

# A Course in Mathematical Biology

Quantitative Modeling  
with Mathematical and  
Computational Methods

Gerda de Vries, Thomas Hillen,  
Mark Lewis, Johannes Müller,  
Birgitt Schönfisch



**siam**

Mathematical Modeling and Computation



---

---

# **A Course in Mathematical Biology**

## **Quantitative Modeling with Mathematical and Computational Methods**

**Gerda de Vries**

University of Alberta  
Edmonton, Alberta, Canada

**Thomas Hillen**

University of Alberta  
Edmonton, Alberta, Canada

**Mark Lewis**

University of Alberta  
Edmonton, Alberta, Canada

**Johannes Müller**

Technical University Munich  
Munich, Germany

**Birgitt Schönfisch**

University of Tübingen  
Tübingen, Germany

**siam**

Society for Industrial and Applied Mathematics  
Philadelphia



Copyright © 2006 by the Society for Industrial and Applied Mathematics.

10 9 8 7 6 5 4 3 2 1

All rights reserved. Printed in the United States of America. No part of this book may be reproduced, stored, or transmitted in any manner without the written permission of the publisher. For information, write to the Society for Industrial and Applied Mathematics, 3600 University City Science Center, Philadelphia, PA 19104-2688.

MAPLE is a registered trademark of Waterloo Maple, Inc.

Mathematica is a registered trademark of Wolfram Research, Inc.

MATLAB is a registered trademark of The MathWorks, Inc. and is used with permission. The MathWorks does not warrant the accuracy of the text or exercises in this book. This book's use or discussion of MATLAB software or related products does not constitute endorsement or sponsorship by The MathWorks of a particular pedagogical approach or particular use of the MATLAB software. For MATLAB information, contact The MathWorks, 3 Apple Hill Drive, Natick, MA, 01760-2098 USA, Tel: 508-647-7000, Fax: 508-647-7001 [info@mathworks.com](mailto:info@mathworks.com), [www.mathworks.com](http://www.mathworks.com)

UNIX is a registered trademark of The Open Group in the United States and other countries.

Windows is a registered trademark of Microsoft Corporation in the United States and/or other countries.

Figure 3.10 is reprinted with permission from page 190, Figure 5.14 of Edelstein-Keshet, L., *Mathematical Models in Biology*, Classics in Applied Mathematics 46, SIAM, Philadelphia, 2005.

Figure 9.3 is reprinted with permission of Kluwer Academic from Figure 4 of Soll, D. R., Behavioral studies into the mechanism of eukaryotic chemotaxis, *J. Chemical Ecology*, 16: 133–150, 1990.

Figures 9.4 and 9.5 are reprinted with permission of the University of Chicago Press from Figure 1 and Table 1, respectively, of Lubina, J. A. and Levin, S. A., The spread of a reinvading species, *AM NAT*, 151(4): 526–543, 1988.

Figure 9.6 is reprinted with permission from Figure 11 on page 94 and Figure 12 on page 95 of Stark, L. W., *Neurological Control Systems: Studies in Bioengineering*, Kluwer Academic/Plenum Publishers, 1968.

Figure 9.8 is reprinted with permission of the Royal Society of London from Figure 24 of Hubel, D. H. and Wiesel, T. N., Functional architecture of Macaque monkey visual cortex. *Proc. Roy. Soc. Lond. B.*, 198: 1–59, 1977.

Cover art courtesy of Dr. R. Wolff, [www.rwphoto.de](http://www.rwphoto.de) (green iguana), and Dr. B. Schönfisch (mollusks).

#### Library of Congress Cataloging-in-Publication Data

A course in mathematical biology : quantitative modeling with mathematical and computational methods / Gerda de Vries... [et al.]

p.cm. – (Mathematical modeling and computation)

Includes bibliographical references (p. ).

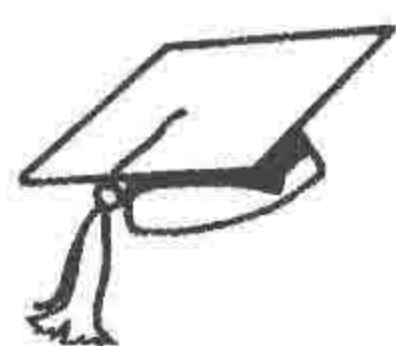
ISBN 0-89871-612-8 (pbk.)

