diffusion | 175 |
| 7.1.3 | Advection | 176 |
| 7.1.4 | Flux of Ions in a Field | 177 |
| 7.1.5 | The Cable Equation | 177 |
| 7.1.6 | Boundary and Initial Conditions | 178 |
| 7.2 | Important Examples with Analytic Solutions | 179 |
| 7.2.1 | Diffusion Through a Membrane | 179 |
| 7.2.2 | Ion Flux Through a Channel | 180 |
| 7.2.3 | Voltage Clamping | 181 |
| 7.2.4 | Diffusion in a Long Dendrite | 181 |
| 7.2.5 | Diffusion into a Capillary | 183 |
| 7.3 | Numerical Solution of the Diffusion Equation | 184 |
| 7.4 | Multidimensional Problems | 186 |
| 7.4.1 | Conservation Law in Multiple Dimensions | 186 |
| 7.4.2 | Fick's Law in Multiple Dimensions | 187 |
| 7.4.3 | Advection in Multiple Dimensions | 188 |

| | | |
|----------|---|------------|
| 7.4.4 | Boundary and Initial Conditions for Multiple Dimensions . . . | 188 |
| 7.4.5 | Diffusion in Multiple Dimensions: Symmetry | 188 |
| 7.5 | Traveling Waves in Nonlinear Reaction–Diffusion Equations | 189 |
| 7.5.1 | Traveling Wave Solutions | 190 |
| 7.5.2 | Traveling Wave in the Fitzhugh–Nagumo Equations | 192 |
| 7.6 | Exercises | 195 |
| 8 | Modeling Intracellular Calcium Waves and Sparks | 198 |
| 8.1 | Microfluorometric Measurements | 198 |
| 8.2 | A Model of the Fertilization Calcium Wave | 200 |
| 8.3 | Including Calcium Buffers in Spatial Models | 202 |
| 8.4 | The Effective Diffusion Coefficient | 203 |
| 8.5 | Simulation of a Fertilization Calcium Wave | 204 |
| 8.6 | Simulation of a Traveling Front | 204 |
| 8.7 | Calcium Waves in the Immature Xenopus Oocyte | 208 |
| 8.8 | Simulation of a Traveling Pulse | 208 |
| 8.9 | Simulation of a Kinematic Wave | 210 |
| 8.10 | Spark-Mediated Calcium Waves | 213 |
| 8.11 | The Fire–Diffuse–Fire Model | 214 |
| 8.12 | Modeling Localized Calcium Elevations | 220 |
| 8.13 | Steady-State Localized Calcium Elevations | 222 |
| | 8.13.1 The Steady–State Excess Buffer Approximation (EBA) | 224 |
| | 8.13.2 The Steady–State Rapid Buffer Approximation (RBA) | 225 |
| | 8.13.3 Complementarity of the Steady-State EBA and RBA | 226 |
| 8.14 | Exercises | 227 |
| 9 | Biochemical Oscillations | 230 |
| 9.1 | Biochemical Kinetics and Feedback | 232 |
| 9.2 | Regulatory Enzymes | 236 |
| 9.3 | Two-Component Oscillators Based on Autocatalysis | 239 |
| | 9.3.1 Substrate–Depletion Oscillator | 240 |
| | 9.3.2 Activator–Inhibitor Oscillator | 242 |
| 9.4 | Three-Component Networks Without Autocatalysis | 243 |
| | 9.4.1 Positive Feedback Loop and the Routh–Hurwitz Theorem . . . | 244 |
| | 9.4.2 Negative Feedback Oscillations | 244 |
| | 9.4.3 The Goodwin Oscillator | 244 |
| 9.5 | Time-Delayed Negative Feedback | 247 |
| | 9.5.1 Distributed Time Lag and the Linear Chain Trick | 248 |
| | 9.5.2 Discrete Time Lag | 249 |
| 9.6 | Circadian Rhythms | 250 |
| 9.7 | Exercises | 255 |

