Preface

It was on a placid canoe trip at a Gordon Conference in 2002 that Lee Segel told me that he was writing a new book in mathematical biology. In the prime of his health and at the peak of his mathematical career, Lee asked me to agree to act as shepherd to this book "in case" anything happened to prevent his completion of the project. The request was purely "academic" at that time, and I agreed to this formal arrangement with the certainty that it would require no actual work. It came as a great shock that Lee Segel passed away on January 31, 2005, after a sudden and devastating illness. This was a great loss to his many friends, students, coworkers, and admirers in the applied mathematics and mathematical biology communities.

Lee Segel had collected material that he had taught over several years at the Weizmann Institute of Science. Some of it (e.g., biochemical kinetics, neurophysiology) is "classic," and part of a solid core of knowledge in mathematical biology. Other parts are newer additions to this "folklore." I have endeavored to present Lee's philosophy and pedagogy mostly in his own words in Chapters 1, 8–11, and parts of Chapters 2 and 13 with some insertions, deletions, reordering, editing, and rearranging of the original text. Material that I deemed to be too specialized or more technical has been moved to Chapter 14 ("For further study") at the end of the book, and extended exercises that Lee Segel had composed for course examinations are now part of a collection in Chapter 15. Some of these problems are suitable for term projects, and most of them are mentioned in the list of exercises in each chapter.

I have added new material, including Chapters 3–7. This has made the analysis of differential equation models and phase plane methods more central to the book. Some parts of Chapters 3 and 7 were destined by Lee Segel for Appendices, but I have elected to expand and weave these into the development of the course. Chapter 6 gives one complete "case study" where the mathematical tools are illustrated on a clear-cut traditional problem of disease dynamics. This way, the student gains familiarity with working tools of the trade, and then sees the benefits of these methods in the deeper analysis possible in Chapters 11–12 of models for excitable systems, bistable switches, and cell cycle oscillations. In one respect I have changed the flavor of the text considerably, by including some focus on exploring problems and models with simple simulations. In making or remaking many of the original figures, I have used simple simulation files (for a popular current simulation platform, XPP[1]). These program files are included in Appendix E and online at www.siam.org/books/SegelLEK. A number of exercises are built on encouraging such explorations. Students or researchers who use alternative simulation platforms will find

[1]Created and maintained by G. Bard Ermentrout, used widely by mathematical biologists, and freely available online.

these useful nevertheless, as all needed information (equations, parameter values, initial conditions, etc.) are preserved for the figures so constructed.

A few difficult decisions had to be made. For instance, a detailed chapter on models of the cell cycle that Lee Segel had written was out of date and difficult to follow. I replaced that material with a shorter and slightly modernized approach emphasizing the stepwise approach to constructing such models and the insights gained through bifurcations and phase plane simulations. This is now a smaller part of a new chapter on biochemical modules in Chapter 12. Here I have tried to "pull together the threads" of the book: that is, show how a number of ideas in previous chapters (enzyme kinetics, dimerization, cooperativity, bistability, excitable systems, limit cycles, and bifurcations) come together in a few simple but elegant recent models in cellular and molecular biology. For this reason, the chapter is placed after material on neurophysiology that Lee had written (but see below for suggestions on how to use this book that abbreviates some of the above).

When Lee Segel was conceiving and creating this book, the analysis of genetic and biochemical networks was emerging as a novel hot area of research. He had written two chapters on discrete networks and Boolean models that spanned some 50 pages. As yet, this field of computational biology is young, and it is not entirely clear (at least to a nonexpert like me) which works and ideas will stand the test of time, to become classics. Moreover, fitting the discrete and continuous approaches together in this book was a challenge. In deference to Lee, I kept some of this material in a slightly abbreviated version in Chapter 13.

While this material was developed expressly for biology graduate students, I think that it deserves a place amongst the collections in mathematical biology also for its historical value, representing Lee Segel's unique perspective. For me, it has been an honor, and a work of dedication to be associated in this way with my mentor and former Ph.D. supervisor, and I dedicate this book to Ruthie Segel and to the rest of the Segel family.

Leah Edelstein-Keshet, August 2012

Lee A. Segel wrote:

For many years I taught a course at the Weizmann Institute of Science on "Mathematical Models in Molecular and Cell Biology." Segel [130] documents the course as it was a couple of decades ago. The present book documents the course in its latest version. From the outset, the biologists required this course of first-year M.Sc. students (Weizmann has only graduate students).

The course (and the book) assumes what seems still to be the median mathematical background for M.Sc. biologists; they had a year of calculus but, virtually never having used it, they forgot it. Essential mathematics is reviewed in the text and in some appendices. The emphasis in the book is on the use of the mathematics. Thus minimal mathematics is introduced, in the simplest way possible. For example, two linear ordinary differential equations with constant coefficients are solved by elimination; thus, introduction of matrices and determinants is avoided, saving valuable time for more applications.

There were four contact hours per week in the course. Two of these were "recitations" taught by Ph.D. students in mathematics (often without experience in biological modeling, or indeed in applied mathematics); the recitation instructors taught the more mathematical material (e.g., phase plane methods, solutions of differential equations). Two hours per week I lectured on the biological applications.