1. Biology–Mathematical models. I. Vries, Gerda de. II. Series.

QH323.5.C69 2006

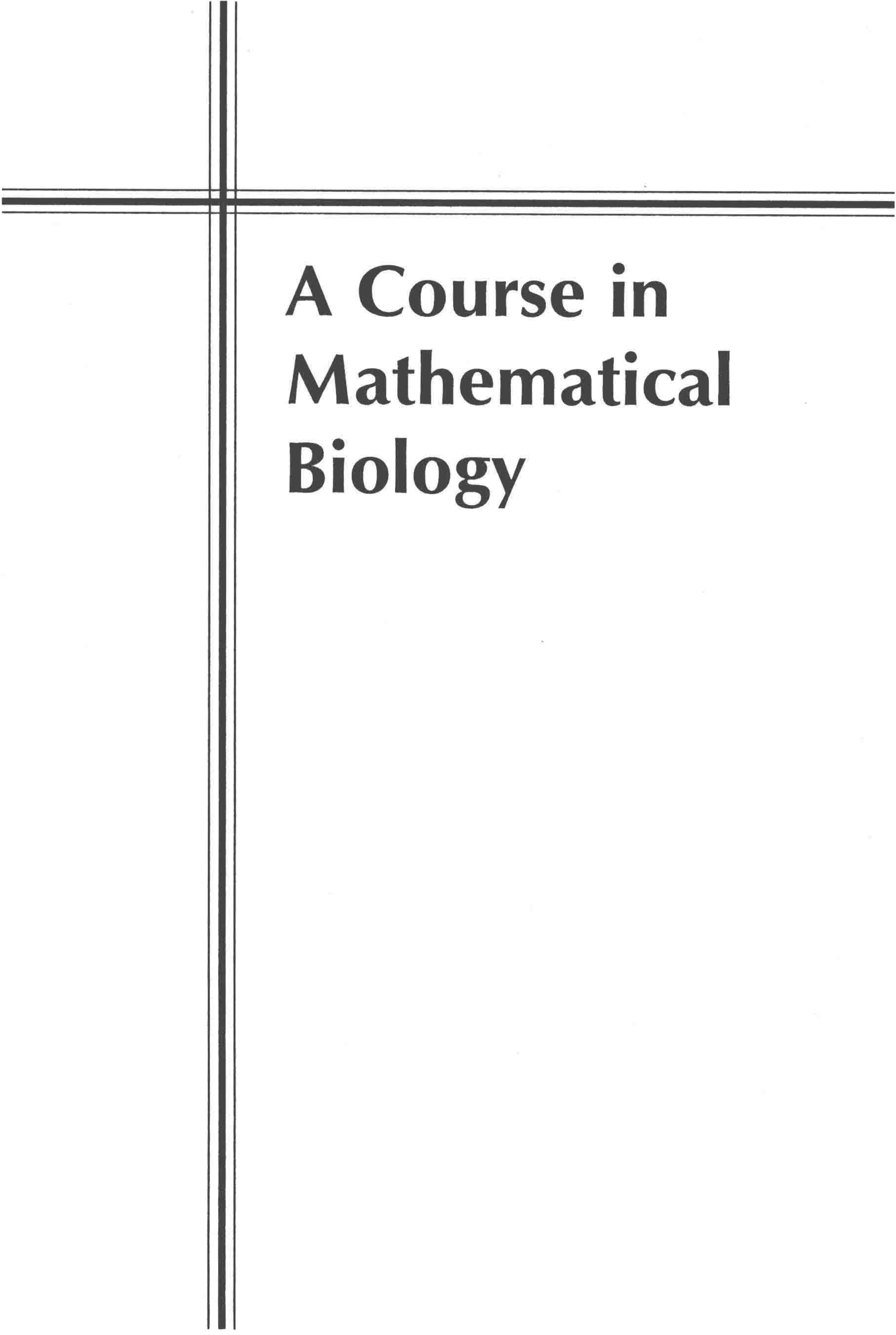
570.1'5118–dc22

2006044305



Partial royalties from the sale of this book are placed in a fund to help students attend SIAM meetings and other SIAM-related activities. This fund is administered by SIAM, and qualified individuals are encouraged to write directly to SIAM for guidelines.

**siam** is a registered trademark.



# **A Course in Mathematical Biology**



# Mathematical Modeling and Computation

## About the Series

The SIAM series on Mathematical Modeling and Computation draws attention to the wide range of important problems in the physical and life sciences and engineering that are addressed by mathematical modeling and computation; promotes the interdisciplinary culture required to meet these large-scale challenges; and encourages the education of the next generation of applied and computational mathematicians, physical and life scientists, and engineers.

The books cover analytical and computational techniques, describe significant mathematical developments, and introduce modern scientific and engineering applications. The series will publish lecture notes and texts for advanced undergraduate- or graduate-level courses in physical applied mathematics, biomathematics, and mathematical modeling, and volumes of interest to a wide segment of the community of applied mathematicians, computational scientists, and engineers.

Appropriate subject areas for future books in the series include fluids, dynamical systems and chaos, mathematical biology, neuroscience, mathematical physiology, epidemiology, morphogenesis, biomedical engineering, reaction-diffusion in chemistry, nonlinear science, interfacial problems, solidification, combustion, transport theory, solid mechanics, nonlinear vibrations, electromagnetic theory, nonlinear optics, wave propagation, coherent structures, scattering theory, earth science, solid-state physics, and plasma physics.

