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# Modeling Life

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The Mathematics of Biological Systems

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ISBN 978-3-319-59730-0      ISBN 978-3-319-59731-7 (eBook)  
DOI 10.1007/978-3-319-59731-7

Library of Congress Control Number: 2017943196

Mathematics Subject Classification (2010): 97MXX, 92BXX, 37N25

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Printed on acid-free paper

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The registered company is Springer International Publishing AG  
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

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# Preface

## Why This Course?

This course was designed to supplant the traditional “Calculus for Life Sciences” course generally required for freshman and sophomore life science students.

The standard course is limited to calculus in one variable and possibly some simple linear differential equations. It stresses the technical development of the subject.

There is an emerging consensus that a more relevant course would feature

- ✓ A significant use of real examples from, and applications to, biology. These examples should come from physiology, neuroscience, ecology, evolution, psychology, and the social sciences.
- ✓ Much greater emphasis on concepts, and less on technical tricks.
- ✓ Learning the rudiments of a programming language sufficient to graph functions, plot data, and simulate differential equations.

This view has been taken by all the leading voices in US biomedical research. For example, the Howard Hughes Medical Institute (HHMI) and the Association of American Medical Colleges, in their 2009 publication “Scientific Foundations for Future Physicians,” identified key “Undergraduate Competencies,” which include the ability to

- “Quantify and interpret changes in dynamical systems.”
- “Explain homeostasis in terms of positive or negative feedback.”
- “Explain how feedback mechanisms lead to damped oscillations in glucose levels.”
- “Use the principles of feedback control to explain how specific homeostatic and reproductive systems maintain the internal environment and identify
  - how perturbations in these systems may result in disease and
  - how homeostasis may be changed by disease.”



Consider those statements. The phrase “dynamical systems” is the key to these competencies. Positive and negative feedback are important types of dynamical systems. The HHMI and AAMC want future physicians to be able to understand the dynamics of feedback-controlled systems. This is the explicit theme of this course. We will begin on the first day of class with an example of a negative-feedback dynamical system, a

predator–prey ecosystem. The central concept of the course is that dynamical systems are modeled by differential equations.

The differential equations that model positive and negative feedback are typically nonlinear, and so they cannot be approached by the paper-and-pencil techniques of calculus. They must be computer-simulated to understand their behaviors.

The same point of view is expressed by the National Research Council of the National Academy of Sciences, in their “Bio 2010” report. They called for a course in which

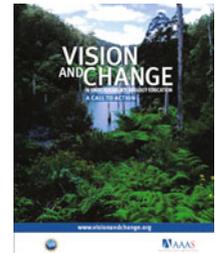
- “Mathematical/computational methods should be taught, but on a need-to-know basis.”
- “The emphasis should not be on the methods per se, but rather on how the methods elucidate the biology” and which uses
- “ordinary differential equations (made tractable and understandable via Euler’s method without any formal course in differential equations required).”



This is exactly what we do in this text. The emphasis is always: how does the math help us understand the science? Note especially the Academy’s stress on differential equations “made tractable and understandable via Euler’s method without any formal course in differential equations required.” That is what this text does; Euler’s method is exactly the technique we will use throughout.

The same emphasis on real examples of nonlinear systems was the theme of the 2011 report by the US National Science Foundation (NSF), together with the American Association for the Advancement of Science (AAAS) called “Vision and Change in Undergraduate Biology Education.” It said, “Studying biological dynamics requires a greater emphasis on modeling, computation, and data analysis tools.” They gave examples:

- “the dynamic modeling of neural networks helps biologists understand emergent properties in neural systems.”
- “Systems approaches to examining population dynamics in ecology also require sophisticated modeling.”
- “Advances in understanding the nonlinear dynamics of immune system development have aided scientists’ understanding of the transmission of communicable diseases.”



We will see each of these examples: neural dynamics, ecological population dynamics, and immune system dynamics will each be featured as examples in this text.

## The UCLA Life Sciences Experience

A course based on these principles has been offered to freshmen Life Sciences students at UCLA since 2013. There is no prerequisite of any calculus course.