My goal was not to teach biologists useful mathematics (although this occurs) but rather to show biologists by example how mathematical modeling can deepen their understanding of biology. There was a four-hour open-book final examination in which achievement of this goal were tested by means of problems, typically drawn from the recent literature.

In both pure and applied mathematics, skills are acquired by action. Some of the exercises in the book ask the reader to fill in details of calculations whose outline or conclusion is presented in the text. In such instances, the reader should attempt to carry out the calculations without looking at "the answer" and only then check whether the answer corresponds to what is given in the text. Some problems are multipart exercises, often taken from old final examinations, where indeed biological intuition is generated by mathematical modeling.

Those not practiced in reading theoretical material might find the book hard going at first. This is not worrisome. It is recommended that a section first be read without worrying about any details, to see what the material is all about. Then read slowly, one sentence at a time (taking the trouble to look back at earlier equations that may be cited). When you understand each sentence in a paragraph, think about what the paragraph implies. Aside from the details, what is the main idea? If you just don't get some part of the material after a reasonable effort, skip it and try again—for sometimes later material can cast light on earlier, and occasionally unconscious rumination leads to understanding.

Lee Segel, 2004

How to use this book (notes by L.E.K.)

Depending on the desired emphasis, an instructor could chose a subset of the material based on some portions of the book as follows:

1. General introduction to mathematical biology

    - Essentials of biochemical kinetics in Chapter 2, in particular Sections 2.1–2.2.3 and 2.3–2.4.2.
    - Chapters 3–7 set up the mathematical structure and one detailed case study that provide ample tools for analysis of models. Some parts of Chapter 3 can be omitted or used as background reference for students who have had a first course in differential equations.
    - Chapters 10–11 are an introduction to excitable systems and neurophysiology. It is possible to use the introductory portion of Chapter 10 as motivation and skip directly to Chapter 11 to save time or avoid technical details of the Hodgkin–Huxley model.
    - Chapter 12 contains a variety of relatively elementary models that students can explore. The material on the cell division cycle is introduced gradually, getting progressively more detailed. It can be abbreviated or omitted depending on time constraints.
    - Chapter 13 presents a distinct perspective using discrete networks. It could be used in parallel with Chapter 12, assigned as independent study, or left out of the syllabus.

2. Applied modeling for mathematics majors

    - The formulation of a differential equation model, as introduced in Sections 2.1.1–2.2 and 2.3 is core material.
    - Section 2.5 is a self-contained module that introduces simple model formulation and analysis. It can be used partially or wholly, or assigned as self-study to illustrate the ideas of model building and analysis.
    - Chapters 3–7 could be used as reference material as well as the important introduction to nondimensionalization (Chapter 4), and to geometric methods (Chapters 5 and 7) that are often missing from traditional differential equations courses.
    - The disease dynamics model in Chapter 6 is a very basic and ubiquitous model. While this model and its more advanced versions have been presented in many texts, here this has been expressly written to illustrate the usefulness of mathematical techniques and concepts. It provides an example of how material in Chapters 4 and 5 can help further understanding of a practical model.
    - Selections from Chapters 11 and 12 could be picked as additional illustrative examples of models with a variety of behaviors. The FitzHugh–Nagumo model in Chapter 11, and several models for bistable behavior and limit cycles in Chapter 12 round out the exposure to interesting dynamics that appears in biological settings and elsewhere.

3. Emphasis on biochemical kinetics

    - Chapter 2 in its entirety would be a useful introduction.
    - Chapters 8–9 present details of the quasi steady state approximation, and could be used in part to further discussion of Michaelis–Menten and cooperative kinetics. Some technical parts of these chapters could be omitted for brevity.
    - Chapter 12 uses the kinetic models to construct small circuits at first, and later a larger model (for the cell division control) based on such modules.
    - Parts of Chapters 3–5 and Chapter 7 can be used to supplement any mathematical methods that students require or need to review.

4. Dynamics of small networks of genes and proteins

    - Interactions and growth of polymers is introduced in Section 2.5. This material illustrates the connection between events at the molecular level and macroscopic observations. It also provides an example of a stepwise construction of a model, aiming to test a variety of underlying hypotheses.
    - Chapter 12 is the centerpiece of this aspect of the course, bridging between the mathematical methods of Chapters 5 and 7 and recent or current ODE models for small functional circuits of molecules or genes. The construction of a model by successive steps, its qualitative analysis, and bifurcations all reappear in this setting. The excitable dynamics found in Chapter 11 is seen again in the cell cycle model of Section 12.3.3.

- Chapter 13, as a finale, provides an alternative viewpoint, based on discrete, rather than continuous models. Some of the circuits seen in the context of Chapter 12 are revisited, and the consequences of the discrete updating is examined.

5. Introduction to simple simulations using XPP or other software

   - Appendix E contains many sample codes for XPP, together with basic instructions on how to run these. Each example is linked to equations in the text and to figures produced by simulating those equations. The first line of each file indicates the file name, and an electronic collection of the same files is available at www.siam.org/books/SegelLEK, avoiding the need to retype. These can be used as a set of increasingly detailed examples of simulation models.
   - Other software packages such as MATLAB, Maple, *Mathematica* can be used to study the same examples. The syntax will of course differ, but the equations, initial conditions, and parameter values can be used as documented in these codes.