Interdisciplinary Applied Mathematics

Volume 20

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

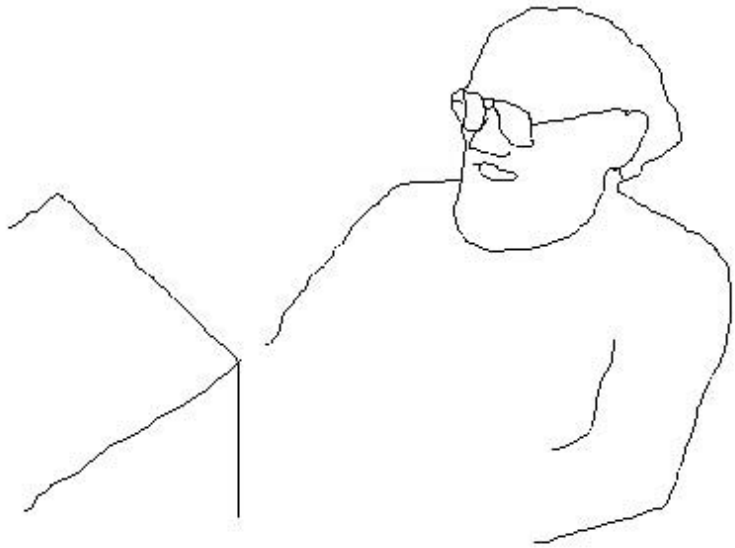
ISBN 0-387-95369-8 Printed on acid-free paper.

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 psuedocode 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