---

Gerda de Vries, Thomas Hillen, Mark Lewis, Johannes Müller, and Birgitt Schönfisch, *A Course in Mathematical Biology: Quantitative Modeling with Mathematical and Computational Methods*

Ivan Markovsky, Jan C. Willems, Sabine Van Huffel, and Bart De Moor, *Exact and Approximate Modeling of Linear Systems: A Behavioral Approach*

R. M. M. Mattheij, S. W. Rienstra, and J. H. M. ten Thijs Boonkkamp, *Partial Differential Equations: Modeling, Analysis, Computation*

Johnny T. Ottesen, Mette S. Olufsen, and Jesper K. Larsen, *Applied Mathematical Models in Human Physiology*

Ingemar Kaj, *Stochastic Modeling in Broadband Communications Systems*

Peter Salamon, Paolo Sibani, and Richard Frost, *Facts, Conjectures, and Improvements for Simulated Annealing*

Lyn C. Thomas, David B. Edelman, and Jonathan N. Crook, *Credit Scoring and Its Applications*

Frank Natterer and Frank Wübbeling, *Mathematical Methods in Image Reconstruction*

Per Christian Hansen, *Rank-Deficient and Discrete Ill-Posed Problems: Numerical Aspects of Linear Inversion*

Michael Griebel, Thomas Dornseifer, and Tilman Neunhoffer, *Numerical Simulation in Fluid Dynamics: A Practical Introduction*

Khosrow Chadon, David Colton, Lassi Päiväranta, and William Rundell, *An Introduction to Inverse Scattering and Inverse Spectral Problems*

Charles K. Chui, *Wavelets: A Mathematical Tool for Signal Analysis*

## Editor-in-Chief

**Richard Haberman**  
Southern Methodist  
University

## Editorial Board

**Alejandro Aceves**  
University of New  
Mexico

**Andrea Bertozzi**  
University of California,  
Los Angeles

**Bard Ermentrout**  
University of Pittsburgh

**Thomas Erneux**  
Université Libre de  
Brussels

**Bernie Matkowsky**  
Northwestern University

**Robert M. Miura**  
New Jersey Institute  
of Technology

**Michael Tabor**  
University of Arizona



# Preface

Mathematical biology is growing rapidly. Mathematics has long played a dominant role in our understanding of physics, chemistry, and other physical sciences. However, wholesale application of mathematical methods in the life sciences is relatively recent. Now questions about infectious diseases, heart attacks, cell signaling, cell movement, ecology, environmental changes, and genomics are being tackled and analyzed using mathematical and computational methods.

While the application of quantitative analysis in the life sciences has borne fruit in the research arena, only recently has it impacted undergraduate education. Until a few years ago, the number of undergraduate texts in mathematical biology could be counted on one hand. Now this has changed dramatically. Recent undergraduate texts range from simple introductions to biological numeracy (Burton [35, 36]), freshman calculus for students in the life sciences (Adler [1], Neuhauser [125]), modeling with differential equations (Taubes [155], Edelstein-Keshet [51], Britton [29]), computer algebra (Yeagers, Shonkwiler, and Herod [168]), and dynamical computer-based systems (Hannon and Ruth [78]), to name but a few.

Despite the plentitude of new books, mathematical biology is still rarely offered as an undergraduate course. This book is designed for undergraduate students. Our target audience are students in mathematics, biology, physics, or other quantitative sciences at the sophomore or junior level. Our aim is to introduce students to problem solving in the context of biology. The focus in our presentation is on integrating analytical and computational tools in the modeling of biological processes.

The book stems from pedagogic material developed by the authors for a 7–11 day workshop in mathematical biology, which has been taught since 1995 at the University of Tübingen (Germany) and since 2001 at the University of Alberta (Canada). Additional material has been added to make the book suitable for use in a full-term course in mathematical biology.

There are three parts to this book: (I) analytical modeling techniques, (II) computational modeling techniques, (III) problem solving.

Part I covers basic analytical modeling techniques. We discuss the formulation of models using difference equations, differential equations, probability theory, cellular automata, as well as model validation and parameter estimation. We emphasize the modeling process and qualitative analysis, rather than explicit solution techniques (which can be found in other textbooks). Classical models for disease, movement, and population dynamics are derived from first principles. Each section provides a number of biologically motivated exercises.



Part II introduces computational tools used in the modeling of biological problems. Students are guided through symbolic and numerical calculations with Maple (for readers who prefer an alternative software package, such as *Mathematica* or MATLAB, see “How to Use This Book” below). Many of the examples and exercises of this part relate directly to the models discussed in Part I. This part of our book has been designed such that students can work through the material independently and at their own pace. Readers without any programming background will pick up valuable computational skills. Readers who already have programming background will be able to skip some elementary exercises and focus attention on the biological applications.

Part III provides open-ended problems from epidemiology, ecology, and physiology. Each problem is formulated in a way that makes it accessible to students. In most cases, questions will guide the student through the modeling process. These problems can be used as the basis for extended investigation, for example, as a term project or as a team project. We conclude Part III with a detailed presentation of two projects (cell competition and the chemotactic paradox) based on solutions developed by teams of undergraduate students who participated in one of our workshops.

The field of mathematical biology is, admittedly, immense. This book does not attempt to achieve a comprehensive introduction to the field. Subjects are tempered by the test of being able to teach them effectively in a short period of time. Problems are biased towards the authors’ interests, but are sufficiently wide-ranging to include something of interest for most students. Ultimately, we hope that this book offers the first step into a detailed modeling of problems in the life sciences.

## How to Use This Book

We envision that this book can be used in a number of ways. Here we list some ideas about how a course could be designed based on the material of this book.

