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Glenn Ledder

Mathematics for the Life Sciences

Calculus, Modeling, Probability, and Dynamical Systems

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Glenn Ledder
Department of Mathematics
University of Nebraska-Lincoln
Lincoln, NE, USA

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To my wife, Susan, for her inexhaustible patience

Preface

> Science is built up with facts, as a house is built with stones. But a collection of facts is no more a science than a heap of stones is a house.
>
> Jules Henri Poincaré

There are several outstanding mathematical biology books at the advanced undergraduate and beginning graduate level, each with its own set of topics and point of view. Personal favorites include the books by Britton, Brauer and Castillo-Chavez, and Otto and Day. These books are largely inaccessible to biologists, simply because they require more mathematical background than most biologists have. This book began as lecture notes for a course intended to help biologists bridge the gap between the mathematics they already know and what they need to know to read advanced books. The only prerequisite for the course was the first semester of the calculus sequence. Topics included mathematical modeling, probability, and dynamical systems. My original notes included a brief review of calculus, which I subsequently expanded into the first chapter of this book so that it could be used for courses that do not require a calculus prerequisite or by biologists whose calculus experience is but a distant memory. Most students will probably find this book to be more challenging than the typical calculus book, albeit in a different way. I do not make as many demands on students' computational skills, but I require a greater conceptual understanding and an ability to harness that conceptual understanding for service in mathematical modeling.

A Focus on Modeling

In its early days, science consisted of careful observation and experimentation, with a focus on collecting facts. However, as eloquently stated by the French mathematician, philosopher, and scientist Henri Poincaré, this is not enough to make science work.

In contrast with science, mathematics is a purely mental discipline focused entirely on structures that we create in our minds. It can be very useful in science, but it has to be connected to science carefully if scientifically valid results are to be achieved. The connection is perhaps best made by a metaphor:

> The muscles of mathematics are connected to the bones of experimental science by the tendons of mathematical modeling.

As you read through this book, you will see that mathematical modeling goes far beyond the "application" problems that mathematics text authors include to make mathematics appear relevant. The problem is that what little modeling work appears in these problems is generally done by the author rather than the students. At best, the experience of doing these problems only benefits science students if their science instructors are also good enough to do the modeling work for them.

This book is written from a modeling perspective rather than a mathematics or biology perspective. The lack of modeling content in the standard mathematics and science curricula means that the typical reader will have little or no modeling experience. Readers may find the modeling skills of Section 1.1 and Chapter 2 to be difficult to learn, but the effort to do so will be well rewarded in the remainder of the book and in any subsequent attempts to read biological literature with quantitative content. While it is unreasonable to expect readers of this book to become expert modelers, my primary goal is to make them sufficiently comfortable with mathematical modeling that they can successfully read scientific papers that have some mathematical content.

Pedagogy

There are a lot of connections between mathematics and biology, yet most students—and even many mathematicians and biologists—are unaware of these connections. One reason for this situation is that neither the historical development nor the pedagogical introduction of either subject involves the other.

Biology grew out of natural philosophy, which was entirely descriptive. Modern biology curricula generally begin with descriptive biology, either organismal or cellular. The mathematically rich areas of genetics, ecology, and physiology make their appearance in advanced courses, after students have come to see biology as a non-mathematical subject.

Calculus and calculus-based mathematics were developed to meet the mathematical needs of physics, and it remains standard practice to use physics to motivate calculus-based mathematics. Other areas of mathematics, such as game theory and difference equations, were motivated to some extent by biology,[1] but these topics appear in specialized courses generally taken only by mathematics majors. Probability is another mathematical topic with strong connections to biology, but it is generally encountered in statistics courses that emphasize social science applications.

The basic premise of this book is that there is a lot of mathematics that is useful in some life science context and can be understood by people with a limited background in calculus, provided it is presented at an appropriate level and connected to life science ideas.

