Mathematical Models in Biology

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Mathematical Models in Biology

Leah Edelstein-Keshet
University of British Columbia
Vancouver, British Columbia, Canada

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Dedicated to my family,

Aviv, Ilan, and Joshua Keshet,

and in loving memory of my parents,

Tikva and Michael Edelstein

Contents

Preface to the Classics Edition

This book originated from interests that I developed while still at graduate school, but its actual writing and evolution spanned the mid 1980s. At that time, I was a visiting assistant professor, at an early career stage. I had the pleasure of teaching undergraduate courses in mathematical biology at both Brown and Duke Universities and this book evolved from those experiences. In a sense, this was a process of discovery: of the many beautiful areas of application of mathematics, and of the interconnections between what, at first glance, seem like distinct topics. It is safe to say that, during this gestation period of *Mathematical Models in Biology* (henceforth abbreviated MMIB), the field of mathematical biology was still quite young. The selection of textbooks and teaching materials at the time was quite limited. At the time, mathematical biology was viewed by many as a "soft version" of mathematics, or an "irrelevant" appendix to biology.

Shortly after the birth of MMIB, a revolution was brewing. This was to make headlines in the 1990s: genomics was about to take center stage. One result of the genomics era has been the astonishing discovery by biologists that mathematics is not only useful, but indispensable. This has meant that mathematical biology has emerged as one of the prominent areas of interdisciplinary research in the new millennium. As a result, there has been much resurgent interest in, and a huge expansion of, the field(s) collectively called "Mathematical Biology." This has also led to numerous books on the subject, at all levels of presentation, and covering a wealth of new aspects. No single book can give justice to this new wealth of interesting developments. (A partial list of popular choices is included below.)

When I wrote this book, I was more absorbed in discovering the beauty of the subject than in writing an authoritative text. The possibility that this collection of material would find favor in others' eyes was too remote to contemplate. It came as a pleasant surprise when the book became a useful text for other faculty and students elsewhere. Some 20 years since its gestation, MMIB is now into its "gray-haired" days, showing signs of age. It is in many respects out of date, as the field has evolved and expanded in so many ways. As a senior citizen, the book has become more costly, and not quite as attractive or fashionable as many of its younger competitors. But at least, in some respects, a few attributes keep it from the mortuary: as a summary of simple ordinary differential equation models (of first and second order), dimensional analysis, phase plane methods, and some basic behavior of classic models in ecology, epidemiology, and other areas, MMIB is still intact. An introductory treatment of partial differential equation models, and especially the linear stability theory applied to Turing reaction-diffusion systems and to slime mould aggregation, is still seen as useful by some readers.

To many students who have stumbled over errors and typographical mistakes that were not cleared up over the years in the first edition, I apologize. In some belated attempt to address these, a list of errata has been assembled to go with this new printing. It is my intent to update this list on my website, www.math.ubc.ca/~keshet/, and I welcome and appreciate the help of readers in spotting other unreported mistakes.

The gaps in coverage of the field have grown and become more prominent with time: there is no treatment of stochastic methods, game theory and evolution, and scarce mention of population genetics. The new developments in cellular and molecular biology (which this author is attempting to follow) are virtually absent, as are bioinformatics and genomics. While the motivation to rewrite a book for the new mathematical biology is strong, the presence of many current offerings, and the continued rush of full academic responsibilities, lengthen the delay. While this long overdue development is being planned, SIAM has graciously accepted the charge of keeping this book alive for readers who still find some of the material useful or instructive. The author hopes that, in this SIAM Classics edition, the availability of this collection of simple, intuitive modeling will continue to facilitate the entry of newcomers into the rich and interesting area of mathematical biology.

Bibliography of Recent Books in Related Areas

For the benefit of newcomers to mathematical biology, the list below, with partial annotations, may be helpful for finding newer books that might complement, replace, or outdo the current text. I have included here some references that were suggested by colleagues (on which I could not yet comment from personal experience).

1. Adler, Frederick R. (1998) Modeling The Dynamics of Life: Calculus and Probability for Life Scientists, Brooks/Cole. (A first-year undergraduate text on calculus for astute life-science students.)

2. Allan, Linda J.S. (2003) An Introduction to Stochastic Processes with Applications to Biology. Pearson Prentice–Hall, Upper Saddle River, NJ. (Discusses nondeterministic models. Includes MATLAB® code.)

3. Altman, Elizabeth S. and Rhodes, John A. (2004) Mathematical Models in Biology, An Introduction, Cambridge University Press, Cambridge, UK. (Introductory text with emphasis on discrete models. Has sections on Markov models of molecular evolution, phylogenetic tree construction, and MATLAB examples, curvefitting, and analysis of numerical data.)

4. Beltrami, Edward J. (1993) Mathematical Models in the Social and Biological Sciences, Jones and Bartlett Publishers, Boston.

5. Bower, James M. and Bolouri, Hamid, eds. (2003) Computational Modeling of Genetic and Biochemical Networks, MIT Press, Cambridge, MA.

6. Brauer, Fred, and Castillo-Chavez, Carlos (2001) Mathematical Models in Population Biology and Epidemiology, Springer-Verlag, New York. (This is a nice recent book that concentrates on models in population biology, epidemiology, and resource management. It is a collection of material used over many years to teach summer courses on the subject at Cornell University.)

7. Britton, Nick F. (2002) Essential Mathematical Biology, Springer, New York. (A slim and very affordable book with many similar topics.)