**Full-Term Course:** During a full-term course, material from Part I can be covered. Students should have access to computers to complete Part II and for the project work of Part III. Although students can work through the computer tutorial on their own, we recommend a two-hour computer lab during which an instructor is available to help the students get started. Projects from the open-ended problems from Part III may be assigned early in the course, with students submitting a written report, or presenting the project in class (or both) towards the end of the course.

**10-Day Workshop:** During the first half of the workshop, the focus should be on learning modeling with analytical and computational tools, based on Parts I and II of this book. Ideally a mixture of discrete-time equations, differential equations, and stochastic models should be covered. Specific topics would depend on the background of the instructor(s). We feel that Sections 2.2, 3.1–3.4, 4.3, and 5.1–5.6 should be included in any course. Lectures on these topics may be supplemented by homework. In our experience, students need about 15 hours to work through the computer tutorial of Part II.

During the second half of the workshop, students should work in teams of two (maybe three) on one of the open-ended problems from Part III. Under the guidance of an instructor, students develop a model, analyze and/or simulate the model, and prepare a presentation. We have found it important to stress that problems are open-ended, and have no “right



solution” *per se*. It is the process of model development that is most important, not necessarily the end product. In many cases, students will need to simplify their problem and build a hierarchy of models, each model incorporating additional realism from the original problem.

**Substituting Maple with Other Software:** Although we have based Part II of this book on Maple, we do not wish to give the impression that Maple is necessarily the ideal software to be used. In fact, we believe that it does not really matter which software package is used. Instructors or students proficient with other software, such as *Mathematica* or MATLAB, will readily be able to adapt the examples and exercises of Part II for the alternative software. A version of Part II in *Mathematica* is available at <http://www.siam.org/books/mm12>.

**Working on Open-Ended Projects:** Since the problems from Part III are open ended there is a danger of aiming too high. Some of the problems are currently being studied by experienced researchers, and it would be impossible to follow all the relevant literature. For a beginning modeler, we give the following guidelines.

From the project description, readers should be able to understand the biological problem at hand to a certain extent. Some reading of supplemental material might be useful. For most projects, a specific reference is given, and the Internet is always a good resource. It is not required to study the biological topic at length. Initial efforts in mathematical modeling require only the identification of basic mechanisms.

When the biological problem at hand is understood, students should determine first which of the model classes presented in Part I might be useful (discrete/continuous, deterministic/stochastic). With the help of an instructor, they then proceed to develop a mathematical model. After the students and the instructors agree upon a reasonable model, the students work on it, do the analysis, and write the software. Many projects are accompanied with data. In that case, data fitting will be an important element of the project. Last but not least, the model should be used to explain important aspects of the biological phenomenon and to make predictions for other experiments or observations.

**Internet Resources:** A webpage related to this book that contains solutions to most of the exercises and the computer tutorial of Part II in *Mathematica* can be found at <http://www.siam.org/books/mm12>.

## Acknowledgments

Although five authors worked on this text, it would not have been written without support from various sources. We express our thanks to Andrew Beltaos, an undergraduate student who helped with editing, making figures, and solving exercises. We are grateful to the Universities of Tübingen and Alberta for providing the environment to run our workshops. We also are grateful to the Pacific Institute for the Mathematical Sciences (PIMS), the Mathematics of Information Technology and Complex System (MITACS), and the Department of Mathematical and Statistical Sciences at the University of Alberta for significant financial support for the Alberta workshops. Moreover, we express our thanks to our colleagues who have taught with us in our workshops; in alphabetical order: Gary de Young, Leah Edelstein-Keshet, K. P. Hadeler, Christina Kuttler, Michael Li, Frithjof Lutscher, Michael Mackey, Annette Rübiger, Rebecca Tyson, and Pauline van den Driessche. Thanks to Michael Baake, Fred Brauer, three anonymous reviewers, and many of our students for valuable comments



on earlier versions of this text. We would particularly like to thank all student participants of our workshops. Their enthusiasm and interest in mathematical modeling was our motivation to write this book. Patient help and guidance from the SIAM editorial staff was invaluable in the finishing stages of this work. We thank our families for their encouragement and support.

June 2006



**Gerda de Vries** is Associate Professor in the Department of Mathematical and Statistical Sciences at the University of Alberta, Canada.



**Thomas Hillen** is Professor in the Department of Mathematical and Statistical Sciences at the University of Alberta, Canada.



**Mark Lewis** is Professor and Senior Canada Research Chair in Mathematical Biology in the Department of Mathematical and Statistical Sciences and Department of Biological Sciences at the University of Alberta, Canada.



**Johannes Müller** is Professor of Mathematical Methods in Molecular Biology and Biochemistry in the Centre of Mathematical Sciences at the Technical University Munich, Germany.



**Birgitt Schönfisch** is a Scientific Employee in the Department of Medical Biometry at the University of Tübingen, Germany.