This is a mathematics book, but it is intended for non-mathematicians. Mathematicians like to have a mathematical definition for a concept and consider the meaning of the concept to be a consequence of that mathematical definition. Contrary to that plan, I prefer to begin with a functional definition and then present the mathematical definition as the solution of a problem. For example, in probability I define each distribution according to its purpose rather than its mathematical representation and then present the mathematical representation as a result. This is pedagogically appropriate; there are infinitely many functions that satisfy the mathematical definition of a probability distribution, and we should only be interested in those that have some practical value. The context should precede the mathematical definition.

[1] Leonardo of Pisa, more commonly known as Fibonacci, developed his famous sequence as the solution of a difference equation model of population growth.

A mathematics book for non-mathematicians needs to be clear about the extent to which rigor matters. A colleague of mine once started a talk to undergraduates with a joke: "An engineer, a physicist, and a mathematician are traveling in a train in Scotland when the train passes a black sheep standing along the track. The engineer concludes that sheep in Scotland are black. The physicist concludes that there is at least one black sheep in Scotland. The mathematician concludes that ..." Mathematicians have no trouble finishing the joke: the mathematician concludes that there is a sheep in Scotland that is black on one side. This insistence on rigor is both a strength and a weakness. It was long the common practice in calculus books (and such books are still popular) not to introduce the logarithmic function until after the definite integral, even though the students have seen logarithmic functions in precalculus. This example and others support my contention that "Mathematicians are people who believe you should not drive a car until you have built one yourself."

It is my aim to provide a balanced approach to mathematical precision. Conclusions should be backed by solid evidence and methods should be supported by an understanding of why they work, but that evidence and understanding need not have the rigor of a mathematical proof. At the risk of stern rebukes from my mathematics colleagues, I will say up front that I believe that students should focus on how we use mathematical results to solve problems. For this goal, we need to know why mathematical results are true, but we do not need to know how we prove them to be true. An example is the limit result needed to derive the formula for the derivative of the exponential function. The proof of this result appears in most calculus books and is indeed a beautiful piece of mathematics; however, understanding it does not help us compute derivatives or apply them to solve problems. Graphs and numerical computations strongly hint at the correct limit result. While not rigorous, these methods are more convincing to anyone but a professional mathematician and use problem solving skills that will be useful in other contexts. Similarly, the derivation of the Akaike information criterion (AIC) is very difficult, otherwise it would have been done prior to its actual discovery in the 1970s; nevertheless, it is not difficult to explain AIC in general terms. The mathematical error of presenting it without proof is far less serious in this book than would be the modeling error of omitting it.

Most of the sections are highly focused, often on one extended example. Mathematics experts know that we learn much more from a deep study of one problem than from many superficial examples. Many of my biological settings are in ecology, the area of biology I know best, but I have also tried to find settings of very broad interest such as environmental biology, conservation biology, physiology, and the biology of DNA. In particular, these areas are more likely to interest lower division undergraduates, many of whom are pre-medicine majors rather than biology majors, and most of whom have very little knowledge of biology.

I have attempted to be brief, in the hope that readers will work harder to read a short presentation than a long one. I use examples as contexts in which to present ideas rather than instances where a formula is used to obtain an answer. Hence, the number of examples is limited, but each example is treated with some depth. Similarly, I include only a small number of figures. Each figure is essential to the presentation, and the reader should work hard to understand each one. Being able to explain[2] a figure represents a high level of understanding.

Broad modeling problems require a variety of mathematical approaches. Hence, some topics are ideal for problems that are distributed among the relevant sections rather than being incorporated into a single project. I have indicated these connections within the problems themselves and also called attention to them in each chapter introduction. It is possible to combine all of the problems on a given model into one large project if desired.

[2] An *explanation* includes context and analysis in addition to mere *description*.

Technology

Some mathematical modeling work must be done by hand, while other work is greatly facilitated by the use of computers. I view both hand methods and computational methods as tools in my modeling toolbox. I try to identify the best tool for any particular task without a bias either for or against technology. I do have a bias against using computer algebra systems to do routine algebra and calculus. This stems from frequently encountering problems where valuable results can be found only with the careful use of algebraic substitution and simplification, which requires a human touch. I could not resist the temptation to point some of these out in the text.