8. Brown, James and West, Geoffrey, eds. (2000) Scaling in Biology, Oxford University Press, Oxford, UK. (An advanced monograph, with a survey of recent developments in the field.)

9. Burton, Richard F. (2000) Physiology by Numbers: An Encouragement to Quantitative Thinking, 2nd ed., Cambridge University Press, Cambridge, UK.

10. Clark, Colin (1990) Mathematical Bioeconomics: The Optimal Management of Renewable Resources, John Wiley & Sons, Inc., New York. (A revision of a classic book; an essential reference for resource management and bio-economic models.)

11. Clark, Colin W. and Mangel, Marc (2000) Dynamic State Variable Models in Ecology. Oxford University Press, Oxford, UK.

12. Daley, Daryl J. and Gani, Joe (1999; reprinted 2001) Epidemic Modelling, An Introduction, Cambridge University Press, Cambridge, UK. (Includes a historical chapter, deterministic and stochastic models in continuous and discrete time, fitting epidemic data, and discussion of control of disease.)

13. de Vries, Gurda, Hillen, Thomas, Lewis, Mark, Müller, Johannes, and Schöenfisch, Birgitt (to appear) Introduction to Mathematical Modeling of the Biological Systems, SIAM, Philadelphia. (Includes material taught at yearly summer workshops in mathematical biology at the University of Alberta.)

14. Denny, Mark and Gaines, Steven (2000) Chance in Biology: Using Probability to Explore Nature. Princeton University Press, Princeton, NJ.

15. Diekmann, Odo and Heesterbeek, J.A.P. (1999) Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation, John Wiley & Sons, Inc., New York. (An introduction to models for epidemics in structured populations.)

16. Diekmann, Odo, Durrett, Richard, Hadeler, Karl P., Smith, Hal, and Capasso, Vincenzo (2000) Mathematics Inspired by Biology, Springer, New York.

17. Doucet, Paul and Sloep, Peter B. (1992) Mathematical Modeling in the Life Sciences, Ellis Horwood Ltd., New York.

18. Ermentrout, Bard (2002) Simulating, Analyzing, and Animating Dynamical Systems: A Guide to XPPAUT for Researchers and Students, SIAM, Philadelphia. (An excellent resource for simulating ODE and some PDE models, with many illustrations from biology.)

19. Fall, Christopher, Marland, Eric, Wagner, John, and Tyson, John, eds. (2002) Computational Cell Biology, Springer-Verlag, New York. (An introduction to modelling in molecular and cellular biology, with emphasis on case studies and a computational approach. Joel Kaiser's death in 1999 halted the development of a book he had planned, and this is a compiled, expanded, edited, and completed version assembled by colleagues and former students.)

20. Farkas, Miklós (2001) Dynamical Models in Biology, Academic Press, New York.

21. Goldbeter, Albert (1996) Biochemical Oscillations and Cellular Rhythms: Molecular Bases of Periodic and Chaotic Behaviour, Cambridge University Press, Cambridge, UK.

22. Haefner, James (1996) Modeling Biological Systems, Principles and Applications, Kluwer, Boston.

23. Hannon, Bruce M. and Matthias, Ruth (1997) Modeling Dynamic Biological Systems, Springer-Verlag, New York. (This book uses software such as STELLA and MADONNA to explore and simulate model behavior.)

24. Harrison, Lionel G. (1993) Kinetic Theory of Living Pattern, Cambridge University Press, Cambridge, UK. (This book concentrates predominantly on pattern formation and is accessible to people with little mathematical background.)

25. Hastings, Alan (1997) Population Biology: Concepts and Models, Springer-Verlag, New York.

26. Heinrich, Reinhart and Schuster, Stefan (1996) The Regulation and Evolution of Cellular Systems, Kluwer, Boston.

27. Hilborn, Ray and Mangel, Marc (1997) The Ecological Detective—Confronting Models with Data. Monographs in Population Biology, no. 28. Princeton University Press, Princeton, NJ.

28. Hoppensteadt, Frank C. and Peskin, Charles S. (2001) Modeling and Simulation in Medicine and the Life Sciences, Springer, New York. (This book includes models of physiological processes (circulation, gas exchange in the lungs, control of cell volume, the renal counter-current multiplier mechanism, and muscle mechanics, etc.) as well as population biology phenomena such as demographics, genetics, epidemics, and dispersal.)

29. Jones, D. S. and Sleeman, Brian D. (2003) Differential Equations and Mathematical Biology, Chapman and Hall/CRC, Boca Raton, FL.

30. Kaplan, Daniel and Glass, Leon (1995) Understanding Nonlinear Dynamics, Springer-Verlag, New York. (An accessible elementary introduction to nonlinear dynamics that includes chapters on Boolean networks and cellular automata, fractals, and time-series analysis.)

31. Kimmel, Marek and Axelrod, David E. (2002) Branching Processes in Biology, Springer-Verlag, New York.

32. Levin, Simon, ed. (1994) Frontiers in Mathematical Biology. Springer, New York. (The final, 100th volume in the series Lecture Notes in Biomathematics, with contributions by many leaders in mathematical biology.)

33. Levin, Simon (2000) Fragile Dominion: Complexity and the Commons, Perseus Books Group, New York. (A book on complexity in ecology for the general reader.)

34. Keener, James and Sneyd, James (1998) Mathematical Physiology, Springer, New York. (An excellent graduate-level text on mathematical physiology.)