# Contents

<b>Preface</b>	<b>ix</b>
<b>I Theoretical Modeling Tools</b>	<b>1</b>
<b>1 Introduction</b>	<b>3</b>
1.1 The Modeling Process . . . . .	3
1.2 Probabilities and Rates . . . . .	4
1.3 Model Classes . . . . .	7
1.4 Exercises for Modeling . . . . .	8
<b>2 Discrete-Time Models</b>	<b>9</b>
2.1 Introduction to Discrete-Time Models . . . . .	9
2.2 Scalar Discrete-Time Models . . . . .	10
2.2.1 Growth of a Population and the Discrete Logistic Equation	10
2.2.2 Cobwebbing, Fixed Points, and Linear Stability Analysis	15
2.2.3 Analysis of the Discrete Logistic Equation . . . . .	18
2.2.4 Alternatives to the Discrete Logistic Equation . . . . .	25
2.2.5 Models in Population Genetics . . . . .	29
2.3 Systems of Discrete-Time Equations . . . . .	36
2.3.1 Love Affairs: Introduction . . . . .	36
2.3.2 Fixed Points and Linear Stability Analysis for Systems of Discrete-Time Equations . . . . .	38
2.3.3 Love Affairs: Model Analysis . . . . .	42
2.3.4 Host–Parasitoid Models . . . . .	44
2.4 Exercises for Discrete-Time Models . . . . .	48
<b>3 Ordinary Differential Equations</b>	<b>55</b>
3.1 Introduction to ODEs . . . . .	55
3.2 Scalar Equations . . . . .	56
3.2.1 The Picard–Lindelöf Theorem . . . . .	59
3.3 Systems of Equations . . . . .	60
3.3.1 Reaction Kinetics . . . . .	60
3.3.2 A General Interaction Model for Two Populations . . . . .	62



3.3.3	A Basic Epidemic Model . . . . .	64
3.3.4	Nondimensionalization . . . . .	65
3.4	Qualitative Analysis of $2 \times 2$ Systems . . . . .	66
3.4.1	Phase-Plane Analysis: Linear Systems . . . . .	67
3.4.2	Nonlinear Systems and Linearization . . . . .	74
3.4.3	Qualitative Analysis of the General Population Interaction Model . . . . .	76
3.4.4	Qualitative Analysis of the Epidemic Model . . . . .	78
3.5	General Systems of Three or More Equations . . . . .	80
3.6	Discrete-Time Models from Continuous-Time Models . . . . .	81
3.6.1	Numerical Methods . . . . .	81
3.6.2	The Time-One Map . . . . .	81
3.7	Elementary Bifurcations . . . . .	83
3.7.1	Saddle-Node Bifurcation . . . . .	84
3.7.2	Transcritical Bifurcation . . . . .	84
3.7.3	Pitchfork Bifurcation . . . . .	85
3.7.4	Hopf Bifurcation . . . . .	86
3.7.5	The Spruce Budworm Model . . . . .	88
3.8	Further Reading . . . . .	89
3.9	Exercises for ODEs . . . . .	90
<b>4</b>	<b>Partial Differential Equations</b>	<b>97</b>
4.1	Partial Derivatives . . . . .	97
4.2	An Age-Structured Model . . . . .	98
4.2.1	Derivation . . . . .	98
4.2.2	Solution . . . . .	100
4.3	Reaction-Diffusion Equations . . . . .	102
4.3.1	Derivation of Reaction-Diffusion Equations . . . . .	102
4.3.2	The Fundamental Solution . . . . .	104
4.3.3	Critical Domain Size . . . . .	106
4.3.4	Traveling Waves . . . . .	111
4.4	Further Reading . . . . .	115
4.5	Exercises for PDEs . . . . .	116
<b>5</b>	<b>Stochastic Models</b>	<b>121</b>
5.1	Introduction . . . . .	121
5.2	Markov Chains . . . . .	122
5.2.1	A Two-Tree Forest Ecosystem . . . . .	122
5.2.2	Markov Chain Theory . . . . .	124
5.2.3	The Princeton Forest Ecosystem . . . . .	124
5.3	Working with Random Variables . . . . .	126
5.3.1	Probability Density . . . . .	126
5.3.2	Probability Mass . . . . .	127
5.3.3	Descriptive Statistics . . . . .	129
5.3.4	The Generating Function . . . . .	130
5.4	Diffusion Processes . . . . .	132