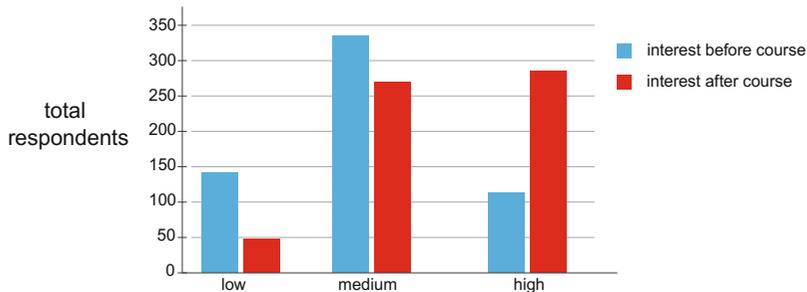
Our approach was to incorporate ALL of the above suggestions into our course and into this text. We “study nonlinear dynamical systems, featuring positive or negative feedback.” We “explain how feedback mechanisms lead to phenomena like switch-like oscillations.” We study examples like “dynamic modeling of neural networks and dynamics in ecology.” Overall, our approach is to “use ordinary differential equations, made tractable and understandable via Euler’s method without any formal course in differential equations.” (The quoted phrases are directly from the above publications.)

In a two-quarter sequence, we were able to cover the elements of all seven chapters. We certainly did not cover every example in this text in two quarters, but we did get to the end of Chapter 7, and all students learned stability of equilibria via the eigenvalue method, as well as getting introductions to calculus and linear algebra.

In teaching this course, we found it to be important to put aside our preconceptions about which topics are easy, which are difficult, and the order in which they should be taught. We have seen students who need to be reminded of the point-slope form of a line learn serious dynamics and linear algebra. While some algebraic competence remains necessary, students do not need to be fluent in complex symbolic manipulations to do well in a course based on this book.

Student reaction to the course has been very positive. In the fall of 2016, we registered 840 freshmen and sophomores in the course.

The course has been studied by UCLA education experts, led by Dr. Erin Sanders, who should be contacted for many interesting results. One of them is that student interest in math was substantially improved by this course.



Student interest in math before and after the course. Source: UCLA Office of Instructional Development, course evaluations from spring 2015, fall 2015, and winter 2016.

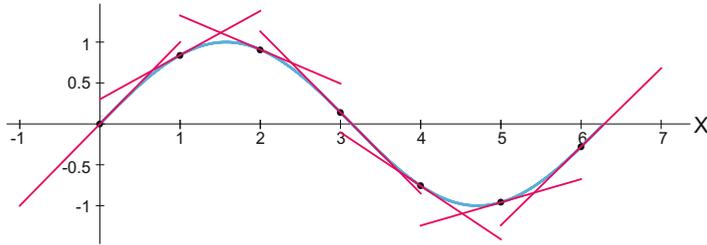
**Does this course meet medical school requirements?** Medical schools, as might be expected from the publications above, have endorsed this new development. For example, the old requirement at Harvard Medical School was called “Mathematics,” and it called for at least “one year of calculus.” Several years ago, the requirement was changed to “Computational Skills/Mathematics.” It should be read in its entirety, but it says that a “full year of calculus focusing on the derivation of biologically low-relevance theorems is less important,” and calls for a course that is “more relevant to biology and medicine than the formerly required, traditional, one-year calculus course.”

## Software

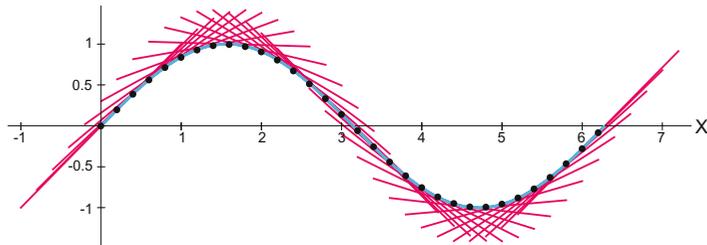
In this course, we will use a software package called SageMath to help us plot graphs and simulate dynamical systems models. SageMath is similar in some ways to the commercial package Mathematica, but it is free and open source (<http://www.sagemath.org> for software download or <https://cocalc.com> for interactive use).