35. Kot, Mark (2001) Elements of Mathematical Ecology. Cambridge University Press, Cambridge, UK.

36. Mahaffy, Joseph M. and Chavez-Ross, Alexandra (2004) Calculus: A Modeling Approach for the Life Sciences, Pearson Custom Publishing, Upper Saddle River, NJ. (Based on a course for life scientists, with ample realistic examples. Developed and taught by J.M. Mahaffy at San Diego State University.)

37. May, Robert M. and Nowak, Martin A. (2000) Virus Dynamics: The Mathematical Foundations of Immunology and Virology, Oxford University Press, Oxford, UK. (A book intended for researchers and graduate students interested in viral diseases, antiviral therapy and drug resistance, HIV, the immune response, and other advanced research topics.)

38. Mazumdar, J. (1999) An Introduction to Mathematical Physiology and Biology, Cambridge University Press, Cambridge, UK.

39. Murray, James D. (2002) Mathematical Biology I and II, 3rd ed., Springer-Verlag, New York. (Originally published one year after MMIB, this was a more advanced book, suitable for graduate students. It has been a vital reference for all practitioners in mathematical biology. Now in its third edition, this book has become a two-volume set.)

40. Neuhauser, Claudia (2003) Calculus for Biology and Medicine, 2nd ed., Pearson Custom Publishing, Upper Saddle River, NJ. (A calculus book aimed at life science students.)

41. Okubo, Akira and Levin, Simon A. (2002) Diffusion and Ecological Problems, 2nd ed. Springer-Verlag, New York. (An expanded edition of the original book by Okubo, with edited versions of his earlier work.)

42. Othmer, Hans, Adler, Fred R., Lewis, Mark A., and Dallon, John C. (1996) Case Studies in Mathematical Modeling: Ecology, Physiology and Cell Biology, Prentice–Hall, Upper Saddle River, NJ. (This is an edited volume that comprises 15 chapters grouped loosely into the three categories. The individual chapters are written by many leading researchers in mathematical biology. This book is suitable for a more advanced level.)

43. Roughgarden, J. (1998) Primer of Ecological Theory. Prentice–Hall, Upper Saddle River, NJ.

44. Segel, Lee A. (1992) Biological Kinetics, Cambridge University Press, Cambridge, UK.

45. Strogatz, Steven H. (2001) Nonlinear Dynamics and Chaos: With Applications in Physics, Biology, Chemistry, and Engineering (Studies in Nonlinearity), Perseus Books Group, New York. (Anything written by this wonderful author has a prominent place on my shelf. It is a pleasure to discover the beautiful explanations and motivations that he has invented. This book makes teaching the material a pleasure.)

46. Stewart, Ian (1998) Life's Other Secret: The New Mathematics of the Living World, John Wiley & Sons, Inc., New York. (An introduction for the general lay reader.)

47. Taubes, Clifford H. (2000) Modeling Differential Equations in Biology, Prentice–Hall, Upper Saddle River, NJ. (This is a lovely book aimed at introducing biological readings and concepts to mathematics students. It has the unique feature of inclusion of a host of interesting and relevant original papers that can be used for discussion.)

48. Thieme, Horst R. (2003) Mathematics in Population Biology, Princeton University Press, Princeton, NJ.

49. Turchin, Peter (2003) Complex Population Dynamics: A Theoretical/ Empirical Synthesis, Princeton University Press, Princeton, NJ. (Combines a theoretical framework with empirical and data-analysis approaches, with interesting case studies. This book is a great sequel to any previous treatise on predator-prey (and other) population cycles. The author's strong opinions, good writing, and eminent good sense make for a great read.)

50. Vogel, Steven (1996) Life in Moving Fluids: The Physical Biology of Flow, Princeton University Press, Princeton, NJ. (A recent edition of a classic with great insights. For readers with little or no mathematical expertise.)

51. Yeargers, Edward K., Shonkwiler, Rau W., and Herod, James V. (1996) An Introduction to the Mathematics of Biology, Birkhäuser, Boston, MA.

Preface

Mathematical Models in Biology began as a set of lecture notes for a course taught at Brown University. It has since evolved through several years of classroom testing at Brown and Duke Universities. The task of setting down words on paper became a cherished hobby that kept the long process of shaping and reshaping the various manuscripts from becoming an arduous job.

My aim has been to present instances of interaction between two major disciplines, biology and mathematics. The goal has been that of addressing a fairly wide audience. It is my hope that students of biology will find this text useful as a summary of modern mathematical methods currently used in modelling, and furthermore, that students of applied mathematics might benefit from examples of applications of mathematics to real-life problems. As little background as possible (both in mathematics and in biology) has been assumed throughout the book: prerequisites are basic calculus so that undergraduate students, as well as beginning graduate students, will find most of the material accessible.

Other background mathematics such as topics from linear algebra and ordinary differential equations are given in full detail herein as the need arises. Students familiar with this material can advance at a more rapid pace through the book.

There is far more material here than can be taught in a single semester. This leaves some room for personal taste on the part of the instructor as to what to cover. (See table for several suggestions.) While necessitating selectivity in class, the length of the book is intended to encourage independent student reading and exploration of material not formally taught. References to additional sources are included where possible so that the text may be used as a reference source for the more advanced reader.

Features of this book are outlined below.

Organization: Models discussed fall into three broad categories: discrete, continuous, and spatially distributed (forming respectively Parts I, II, and III in the text). The first describes populations that reproduce at fixed intervals; the second pertains to processes that may be viewed as continuous in time; the last treats systems for which distribution over space is an important feature.