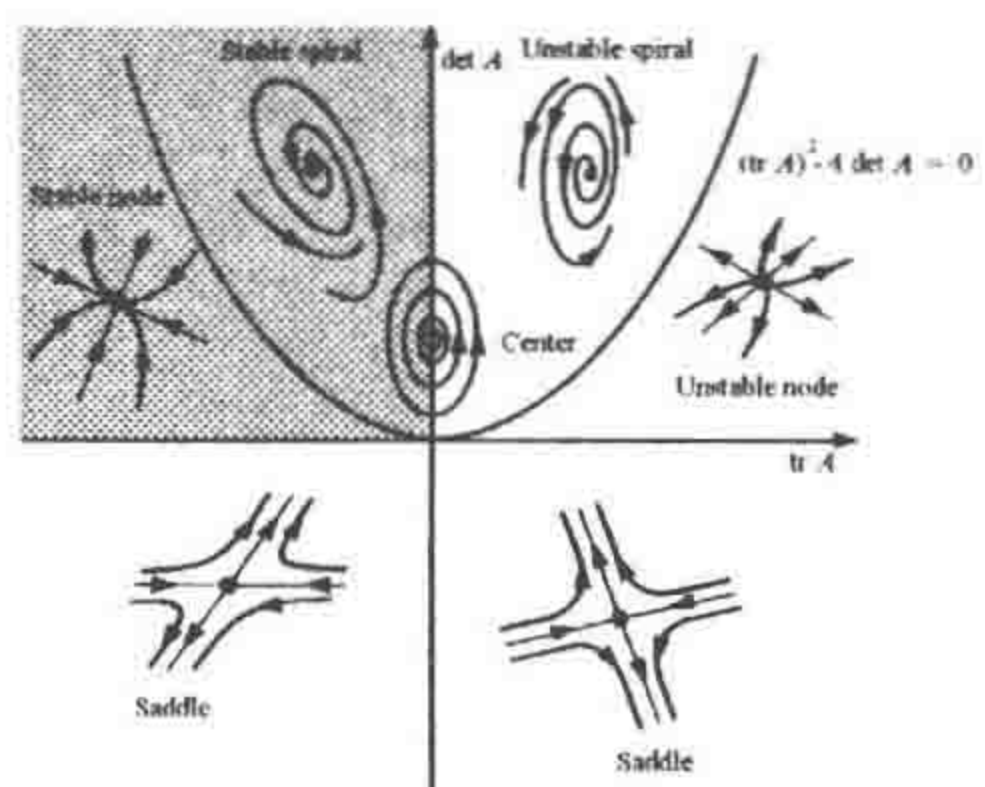


5.4.1	Random Motion in One Dimension . . . . .	133
5.4.2	Diffusion Equation . . . . .	135
5.5	Branching Processes . . . . .	136
5.5.1	Galton–Watson Process . . . . .	136
5.5.2	Polymerase Chain Reaction . . . . .	139
5.6	Linear Birth and Death Process . . . . .	141
5.6.1	Pure Birth Process . . . . .	141
5.6.2	Birth and Death Process . . . . .	144
5.7	Nonlinear Birth-Death Process . . . . .	147
5.7.1	A Model for the Common Cold in Households . . . . .	148
5.7.2	Embedded Time-Discrete Markov Process and Final Size Distribution . . . . .	149
5.8	Exercises for Stochastic Models . . . . .	151
<b>6</b>	<b>Cellular Automata and Related Models</b>	<b>155</b>
6.1	Introduction to Cellular Automata . . . . .	155
6.1.1	Wolfram’s Classification . . . . .	157
6.1.2	The Game of Life . . . . .	159
6.1.3	Some Theoretical Results on Cellular Automata . . . . .	160
6.2	Greenberg–Hastings Automata . . . . .	161
6.2.1	Relation to an SIR Model . . . . .	164
6.3	Generalized Cellular Automata . . . . .	165
6.3.1	Automata with Stochastic Rules . . . . .	165
6.3.2	Grid Modifications . . . . .	167
6.3.3	Asynchronous Dynamics . . . . .	168
6.4	Related Models . . . . .	170
6.5	Further Reading . . . . .	171
6.6	Exercises for Cellular Automata . . . . .	172
<b>7</b>	<b>Estimating Parameters</b>	<b>175</b>
7.1	Introduction . . . . .	175
7.2	The Likelihood Function . . . . .	176
7.2.1	Stochastic Models without Measurement Error . . . . .	176
7.2.2	Deterministic Models . . . . .	181
7.3	Model Comparison . . . . .	187
7.3.1	Akaike Information Criterion . . . . .	187
7.3.2	Likelihood Ratio Test for Nested Models . . . . .	189
7.3.3	Cross Validation . . . . .	192
7.4	Optimization Algorithms . . . . .	193
7.4.1	Algorithms . . . . .	193
7.4.2	Positivity . . . . .	194
7.5	What Did We Learn? . . . . .	195
7.6	Further Reading . . . . .	196
7.7	Exercises for Parameter Estimation . . . . .	196