There are a multitude of platforms for doing mathematical modeling tasks on computers. None of these is ideal, and the choice of which to use is a matter of taste. Rather than trying to find the very best tool for each individual task, my preference is to work with one tool that is reasonably good for any task (save symbolic computation) and is readily available. By these criteria, my choice is R, which runs smoothly in any standard operating system and is popular among biologists. Matlab is also an excellent choice. Both R and Matlab are programming environments, as opposed to packaged software or programming languages. Spreadsheets and other packaged software provide easy access to mathematics because of their intuitive graphical interface; however, programming is limited and the details of formulas are hidden from view, making it impossible to see the overall structure of a program at a glance. Reusability is limited, as anyone who has tried to modify a spreadsheet created by another author can attest. By comparison, one can see an entire R or Matlab program at a glance and adapt prior work to a similar context with minimal changes. High-level languages, such as Java and C++, offer sophisticated programming capabilities, but they are difficult to learn compared to the languages used in programming environments such as R or Matlab.

The choice between R and Matlab is a matter of personal taste. It is easier to get professional-quality graphics with Matlab, but R has a more intuitive syntax that facilitates programming. Matlab requires an add-on toolbox for probability and statistics, while R requires supplementation for dynamical systems. I use R because students can get it for free and install it seamlessly in any operating system. R lacks the excellent documentation that comes with Matlab; however, I maintain a collection of R scripts for various algorithms presented in the text, and these are readily available http://www.springer.com/978-1-4614-7275-9. These scripts are designed to be simple rather than robust; that is, compared to professionally written programs, they are easier to understand but less efficient and they lack error detection machinery. Their presence allows students to replace the difficulty of having to learn R from scratch with the much lesser difficulty of having to be able to read an R program and make minor modifications.

Topics

Of course, no book on mathematics for the life sciences can be complete. Some important areas do not appear here at all because, they do not fall into the broad categories of mathematical modeling, probability, and dynamical systems. Several concessions have been made in the interest of accessibility. Some topics are given only a partial treatment as compared to the treatment they would receive in a higher level course; for example, I do not find eigenvectors for complex eigenvalues, since they are not generally needed in biology. Others are presented in a roundabout way.

Finding the "correct" order of topics in this book was an insoluble problem. Mathematics is a hierarchical subject, but the hierarchy is not linear. Arguments can be given for significant rearrangements of the topics that are included here. Ultimately, the only reasonable solution was to group topics into related clusters. In particular, Parts II and III could easily have been reversed. Those who read this book for their own benefit or to design a course should be flexible in the way they structure their study. Each part introduction contains a graph with sections as nodes and arrows indicating which sections are necessary background for others. A syllabus that moves frequently between chapters is entirely possible, but for me to have written the book in that way would have excluded other topic orders.

One feature of mathematical models that causes difficulties for students is the appearance of parameters, which are constants whose values are not necessarily assigned. Without parameters, a function is merely an example to be used for routine calculations. With parameters, a function can be a model, which can serve as an environment for theoretical experimentation. Even the reader with a solid background in calculus should study Section 1.1.

The remainder of Chapter 1 can serve as a review of calculus or a conceptually oriented calculus primer. This chapter is not a complete treatment of calculus, which would require far more space than is available in one chapter. I present here only those aspects of calculus that provide the necessary background for the modeling, probability, and dynamical systems that make up the rest of the book. The reader who works through this chapter will be well equipped with the calculus background needed for the purpose at hand. The material in this book has been used successfully with life science graduate students who had no background in calculus. Anyone who requires a more complete understanding of calculus can consult any calculus book.