Approach: (1) Concepts basic in modelling are introduced in the early chapters and reappear throughout later material. For example *steady states, stability,* and *parameter variations* are first encountered within the context of difference equations and reemerge in models based on ordinary and partial differential equations.

(2) An emphasis is placed on mathematics as a means of unifying related

concepts. For example, we often observe that certain models formulated to describe a given process, whether biological or not, may apply to a different situation. (An illustration of this is the fact that molecular diffusion and migration of a population are describable by the same formal model; see 9.4–9.5, 10.1).

(3) Contrasting modelling approaches or methods are applied to certain biological topics. (For instance a problem on plant-herbivore dynamics is treated in three different ways in Chapters 3, 5, and 10.)

(4) Mathematics is used as a means of obtaining an appreciation of problems that would be hard to understand through verbal reasoning alone. Mathematics is used as a tool rather than as a formalism.

(5) In analyzing models, the emphasis is on qualitative methods and graphical or geometric arguments, not on lengthy calculations.

Scope: The models treated are deterministic and have deliberately been kept simple. In most cases, insight can be acquired by mathematical analysis alone, without the need for extensive numerical simulation. This sometimes restricts realism, but enhances appreciation of broad features or general trends.

Mathematical topics: Material in this book can be used as an introduction to or as a review of topics from linear algebra (matrices, eigenvalues, eigenvectors), properties of ordinary differential equations (classification, qualitative solutions, phase plane methods), difference equations, and some properties of partial differential equations. (This is not, however, a self-contained text on these subjects.)

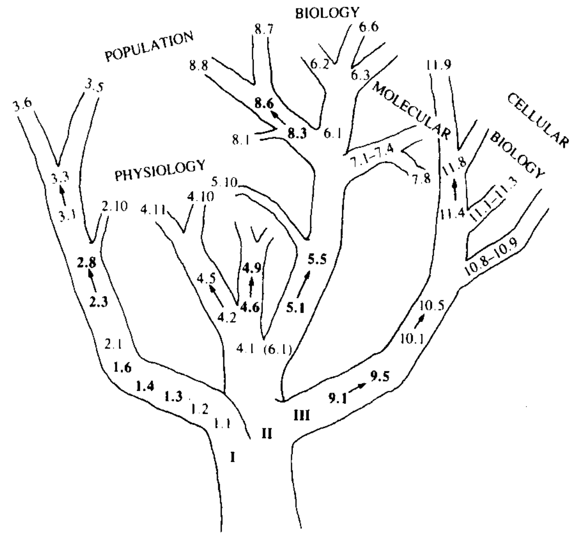
Biological topics: Biological applications discussed range from the subcellular molecular systems and cellular behavior to physiological problems, population biology, and developmental biology. Previous biological familiarity is not assumed.

Problems: Problems follow each chapter and have different degrees of difficulty. Some are geared towards helping the student practice mathematical techniques. Others guide the student through a modelling topic in which the formulation and analysis of equations are carried out. Certain problems, based on models which have been published elsewhere, are meant to promote an appreciation of the literature and encourage the use of library resources.

Possible usage: The table indicates three possible courses with emphasis on (a) population biology, (b) molecular, cellular and physiological topics, and (c) a general modelling survey, which could be taught using this book. Parentheses ( ) indicate optional material which could be omitted in the interest of saving time. Curly brackets { } denote that some selection of the indicated topics is advisable, at the instructor's discretion. It is possible to omit Chapter 4 and Section 5.10 if Chapter 6 is covered in detail so that methods of Chapter 5 are amply illustrated. While it is advisable to combine material from Parts I through III, there is ample material in Part II alone (Chapters 4–8) for a one-semester course on ordinary differential equation models.

The relationship of various sections in the book is depicted in the following figure. Beginning at the trunk and ascending upwards along various branches, boldface section numbers denote material that is basic and essential for the understanding of topics higher up.

The interrelationships of sections and chapters are shown in this tree. Ascending from the trunk, roman numerals refer to Parts I, II, and III of the book. Boldface section numbers highlight important background material. Branches converge on several topics, as indicated in the diagram.



Selected material for three possible courses, with different emphasis.

	Chapter	Population Biology	Molecular, Cellular, and Physiological Topics	General Survey
I	1	1.1–1.6 (1.9, 1.10)	1.1, 1.3, 1.4, 1.6–1.9	1.1–1.7, (1.8), 1.9, (1.10)
	2	2.1–2.3, 2.5–2.8	2.1–2.8, 2.10	2.1–2.3, (2.4), 2.5–2.8, (2.9–2.10)
	3	3.1–3.4, (3.5), 3.6	(3.6)	3.1–3.3, (3.6)
II	4	4.1, (4.2–4.10)	all	4.1–4.7, (4.8), 4.9–4.10, (4.11)
	5	all	all	all but (5.3, 5.10–5.11)
	6	all	(6.3, 6.6–6.7)	6.1, {6.2–6.3, 6.6}
	7		7.1–7.4, (7.5–7.9)	7.1–7.3, {7.5–7.8}
	8	8.3, (8.6), 8.7	8.1–8.5, (8.6–8.7), 8.8, (8.9)	8.1–8.5, {8.7–8.9}
II	9	(9.1), 9.2, 9.4–9.5	(9.1), 9.2, (9.3), 9.4–9.8, (9.9)	(9.1), 9.2, (9.3), 9.4–9.5, {9.6–9.9}
	10	10.1, {10.2–10.4} 10.5–10.6, (10.8, 10.9)	10.1–10.2, 10.5–10.6, {10.7–10.10}	10.1–10.2, {10.3–10.4}, 10.5–10.6, {10.7–10.10}
	11	(11.4–11.6, 11.9)	11.1–11.3 or 11.4–11.8 or both	11.1–11.3 or 11.4–11.8, (11.9)