<b>II</b>	<b>Self-Guided Computer Tutorial</b>	<b>199</b>
<b>8</b>	<b>Maple Course</b>	<b>201</b>
8.1	First Steps in Maple . . . . .	201
8.1.1	Constants and Functions . . . . .	201
8.1.2	Working with Data Sets . . . . .	205
8.1.3	Linear Regression . . . . .	207
8.2	Discrete Dynamical Systems: The Ricker Model . . . . .	212
8.2.1	Procedures in Maple . . . . .	215
8.2.2	Feigenbaum Diagram and Bifurcation Analysis . . . . .	217
8.2.3	Application of the Ricker Model to <i>Vespula vulgaris</i> . . .	219
8.3	Stochastic Models with Maple . . . . .	220
8.4	ODEs: Applications to an Epidemic Model and a Predator–Prey Model	223
8.4.1	The SIR Model of Kermack and McKendrick . . . . .	223
8.4.2	A Predator–Prey Model . . . . .	225
8.5	PDEs: An Age-Structured Model . . . . .	228
8.6	Stochastic Models: Common Colds in Households . . . . .	232
8.6.1	Application to Data . . . . .	234
<b>III</b>	<b>Projects</b>	<b>237</b>
<b>9</b>	<b>Project Descriptions</b>	<b>239</b>
9.1	Epidemic Models . . . . .	239
9.2	Population Dynamics . . . . .	245
9.3	Models for Spatial Spread . . . . .	249
9.4	Physiology . . . . .	254
<b>10</b>	<b>Solved Projects</b>	<b>263</b>
10.1	Cell Competition . . . . .	263
10.1.1	<i>Paramecium caudatum</i> in Isolation . . . . .	263
10.1.2	The Two Populations in Competition . . . . .	266
10.1.3	Phase-Plane Analysis of the Competition Model . . . . .	269
10.1.4	Model Prediction . . . . .	273
10.1.5	An Alternative Hypothesis . . . . .	273
10.2	The Chemotactic Paradox . . . . .	274
10.2.1	A Resolution of the Chemotactic Paradox . . . . .	274
10.2.2	Discussion . . . . .	278
	<b>Appendix: Further Reading</b>	<b>283</b>
	<b>Bibliography</b>	<b>287</b>
	<b>Author Index</b>	<b>297</b>
	<b>Index</b>	<b>301</b>





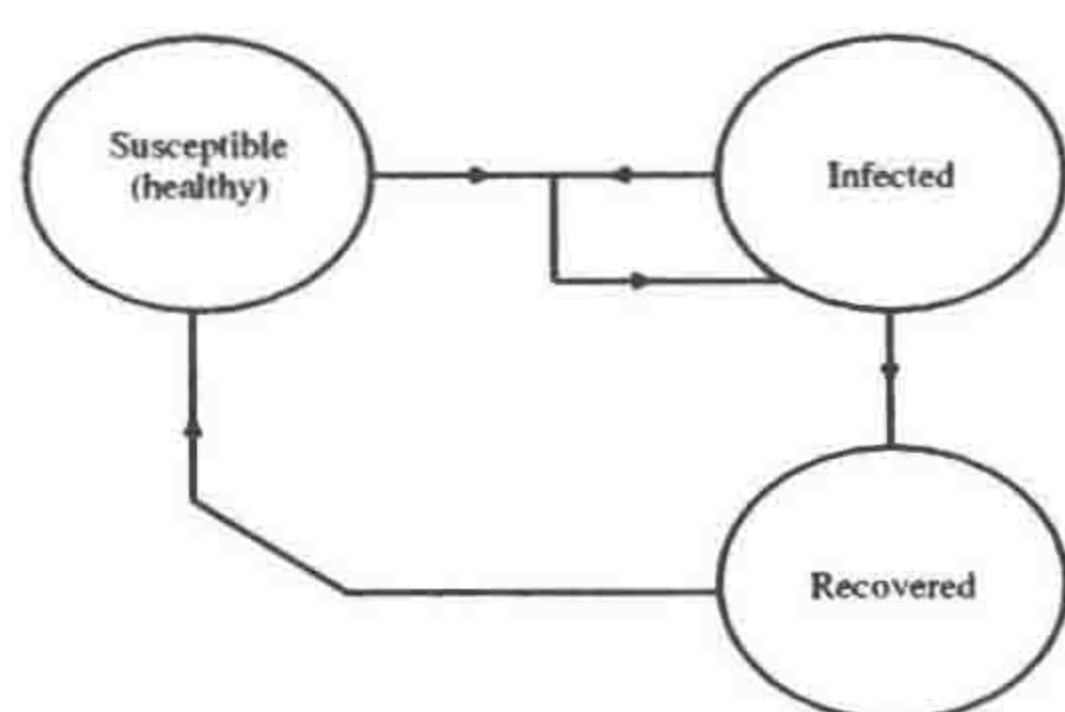
## Part I

# Theoretical Modeling Tools









## Chapter 1

# Introduction

### 1.1 The Modeling Process

Mathematical biology dwells at the interface of two fields: applied/computational mathematics and biology. Individually, these fields are growing quickly due to rapidly changing technology and newly emerging subdisciplines. Coupled together, the fields provide the basis for the emerging scientific discipline of mathematical biology, whose focus is interdisciplinary scientific problems in quantitative life sciences.