The syntax of SageMath is very close to the popular scientific computing environment called Python, so students are learning a syntax they will use for the rest of their scientific lives. Here is a sample of SageMath in action: the following syntax produced the figure on the next page.

```
>>> v=[(p, sin(p)) for p in [0..2*pi, step=1]] # generate points list v
>>> pts=points(v, color="black", pointsize=30) # plot points
>>> curv=plot(sin(x), xmin=0, xmax=2*pi,
              thickness=2, color="blue") # plot sine curve
>>> tangents=sum([plot(cos(x0)*(x-x0)+y0, xmin=x0-1, xmax=x0+1, color="red",
                       thickness=1) for (x0,y0) in v]) # plot tangent lines
>>> show(curv+tangents+pts, aspect_ratio=1) # combine the sine curve, points
# and tangent lines at each point
```



The power of a programming language is that if we want more tangent lines, a single change in the parameter from “step=1” to “step=0.2” carries this out.



## Course Roadmaps

There is a variety of courses that can be taught out of this text. At UCLA, we teach a two-quarter sequence, called Life Sciences 30AB. (Our Life Sciences division includes Ecology and Evolutionary Biology, Microbiology, Immunology and Molecular Genetics, Molecular Cell and Developmental Biology, Integrative Biology and Physiology, and Psychology.) The course is intended to replace the traditional “Calculus for Life Sciences” and is offered to freshmen and sophomores in Life Sciences, as an alternative to Calculus in fulfillment of two-thirds of the one-year “Quantitative Reasoning” required of all LS majors.

*Note that there is no calculus prerequisite; the necessary concepts of calculus are developed de novo in Chapter 2.* In our view, students truly need to understand the notion of the derivative as sensitivity, and as a linear approximation to a function at a point. We feel that the extensive technical development of elementary calculus: intermediate value theorem, Rolle’s theorem, L’Hôpital’s rule, infinite sequences and series, proofs about limits and the derivation of the derivatives of elementary functions, are less necessary than the fundamental concepts, which are critical. A similar point holds for integration, where the analytic calculation of antiderivative functions has little application at higher levels, while the idea of “adding up the little products” is truly important.

In the first quarter, we cover all of Chapters 1 and 2, then the basic concepts and selected examples from Chapters 3 and 4 (equilibrium points and oscillations). Our examples are drawn roughly 50/50 from ecology and evolutionary biology, on the one hand, and physiology on the other, so that courses can also be fashioned that focus on the one subject or the other.

The second quarter covers Chapters 5–7. We cover only selected examples in these chapters, and our goal is to complete the understanding of eigenvalues and eigenvectors (Chapter 6), and use them to determine the stability of equilibrium points in multidimensional differential equations (Chapter 7).

We have also used the text as the basis for a one-quarter upper-division course in modeling physiological systems for physiology majors, many of whom are pre-med. In this course, we

went quickly through Chapter 1, skipped Chapter 2, and focused on the theory and physiological examples in Chapters 3, 4, and 5. We did not get to linear algebra (Chapter 6) or its applications (Chapter 7) in that one-quarter course. A similar one-quarter course could be taught focusing on the theory and the ecosystem/evolutionary biology examples in Chapters 3, 4, and 5.

Finally, the text can be used as a guide to a first-year graduate course in modeling for students in the biosciences, neuroscience, etc.

## The Math Behind This Text

The text follows what we consider to be a twentieth-century math approach to the subject. The technical development of calculus in the eighteenth and nineteenth centuries saw differential equations as pieces of language, which were then to be operated on by paper-and-pencil techniques to produce other pieces of language (the “solutions”). This had worked well for Newton in the gravitational 2-body problem (1687), and was the paradigm for applied math in the centuries that followed. The Newtonian program came to a dramatic dead end with the 3-body problem, an obvious and more valid extension of the 2-body problem. The 3-body problem had proved analytically intractable for centuries, and in the late nineteenth century, results by Haretu and Poincaré showed that the series expansions that were the standard technique actually diverged. Then the discovery by Bruns that no quantitative methods other than series expansions could resolve the  $n$ -body problem meant the end of the line for the Newtonian program of writing a differential equation and solving it (Abraham and Marsden, 1978).