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The teaching styles, ideas, and specific lectures given by several colleagues and peers have strongly influenced the selection and treatment of many subjects included here: Among these are Peter Kareiva, University of Washington, with whom the original course was designed and taught (Sections 1.10, 3.1–3.4, 3.6, 6.6–6.7, 10.1, 11.8–11.9); Lee A. Segel, Weizmann Institute of Science (4.2–4.5, 4.10, 5.10, 7.1–7.2, 9.3, 10.2, 11.1–11.6); H. Tom Banks, Brown University (9.3); and Michael Reed, Duke University (10.7). I am also greatly indebted to Douglas Lauffenburger and Elizabeth Fisher, University of Pennsylvania, for providing references and prepublication data and results for the material in Section 9.7.

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Any comments from readers on the material, or on errors and misprints would be welcomed.

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Errata

The notation for line numbers refer to lines counting down from the top of the page (positive values) and lines counting up from the bottom of the page (negative values). I include footnotes and section headings in the line count.

An updated Errata is maintained at www.math.ubc.ca/~keshet/

Preface.

- Page xv, bottom: Last brace should be labeled III.

Chapter 1.

- Page 12, line –7: Insert C in the last term:

$$C\lambda^{n+2} - (a_{11} + a_{22})C\lambda^{n+1} + (a_{11}a_{22} - a_{12}a_{21})C\lambda^{n} = 0.$$

- Page 17, line –16: $\gamma = 2.0$ (not 0.2).
- Page 18: The caption to Table 1.1 should include $p_0 = 100$, and (a) $p_1 = 80$, (b) $p_1 = 96$.
- Page 19: In Section 1.6, delete the subscript n in all occurrences of b_n (in properties 1 and 3).
- Page 25, caption to Figure 1.5: Replace the last sentence with "The amplitude of oscillation is related to r^n and the frequency is ϕ...".
- Page 27, line –9: "As in problem 1, ..."
- Page 29, Problem 1: Change last sign: $x_{n+2} - 3x_{n+1} + 2x_n = 0$. Disregard 3(b).

- Page 30: The Taylor series for sine and cosine in Problem 5 are incorrect and should be replaced by

$$\sin(x) = x - \frac{x^3}{3!} + \frac{x^5}{5!} - \frac{x^7}{7!} + \frac{x^9}{9!} + \dots$$

$$\cos(x) = 1 - \frac{x^2}{2!} + \frac{x^4}{4!} - \frac{x^6}{6!} + \frac{x^8}{8!} + \dots$$

  Disregard Problem 6(c).

  Problem 6(f) should read

$$x_{n+1} = -\frac{x_n}{4} + 3y_n$$

- Page 31, Problem 9(c): $x_{n+2} + 2x_{n+1} + 2x_n = 0$.
- Page 33: The historical note is irrelevant to problem 14(b). Disregard.
- Page 34, line 7: $a + b > 1$.
- Page 34, problem 19(b): The first equation is missing σ:

$$S^0_{n+1} = \sigma\gamma(\beta S^1_n + \alpha S^0_n)$$

- Page 35: The diagram in the figure for problem 19 is confusing and needs to be improved. Problem 19(c)(ii) should read

$$p_{n+2} - \alpha\sigma\gamma p_{n+1} - \beta\sigma^2\gamma(1-\alpha)p_n = 0.$$

  The matrix in Problem 19(d) should be

$$\begin{pmatrix} \sigma\gamma\alpha & \sigma\gamma\beta & \sigma\gamma\delta & \sigma\gamma\epsilon \\ \sigma(1-\alpha) & 0 & 0 & 0 \\ 0 & \sigma(1+\alpha-\beta) & 0 & 0 \\ 0 & 0 & \sigma(1+\alpha+\beta-\delta) & 0 \end{pmatrix}$$

Chapter 2.

- Page 48, line –3: "The two possible roots,... are real if $r > -1$ and ...".
- Page 59, line –4: Condition 2 should read $(-1)^4 P(-1) = \ldots$
- Page 65: In Problem 16(f) the value "$B = 12$ births per 1000 people" may be incorrect for the desired effect.
- Page 66, Problem 17: "This problem pursues further the topic... first described in Section 1.9 and problem 3 (page 27) of Chapter 1."
- Page 71, caption to Figure 2.13, second-to-last sentence: "P_3 is actually the height [at (x, y)]..."

Chapter 3.

- Page 80: After equation (16), insert "and $r! = r(r-1)(r-2)\ldots 1$." Before equation (19) insert "(Recall that $0! = 1$ by definition.)"
- Page 82, line 1: Replace $\bar{N}$ with $\bar{P}$.

  Line –3 in box: "consequently $S(\lambda) < 0$ for $\lambda > 1$."
- Page 85, line 12: "In Figures 3.6 through 8 $q = 0.40$, $a = 0.2$ are kept fixed..."
- Pages 89–99: This material on plant-herbivore interactions should be disregarded.
- Page 94: Equations (43) and (44), and the line immediately following, should have lowercase v_n or v_{n+1} (not uppercase).
- Page 103: In Problem 4(b), the equation should read

$$\bar{N} = \frac{\lambda^{1/b} - 1}{a}$$

- Page 105: In Problem 11(e) insert the constant c:

$$P_{t+1} = c(N_t - EK)(1 - e^{-aP_t}).$$

- Page 106: Problem 15(c) should read $\bar{V} = \bar{H} = 1$.