| | |
|--|------------|
| 10 Cell Cycle Controls | 261 |
| 10.1 Physiology of the Cell Cycle in Eukaryotes | 261 |
| 10.2 Molecular Mechanisms of Cell Cycle Control | 263 |
| 10.3 A Toy Model of Start and Finish | 265 |
| 10.3.1 Hysteresis in the Interactions Between Cdk and APC | 266 |
| 10.3.2 Activation of the APC at Anaphase | 267 |
| 10.4 A Serious Model of the Budding Yeast Cell Cycle | 269 |
| 10.5 Cell Cycle Controls in Fission Yeast | 273 |
| 10.6 Checkpoints and Surveillance Mechanisms | 276 |
| 10.7 Division Controls in Egg Cells | 276 |
| 10.8 Growth and Division Controls in Metazoans | 278 |
| 10.9 Spontaneous Limit Cycle or Hysteresis Loop? | 279 |
| 10.10 Exercises | 281 |
| | |
| 11 Modeling the Stochastic Gating of Ion Channels | 285 |
| 11.1 Single-Channel Gating and a Two-State Model | 285 |
| 11.1.1 Modeling Channel Gating as a Markov Process | 286 |
| 11.1.2 The Transition Probability Matrix | 288 |
| 11.1.3 Dwell Times | 289 |
| 11.1.4 Monte Carlo Simulation | 290 |
| 11.1.5 Simulating Multiple Independent Channels | 291 |
| 11.1.6 Gillespie's Method | 292 |
| 11.2 An Ensemble of Two-State Ion Channels | 293 |
| 11.2.1 Probability of Finding N Channels in the Open State | 293 |
| 11.2.2 The Average Number of Open Channels | 296 |
| 11.2.3 The Variance of the Number of Open Channels | 297 |
| 11.3 Fluctuations in Macroscopic Currents | 298 |
| 11.4 Modeling Fluctuations in Macroscopic Currents with Stochastic ODEs | 302 |
| 11.4.1 Langevin Equation for an Ensemble of Two-State Channels | 304 |
| 11.4.2 Fokker-Planck Equation for an Ensemble of Two-State Channels | 306 |
| 11.5 Membrane Voltage Fluctuations | 307 |
| 11.5.1 Membrane Voltage Fluctuations with an Ensemble of Two-State Channels | 309 |
| 11.6 Stochasticity and Discreteness in an Excitable Membrane Model | 311 |
| 11.6.1 Phenomena Induced by Stochasticity and Discreteness | 312 |
| 11.6.2 The Ensemble Density Approach Applied to the Stochastic Morris-Lecar Model | 313 |
| 11.6.3 Langevin Formulation for the Stochastic Morris-Lecar Model | 314 |
| 11.7 Exercises | 317 |

| | |
|--|------------|
| 12 Molecular Motors: Theory | 320 |
| 12.1 Molecular Motions as Stochastic Processes | 323 |
| 12.1.1 Protein Motion as a Simple Random Walk | 323 |
| 12.1.2 Polymer Growth | 325 |
| 12.1.3 Sample Paths of Polymer Growth | 327 |
| 12.1.4 The Statistical Behavior of Polymer Growth | 329 |
| 12.2 Modeling Molecular Motions | 330 |
| 12.2.1 The Langevin Equation | 330 |
| 12.2.2 Numerical Simulation of the Langevin Equation | 332 |
| 12.2.3 The Smoluchowski Model | 333 |
| 12.2.4 First Passage Time | 334 |
| 12.3 Modeling Chemical Reactions | 335 |
| 12.4 A Mechanochemical Model | 338 |
| 12.5 Numerical Simulation of Protein Motion | 339 |
| 12.5.1 Numerical Algorithm that Preserves Detailed Balance | 340 |
| 12.5.2 Boundary Conditions | 341 |
| 12.5.3 Numerical Stability | 342 |
| 12.5.4 Implicit Discretization | 344 |
| 12.6 Derivations and Comments | 345 |
| 12.6.1 The Drag Coefficient | 345 |
| 12.6.2 The Equipartition Theorem | 345 |
| 12.6.3 A Numerical Method for the Langevin Equation | 346 |
| 12.6.4 Some Connections with Thermodynamics | 347 |
| 12.6.5 Jumping Beans and Entropy | 349 |
| 12.6.6 Jump Rates | 350 |
| 12.6.7 Jump Rates at an Absorbing Boundary | 351 |
| 12.7 Exercises | 353 |
| 13 Molecular Motors: Examples | 354 |
| 13.1 Switching in the Bacterial Flagellar Motor | 354 |
| 13.2 A Motor Driven by a “Flashing Potential” | 359 |
| 13.3 The Polymerization Ratchet | 362 |
| 13.4 Simplified Model of the F_0 Motor | 364 |
| 13.4.1 The Average Velocity of the Motor in the Limit of Fast Diffusion | 366 |
| 13.4.2 Brownian Ratchet vs. Power Stroke | 369 |
| 13.4.3 The Average Velocity of the Motor When Chemical Reactions Are as Fast as Diffusion | 369 |
| 13.5 Other Motor Proteins | 374 |
| 13.6 Exercises | 376 |
| A Qualitative Analysis of Differential Equations | 378 |
| A.1 Matrix and Vector Manipulation | 379 |