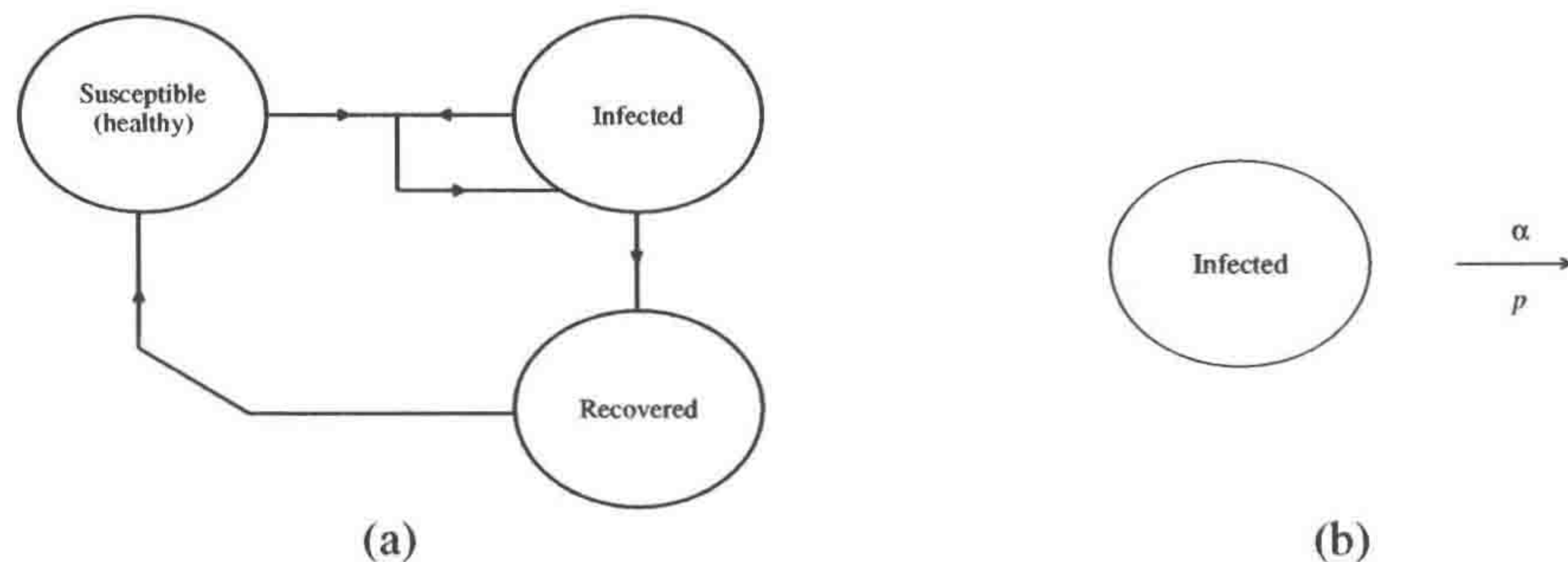
What can biology offer mathematics and computation? Biological models offer a seemingly endless supply of challenging and interesting nonlinear problems to solve. These nonlinear problems can provide a testing ground for applied mathematical and computational methods, and generate the impetus to develop new mathematical and computational methods and approaches.

What can mathematics and computation offer biology? Mathematics and computation can help solve a growing problem in biological research. Data collection, varying from gene sequencing to remote sensing via satellites, is now inundating biologists with complex patterns of observations. The ability to collect new data outstrips our ability to heuristically reason mechanisms of cause and effect in complex systems. It is the analysis of mathematical models that allows us to formalize the cause and effect process and tie it to the biological observations.

The mathematical model describes interactions between biological components. Analysis of the model, via computational and applied mathematical methods, allows us to deduce the consequences of the interactions. For example, voltage-dependent data on movement of electrically charged ions across a nerve membrane are inputs for models of electrophysiology. The output is a prediction of the dynamics of electrical activity in nerves. The behavior and survival of newly infected individuals are inputs to disease models. The output is a prediction of when and where the disease will outbreak, and how it can be controlled.

To become a successful modeler, modeling tools are required. The first part of this book gives an introduction to some of the more powerful modeling tools, such as discrete models, ordinary differential equations, partial differential equations, stochastic models,





**Figure 1.1.** (a) Arrow diagram for a simple epidemic model, showing the relationships between the classes of susceptible, infected, and recovered individuals. (b) Subgraph of the arrow diagram in (a) representing the recovery of infected individuals, with probability  $p$  or rate  $\alpha$ .

cellular automata, and parameter estimation techniques. The second and third parts of the book apply the modeling tools to biological problems.

## 1.2 Probabilities and Rates

We start with the derivation of a simple epidemic model for the spread of an infectious disease, such as influenza, through a population of healthy individuals. Assume that one infected individual is introduced into the population. In addition, assume that the infection is spread from individual to individual through contact, and that the infected recover after a certain period of time (two weeks for influenza). Recovered individuals are not available to catch the disease again.

Thus, after some time, the population consists of three types of individuals, namely, susceptible (healthy), infected, and recovered individuals. The relationships between these three classes are shown in Figure 1.1 (a). Note that in the diagram, recovered individuals can become susceptible again. In this case, we can think of recovered individuals being temporarily immune to the disease. Individuals return to the susceptible class when the immunity wears off.

In order to create a model for this situation, we need to quantify this diagram. To do that, we follow these three steps:

1. First, we identify the important quantities (the *dependent variables*) to keep track of. In our example, there are three classes of individuals. Let  $S$  be the number of susceptibles in the population,  $I$  the number infected, and  $R$  the number recovered.
2. Second, we identify the *independent variables*, such as time  $t$ , space  $x$ , or age  $a$ , and so on. For our example, we write  $S(x, t)$ ,  $I(x, t)$ , and  $R(x, t)$  if we wish to include time and space dependence, but not age dependence.
3. Finally, we quantify the transitions and/or interactions between these classes, as indicated by the arrows in Figure 1.1 (a). To do this, we use either *probabilities* or *rates*, as explained below.