- Page 109, line –8: "*Journal Article Report on Difference Equations*"

Chapter 4.

- Page 123: To avoid confusion, equation (11) should be clearly labeled "Wrong". The corrected version is shown further on in equation (12).

- Page 131, Example 1, first term labeled "nonlinear term": The arrow should point to the entire group $2x\dfrac{dx}{dt}$.

- Page 132: Equation (34) should read

$$a\frac{d^2x}{dt^2} + b\frac{dx}{dt} + cx = 0.$$

- Page 134: Equation (43a) should have a boldface x:

$$\frac{d\mathbf{x}}{dt} = \mathbf{A}\mathbf{x}$$

- Page 134, line –11: Replace sentence with "The notation in equation (43a) denotes matrix multiplication, and $\frac{d\mathbf{x}}{dt}$ stands for a vector whose entries are $\frac{dx}{dt}, \frac{dy}{dt}$."

- Page 135: After equation (45b), it should read "where **I** is the identity matrix ($\mathbf{I}\mathbf{v} = \mathbf{v}$)."

  In the paragraph after equation (46), it should read "As in the subsection "Second-Order ODEs" ....

  Equation (47) should read

$$\mathbf{v}_i = \begin{pmatrix} 1 \\ \frac{\lambda_i - a_{11}}{a_{12}} \end{pmatrix}$$

- Page 144, line –5: "... the bacteria will **not** be washed out...".

  Equation (81) should read

$$\frac{C_0}{K_n} > \bar{C}_1, \text{ or } C_0 > \frac{K_n/K_{max}}{V/F - 1/K_{max}}.$$

- Page 149, line 20 (middle of page): "(Generally it is *not* possible to measure concentrations in compartments other than blood.)"

- Page 151, line −13: "Now suppose that a mass m_0..."

- Page 153: Problem 9(a) refers to equation (14a), and problem 9(b) to equation (14b).

- Page 157: Problem 25(e): Note that here α does not have the same meaning as in the chemostat model.

- Page 161, Problem 31(a): The equation should read

$$x_1(t) = ae^{-\lambda_1 t} + a_2 e^{-\lambda_2 t}.$$

  Problem 32(a) should read

$$\begin{aligned} -\lambda_1 a_1 &= +K_1 a_1 + K_{21} b_1, \\ -\lambda_1 b_1 &= K_{12} a_1 - K_2 b_1, \\ -\lambda_2 a_2 &= +K_1 a_2 + K_{21} b_2, \\ -\lambda_2 b_2 &= K_{12} a_2 - K_2 b_2, \end{aligned}$$

Chapter 5.

- Page 164, first paragraph, line 4: "purporting"

- Page 165: For consistency, equation (2a) should read $\frac{dy}{dt} = f(t, y)$.

- Page 183, Table 5.1, first column: "Identities": $\lambda_1 \lambda_2 = \gamma$ (not β).

- Page 190, top of page: $\lambda = \frac{1}{2}(\beta \pm i|\delta|^{1/2})$. The first three cases also have to specify $\delta > 0$.

- Page 191: End of second paragraph of Section 5.9: "Problem 17 gives some intuitive feeling..."

- Page 197, in equation (29):

$$\mathbf{v}_2 = \begin{pmatrix} \alpha_1 A \\ -1 \end{pmatrix}$$

- Page 201, Problem 7(e): $\frac{dx}{dt} = -4x - 2y$.

- Page 206, line 1: "(2) Section 5.9 tells us..."

  Problem 19: "Use methods similar to those mentioned in problem 18..."

- Page 208: Problem 23(d) should read

$$E = \frac{1 \pm (1 - 4\alpha^2\beta^2)^{1/2}}{2\alpha\beta}.$$

- Page 209: Odell reference is "In L. A. Segel" (note spelling).

Chapter 6.

- Page 234, top of page: The Routh-Hurwitz Criteria for $k = 4$, second inequality, should read $a_1 a_2 > a_3$. (Thanks to D. Thron)

- Page 248, top of page: The second steady state is

$$(\bar{S}_2, \bar{I}_2) = \left(\frac{\nu}{\beta}, \frac{\gamma[N - (\nu/\beta)]}{\nu + \gamma}\right)$$

- Page 253, Table 6.1, top line (SIS) under "Significant quantity": The entry should be

$$\sigma = \frac{\beta S_0}{\gamma + \delta}$$

  ($S_0 =$ initial S).

  SIR: Same correction as for "Significant quantity" entry corresponding to birth\death "rate = δ" and inequality (1) should be $\sigma > 1$.

  SIRS: Same as correction for "Significant quantity" entry.

- Page 259, Problem 10(a): The second equation should read

$$y^a e^{-by} = K x^{-c} e^{dx}$$

- Page 261, Problem 17: The equations should read

$$\frac{dN_1}{dt} = rN_1\left[1 - \frac{N_1}{\kappa_1 + \alpha N_2}\right]$$

$$\frac{dN_2}{dt} = rN_2\left[1 - \frac{N_2}{\kappa_2 + \beta N_1}\right]$$

- Page 265, Problem 32: The equations should read

$$\text{krill}: \ \dot{x} = rx\left(1 - \frac{x}{K}\right)$$

$$\text{whales}: \ \dot{y} = sy\left(1 - \frac{y}{bx}\right)$$

- Pages 266–267, Problem 34: The equations should read

$$\beta_{12} = \frac{K_1 r_1 N_1 - (dN_1/dt)K_1 - r_1 N_1^2}{r_1 N_1 N_2}$$

$$\beta_{21} = \frac{K_2 r_2 N_2 - (dN_2/dt)K_2 - r_2 N_2^2}{r_2 N_1 N_2}$$

Chapter 7.