It was Poincaré’s genius to see that while this represented “calculus: fail,” it was also the springboard for an entirely new approach that focused on topology and geometry and less on analytical methods. His groundbreaking paper was called “On the curves defined by a differential equation,” linking two very different areas: differential equations (language) and *curves*, which are geometrical objects. The distinction is critical: solution curves almost always exist (Picard–Lindelöf theorem), but their equations almost never do.

Poincaré went on to redefine the purpose of studying differential equations. With his new invention, topology, he was able to define qualitative dynamics, which is the study of the forms of motion that can occur in solutions to a differential equation, and the concept of bifurcation, which is a change in the topological type of the solution.

The subsequent development of mathematics in the twentieth century saw many previously intuitive concepts get rigorous definitions as mathematical objects. The most important development for this text was the replacement of the vague and unhelpful concept of a differential equation by the rigorous geometric concept of a vector field, a function from a multidimensional state space to its tangent space, assigning “change vectors” to every point in state space. (In its full generality, the state space is a multidimensional differentiable manifold  $M$ , and the vector field is a smooth function from  $M$  into its tangent bundle  $T(M)$ . Here, with a few exceptions,  $M$  is Euclidean  $n$ -space  $\mathbb{R}^n$ .) It is this concept that drives our entire presentation: a model for a system generates a differential equation, which is used to set up a vector field on the system state space. The resulting behavior of the system is to evolve at every point by moving tangent to the vector field at that point.

We believe that this twentieth-century mathematical concept is not just more rigorous, but in fact makes for superior pedagogy.

## The Authors

*Alan Garfinkel* received his undergraduate degree from Cornell in mathematics and philosophy, and a PhD from Harvard in philosophy and mathematics. He remembers being a graduate student and hearing a talk by the French topologist René Thom. Thom was arguing for qualitative dynamics, and gestured with his hands to indicate the back-and-forth fluttering motion of a falling leaf. “That,” Thom said, “is what we are trying to explain.” After some years of practicing philosophy of science, he transitioned to medical research, applying qualitative dynamics to phenomena in medicine and physiology. At UCLA, he studies cardiac arrhythmias from the point of view of nonlinear dynamics as well as pattern formation in physiology and pathophysiology.

*Jane Shevtsov* earned her BS in ecology, behavior and evolution from UCLA, and her PhD in ecology from the University of Georgia. After hating math for much of her life, she took a mathematical ecology course during her fourth year of college and proceeded to fail the midterm. Following the advice of Prof. Rick Vance, she stayed in the course, got help, and developed both a love for the subject and a passion for teaching it. She went on to do research on mathematical models of food webs and ecosystems, which remain her top research interests.

*Yina Guo* received her PhD from Nankai University in control engineering. Her PhD thesis used partial differential equations to explain the branching structure of the lung. Her computer simulations of branching processes were featured on the cover of the *Journal of Physiology*. She is particularly interested in the use of graphics and visualization techniques in both research and teaching.

## Acknowledgements

This text grew out a course developed by us at UCLA, on the initiative of deans Blaire van Valkenburgh and Victoria Sork, who saw the need to reform mathematics education for Life Science majors. Their leadership was essential in establishing the course and nurturing it. Along the way, we have also had excellent support from the Center for Education Innovation and Learning in the Sciences, led by Erin Sanders. CEILS, in collaboration with Professor Kevin Eagan in UCLA's Graduate School of Education and Information Studies, studied our course and its reception among students, providing invaluable data to measure our progress. It is a pleasure to acknowledge their support. The evaluation of our course, as well as one of the authors (J. Shevtsov), was supported by a grant from the National Science Foundation (NSF Award No. 1432804).<sup>1</sup>

We are grateful to our co-instructors Will Conley and Sharmila Venugopal, who made many helpful suggestions to improve the text. We also thank all the students and TAs who were subjected to earlier versions of the text for putting up with frequent updates and ideas that seemed good at the time, and thank Will Conley for providing some of the exercises and technical and pedagogical improvements.

In addition, many students, former students, and friends read the manuscript, caught typos, and made many helpful suggestions. We would especially like to thank Nicole Truong, Walt Babiec, and Eric Demer.

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<sup>1</sup>Any opinions, findings, conclusions, or recommendations expressed in this textbook are those of the authors and do not necessarily reflect the views of the National Science Foundation.

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