After the calculus primer comes a chapter on mathematical modeling, which is the necessary focus of any study of mathematics for those whose purpose is to use mathematics to better understand science. Even the most mathematical of topics, such as probability, are best seen by scientists from a viewpoint of mathematical modeling. Unfortunately for the science student, mathematical modeling has not been granted a place in the standard mathematics and science curricula. In mathematics books, we generally present mathematical ideas and then look for their applications to science. The result is a collection of idiosyncratic examples devoid of the analysis necessary for good mathematical modeling. In science books, the mathematics is usually presented as a collection of formulas, to be used as facts when required. Neither approach teaches modeling skills. If we are to use mathematics to improve our understanding of the natural and physical world, we must focus on the connections of mathematics to science.

Chapters 3 and 4 present the basic ideas and some applications of probability, including applications commonly classified as statistics. The treatment given here is organized differently from the treatment of this topic in statistics or probability books. Mathematicians generally use an axiomatic approach to introduce probability. My colleagues in biology helped me appreciate that the central topic of probability for scientists is that of the probability distribution, and this topic is best approached informally by thinking of a probability distribution as a mathematical model of a data set. My aim has been to get to probability distributions as quickly as possible while saving other topics, such as conditional probability, for later. The essentials of probability distributions form the subject of Chapter 3. Chapter 4 includes additional topics that build onto or supplement the basic material on probability distributions. The high point of these two chapters is Section 4.4, which looks at the question of how likely it is that a subpopulation used to provide sample data is distinct from some larger population.

The final three chapters introduce the mathematics of dynamical systems, which consist of one or more related quantities that change in time according to prescribed rules. These rules may be in the form of difference equations, where time is taken as discrete, or differential equations, where time is taken as continuous. It is usual to make this the primary distinction within the area of dynamical systems; however, there are valuable connections to be made between the two kinds, particularly for models with only one dynamic quantity. For this reason, I have chosen to treat all dynamic models of one variable together in Chapter 5 before presenting multivariable discrete systems in Chapter 6 and multivariable continuous systems in Chapter 7. For reasons presented in the modeling chapter, I believe that continuous models are almost always preferable to discrete models. Nevertheless, the analysis of continuous models requires an understanding of some discrete mathematics. Hence, Chapter 6 precedes Chapter 7. The reader whose primary interest is in continuous dynamical systems needs the tools developed in Section 6.3, and these tools are more easily acquired with Sections 6.1 and 6.2 as background. The high points of the three chapters on dynamical systems are the graphical and analytical tools used for continuous systems; these are the topics of Sections 7.3 and 7.5 respectively. The book contains three additional sections on discrete dynamical systems, presented in Appendix A.

Advice for the Reader

How one reads a book depends on what one wishes to get from the reading. I assume that my reader wants a working knowledge of mathematics that will enable him/her to read biological literature with quantitative content or to read a more advanced book on mathematical biology. At the same time, many readers will be interested in only a portion of the topics presented here. As noted above, each part begins with a schematic diagram showing the logical relationships among the topics of that part and any essential topics from earlier parts. In particular, the reader is cautioned not to skip Chapters 1 and 2 to get to some other topic more quickly. People who try to learn to play the organ without having already learned to play the piano are starting with an enormous handicap; the same is true for anyone who attempts to learn probability or dynamical systems without an adequate mastery of calculus and mathematical modeling. Not every section in Chapters 1 and 2 is essential for the remainder of the book; however, parts of these chapters are indispensable background and should be mastered before moving on. In particular, an understanding of parameters (Section 1.1) and the basic concepts of mathematical modeling (Section 2.2) is essential.

It is natural to try to work a large number of problems as quickly as possible. However, this is not the best way to learn mathematics. A mathematician learning something new will work through a relatively small number of examples carefully rather than a large number of examples superficially. At a talk I heard on mathematics pedagogy, the speaker asked the audience, “Why do we ask our students to work problems? Is it because we want to know the answer?” Usually we don’t care about the answer; we work problems to learn mathematics. Keep this in mind when you are working a problem: your goal is to learn mathematics, not to get the answer to the problem. There are only a small number of routine problems in this book. Most problems are guided case studies and require quite a bit of time for a thorough understanding. Carefully working a small number of these will benefit the reader more than a cursory look at a larger number.