- Page 277, Equations 14(a,b): The variable t should be t^* on the denominator of the left-hand sides.
- Page 279, Equations 17a and 18: The right-hand side should be multiplied by 2.
- Page 295, Section 7.8: The term "substrate depletion" may be more descriptive than "positive feedback" in all occurrences in this section.
- Page 297, bottom of page: Insert "If $det\mathbf{J} < 0$ then $s_2 < s_1$ and the steady state is a saddle point."
- Page 304, Problem 19: Replace the notation GGP $\rightarrow$ G6P and FGP $\rightarrow$ F6P in all places.
- Page 305, Problem 20(c): The inequality should read $B > 1 + A^2$.
- Page 308, Problem 24(d): ... provided $O_T \ll R_T$

Chapter 8.

- Page 312, Figure 8.1 caption: (e) and (f) are meta-stable.

- Page 320: Equation (4b) should read $V(t) = q(t)/C$.

- Page 321, entry in box (middle of page): "$I_i(x,t)$ = net rate of flow of positive ions from the interior to the exterior..." After last entry, insert: "$v < 0$ when membrane negative on inside."

- Page 336, caption to Figure 8.17: "V satisfies an equation like (9)..." Delete dot over entry dN/dt in first equation. Replace $\tan h$ with tanh in second equation.

- Page 342, box: It should be assumed that $da/d\gamma > 0$ so that the steady state is unstable for $\gamma > \gamma*$ as in Figure 8.19. (Otherwise, if $da/d\gamma < 0$, redefine $\gamma \to -\gamma$.)

- Page 344, line 7: Box on The Hopf Bifurcation Theorem: "with the appropriate smoothness assumptions on f_i..."

  In equation (35), the matrix should read

$$\begin{pmatrix} 0 & b \\ -b & 0 \end{pmatrix}$$

- Page 345, equation (36):

$$V''' = \frac{3\pi}{4|b|}(f_{xxx} + \text{etc }) + \frac{3\pi}{4b^2}[-f_{xy}(f_{xx} + f_{yy}) + \text{etc }].$$

  The conclusions in the box were misleading. A supercritical Hopf bifurcation denotes a bifurcation to asymptotically stable periodic orbits. The periodic orbits occur on one side of γ^* (but not necessarily for $\gamma > \gamma^*$). Whether the periodic orbits are to the right or to the left of the critical value of the bifurcation also depends on a transversality condition (the sign of $da/d\gamma$ at γ^*). See Marsden and McCracken for other details. The stable periodic orbit would occur with the unstable equilibrium and the unstable periodic orbit with the asymptotically stable equilibrium. (N.B. Thanks to Gail Wolkowicz for pointing out this error.)

  In the last sentence of this box: receipe $\to$ recipe.

- Page 354: In equation (60) delete ", 1" from definition of M.

- Page 357: The radical in equation (69) should read

$$\sqrt{(1-a^2)^2 - 4a^2}$$

- Page 358: The caption to Figure 8.22(b) is inaccurate. Disregard.
- Page 363: In Problem 6, insert "assume $k > 0, \mu > 0$".
- Page 364: Figure 7(b) is incorrect (there are incorrect arrows and misplaced heavy dots). Disregard.
- Page 368, Problem 19: Insert "Assume all parameters are positive."

Chapter 9.

- Page 402: Some units are missing in the box and should be inserted as follows:

  $\mathbf{J}(x, t)$ = current in amps (coulombs/sec).

  v = voltage (volts).

  $q(x, t)$: units of (coulombs/unit length).

  C = capacitance in units of (farad/unit area).

  I_i is net ionic current per unit area.

- Pages 405–406: We note the following results in dimensions 1, 2, 3, which follow by straightforward generalization:

  In 1 dimension $\mathcal{D} = \dfrac{\Delta x^2}{2\tau}$.

  In 2 dimensions $\mathcal{D} = \dfrac{\Delta x^2}{4\tau}$.

  In 3 dimensions $\mathcal{D} = \dfrac{\Delta x^2}{6\tau}$.

- Page 413: Equation (83) should read

$$\tau = \frac{L^2}{2\mathcal{D}} \ln \frac{L}{a} = \dots$$

- Page 414: In equation (88), the right-hand side should read $-\lambda^2 f$.

  Equations (89a,b,c) should read $f_1(x) = \exp(-i\lambda x)$, $f_2(x) = \sin(\lambda x)$, $f_3(x) = \cos(\lambda x)$.

- Page 422, Problem 18(b): See Section 8.1.
- Page 424, Problem 22: $\mathcal{D} = \dfrac{(\Delta x)^2}{2\epsilon}$
- Page 425: Both bibliography items under Hardt should have the name "Hardt, S. L."

Chapter 10.