| | | |
|----------|---|------------|
| A.2 | A Brief Review of Power Series | 380 |
| A.3 | Linear ODEs | 382 |
| | A.3.1 Solution of Systems of Linear ODEs | 383 |
| | A.3.2 Numerical Solutions of ODEs | 385 |
| | A.3.3 Eigenvalues and Eigenvectors | 386 |
| A.4 | Phase Plane Analysis | 388 |
| | A.4.1 Stability of Linear Steady States | 390 |
| | A.4.2 Stability of a Nonlinear Steady States | 392 |
| A.5 | Bifurcation Theory | 395 |
| | A.5.1 Bifurcation at a Zero Eigenvalue | 396 |
| | A.5.2 Bifurcation at a Pair of Imaginary Eigenvalues | 398 |
| A.6 | Perturbation Theory | 401 |
| | A.6.1 Regular Perturbation | 401 |
| | A.6.2 Resonances | 403 |
| | A.6.3 Singular Perturbation Theory | 405 |
| A.7 | Exercises | 408 |
| B | Solving and Analyzing Dynamical Systems Using XPPAUT | 410 |
| B.1 | Basics of Solving Ordinary Differential Equations | 411 |
| | B.1.1 Creating the ODE File | 411 |
| | B.1.2 Running the Program | 412 |
| | B.1.3 The Main Window | 413 |
| | B.1.4 Solving the Equations, Graphing, and Plotting. | 414 |
| | B.1.5 Saving and Printing Plots | 416 |
| | B.1.6 Changing Parameters and Initial Data | 418 |
| | B.1.7 Looking at the Numbers: The Data Viewer | 419 |
| | B.1.8 Saving and Restoring the State of Simulations | 420 |
| | B.1.9 Important Numerical Parameters | 421 |
| | B.1.10 Command Summary: The Basics | 422 |
| B.2 | Phase Planes and Nonlinear Equations | 422 |
| | B.2.1 Direction Fields | 423 |
| | B.2.2 Nullclines and Fixed Points | 423 |
| | B.2.3 Command Summary: Phase Planes and Fixed Points | 426 |
| B.3 | Bifurcation and Continuation | 427 |
| | B.3.1 General Steps for Bifurcation Analysis | 427 |
| | B.3.2 Hopf Bifurcation in the FitzHugh–Nagumo Equations | 428 |
| | B.3.3 Hints for Computing Complete Bifurcation Diagrams | 430 |
| B.4 | Partial Differential Equations: The Method of Lines | 432 |
| B.5 | Stochastic Equations | 434 |
| | B.5.1 A Simple Brownian Ratchet | 434 |
| | B.5.2 A Sodium Channel Model | 434 |
| | B.5.3 A Flashing Ratchet | 436 |

| | |
|-------------------------------|------------|
| C Numerical Algorithms | 439 |
| References | 451 |
| Index | 463 |