Course Designs

There is no standard curriculum of mathematics for biology. Mathematical biology can be incorporated into a calculus course, or calculus can be incorporated into a mathematical biology course for students who have not had calculus. There are also mathematical biology courses with a calculus prerequisite, and these can be offered for students with or without backgrounds in linear algebra and differential equations. Many institutions treat probability/statistics as being distinct from mathematics. However, the difficulty of finding room for either in the program of a biology major suggests the idea of incorporating some probability and some topics often included in a statistics course within the mathematical biology or calculus-for-biology course. I have tried to make this book suitable for a variety of plans.

Before listing possible course plans using the material in this book, it is important to start with a broad discussion of pacing. Books for some lower division courses are generally written under the assumption that each section will require 1 day of class. At this pace, it is not difficult to put more than 30 sections into a standard 3-credit course. This is typically what is done in a differential equations course, but not a calculus course. At the University of Nebraska, we cover something like 32 sections in our first-semester calculus course; however, we structure this course with a lecture-recitation format and offer it for 5 credits. This means that our actual rate of coverage is more like 6 sections per credit hour than 10 sections per credit hour. My own mathematics-for-biology course was originally a 5-credit course with a one-semester calculus prerequisite, and I covered approximately 32 sections of this book, which is again an average of only 6 sections per credit hour. The next time I use this book for a course, it will be a 5-credit calculus-for-biology course with 3 h of lecture and 2 h of recitation/laboratory. I expect to do only the 24 sections of Chapters 1, 2, 5, and 6. For students at the calculus level, I would certainly not try to do more than 16 sections for a 3-credit course. A slightly faster pace could be used with students who are more sophisticated or very highly motivated. I spend less than half of the total class time presenting lectures; in particular, I mark out days for laboratory-style activities such as collecting data from a virtual laboratory, writing a computer program to run a computer simulation, or working through one of the more difficult problems either in small groups or as a ”committee of the whole.” The standard requirement that mathematics courses cover as much material as possible sacrifices depth for breadth; a mathematics course for biology students should have some balance between the two, with some case studies being included at the expense of broad coverage.

A 2-Course Sequence of 4-Credit Courses

It should be possible to do almost the entire book with a total of 8 credit hours. I would do Chapters 1, 2, and 5 in a first-semester calculus-for-biology course and most of Chapters 3, 4, 6, and 7 in a second-semester probability and dynamical systems course.

A 2-Course Sequence of 3-Credit Calculus-for-Biology Courses

Given two courses for students with no calculus background, I would use Chapters 1 and 2 for the first semester and then make the second semester a dynamical systems course that would include Chapters 5–7, and possibly with parts of Appendix A. Both of these courses would be well focused, and the second course could be open to strong students with a background somewhat beyond one course in calculus.

A 3-Credit Calculus-for-Biology Course

In a 3-credit calculus-for-biology course, I would expect to complete all of Chapter 1 in about half of the semester or perhaps a little more. I would probably try to do some dynamical systems rather than a complete treatment of Chapter 2. It would be possible to do Sections 2.1, 2.2, 2.5, and 2.6 along with all of Chapter 5. I would present only a minimal version of Section 2.5, the point being to do just enough to set up Section 2.6.

A 3-Credit Empirical Modeling and Probability Course with a Calculus I Prerequisite

One could teach a course on empirical modeling and probability as an alternative to a standard statistics course. For such a course, I would do Sections 1.1, 2.1–2.4, 2.7, all of Chapter 3, and as much of Chapter 4 as could be done without rushing.

A 3-Credit Dynamical Systems Course with a Calculus I Prerequisite

A course on dynamical systems could not reasonably assume an adequate modeling background, so it would be necessary to start with Sections 1.1, 2.1, 2.2, 2.5, and 2.6, with 2.1 done in a cursory manner. It would then be possible to cover all of the material in Chapters 5–7. If any extra time is available, Section A.1 would round out the course.

Lincoln, NE, USA Glenn Ledder

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