- Page 444, line 2: "where $K = k/(m+1)$."
- Page 452, line −5: "a population of individuals carrying a slightly advantageous recessive allele"...
- Page 454: The top figure is incorrect. Disregard.
- Page 464, line before Figure 10.8: "per unit time μ_j."
- Page 477, Problem 2(a): The right-hand side of the equation should read $-\nabla \cdot (f\mathbf{v}) - \mu f$ ....
- Page 479, Problem 6(b): $C_0 = 7 \times 10^7$.
- Page 480, Problem 7: Note that if step length Δx is constant, then in 3 dimensions, $\mu = \frac{(\Delta x)^2}{6\tau}$. Lovely and Dahlquist (1975) consider a more general problem, where the step length is Poisson distributed to get $\mu = (1/3)v\lambda$.
- Page 487: Delete problem 21(b).
- Page 481, Problem 8(e): A better scaling suggested is:

$$u = \frac{s}{K}, \quad v = \frac{b}{YK}, \quad \xi = \frac{x}{\sqrt{\mathcal{D}/k}}, \quad \tau = kt.$$

- Page 493: The Takahashi references are identical. Replace the second one with

Takahashi, M. (1968) Theoretical basis for cell cycle analysis II. Further studies on labeled mitosis wave method, *J. Theor. Biol., 18*, 195–209.

Chapter 11.

- Page 502: Equation (2b) should have the corrected term

$$\left(-D\frac{\partial c}{\partial x}\right)$$

- Page 506, bottom third of page: Second condition should read "2. Values of L must not be too small."

- Page 507, top part of page: replace first two comments as follows:

  1. Aggregation is favored more highly in larger domains than in smaller ones at fixed $\bar{a}$.

  2. The perturbations most likely to be unstable are those with low wavenumbers....

  The perturbation whose wavenumber is $q = \pi/L$...

  Comment (due to John Tyson): Let $\chi\bar{a}f$ be the bifurcation parameter. For $\chi\bar{a}f < \mu k$, the homogeneous solution is stable with respect to perturbations of all wavenumbers q. As $\chi\bar{a}f$ increases above μk, the homogeneous solution becomes unstable with respect to long wavelength perturbations. The first possible pattern is 11.3(a), and this arises when $\chi\bar{a}f > \mu k + \frac{\mu D\pi^2}{L^2}$. As $\chi\bar{a}f$ increases further, other patterns become possible.

- Page 513: Equation (37) should have the corrected term:

$$-\frac{1}{4}\left(\frac{(D_1a_{22} + D_2a_{11})^2}{D_1D_2}\right)$$

- Page 516, bottom of page: The heading *Positive feedback* is better described as *Substrate depletion.*

- Page 517: After equation (43) it should read "... otherwise the inequality $a_{11} + a_{22} > 0$ contradicts (32a)."

  In equations (44a,b) the tau's would be better defined as time constants:

$$\tau_1 = |a_{11}|^{-1}, \qquad \tau_2 = |a_{22}|^{-1}.$$

  Then equation (45) can be replaced by the condition for instability:

$$L_1^2 < L_2^2$$

where $L_1 = D_1\tau_1$ is the range of the activator and $L_2 = D_2\tau_2$ is the range of the inhibitor.

- Page 519: Comment about equation (46) by John Tyson:

$$\hat{d} = 2\pi\sqrt{2\left(\frac{1}{\frac{1}{L_1^2}+\frac{1}{L_2^2}}\right)}.$$

The term in round braces is then the harmonic mean of the ranges of activation and inhibition. Further, $\hat{d} \approx qL_1$ since $L_1 << L_2$.

- Page 521: Comment about q_1, q_2 by John Tyson: We expect that $q_1 \approx q_2$, so that $Q^2 \approx 2q^2$. Amplified waves are then those with

$$q = \frac{1}{2}\sqrt{\frac{1}{L_1^2}+\frac{1}{L_2^2}} \approx \frac{1}{2L_1}.$$

- Page 522, top of page: $\frac{D}{a} \approx$ area of range of activator, $\frac{L^2 a}{D} \approx$ ratio of area characterizing domain to range of activation, $\frac{\alpha}{\beta}$ = ratio of range of activation to range of inhibition.

$$E^2 = \frac{\text{area of domain}}{\text{area of activator}}\left(1+\left(\frac{\text{area of activation}}{\text{area of inhibition}}\right)\right)$$

- Page 531: The left-hand side of equation 62(a) should read $\mu D_h - \nu D_a > \ldots$

- Page 545, Problem 3: the inequality is incorrect. Disregard.

- Page 548, Problem 15(g):

$$R_1 = \frac{1}{\epsilon}\left[c_1(1-c_1) - \frac{bc_1(c_2-a)}{c_2+a}\right]$$

Selected Answers.

- Page 556, Chapter 1, Problem 3: Mislabeling should be corrected as follows: (i) $\to$ (ii); (ii) $\to$ (iii); (iii) $\to$ (iv).

  Chapter 1, Problem 9(c): Argument of trig functions should be $\frac{\pi n}{4}$.

- Page 557, Chapter 2, Problem 1(a): $x_n = C\left(\frac{1-\alpha}{1-\beta}\right)^n \ldots$.

- Page 558, Chapter 3, 4(c): stable for $|1 + b(\lambda^{-1/b} - 1)| < 1$.
- Page 560, 5(e): Rightmost arrow should point right instead of left.
- Page 562: Problems mislabled: $20 \to 21$; $21 \to 22$
- Page 568: 8(b) is incorrect. Disregard.
- Page 569, 8(e): Replace K with κ.

I would like to thank those people who submitted errata. Special thanks to John Tyson for many helpful comments and for the extended loan of his personal annotated copy.