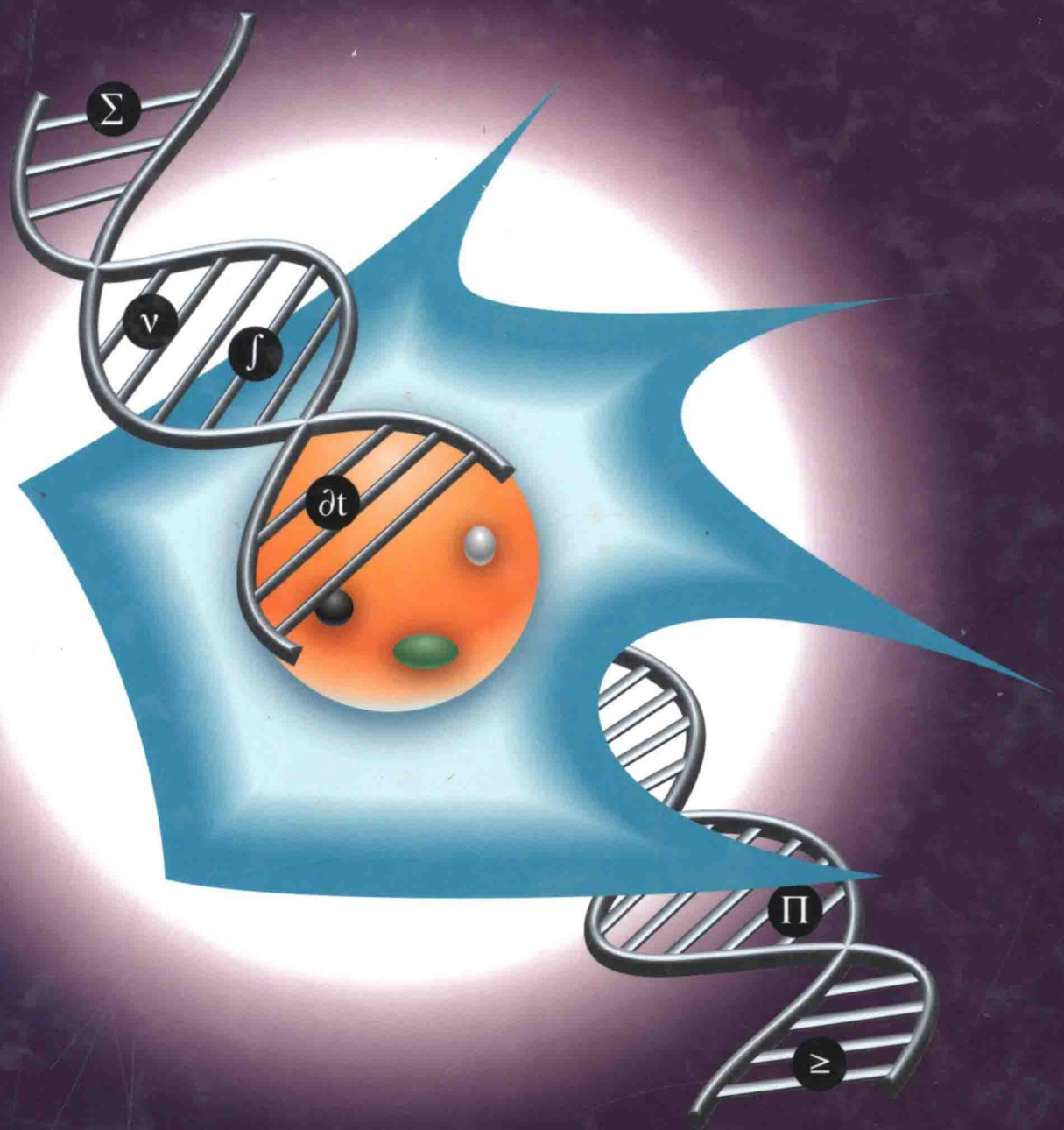# An Invitation to Biomathematics

Raina S Robeva James R Kirkwood Robin L Davies Leon S Farhy
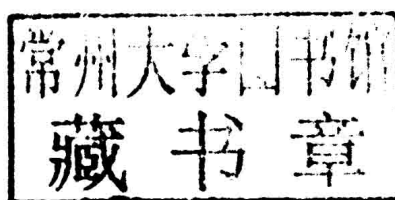Michael L Johnson Boris P Kovatchev Marty Straume

An Invitation to Biomathematics

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An Invitation to Biomathematics

PREFACE

In the not so distant past, the sciences of biology, chemistry, and physics were seen as more or less separate disciplines. Within the last half-century, however, the lines between the sciences have become blurred, to the benefit of each. Somewhat more recently, the methods of mathematics and computer science have emerged as necessary tools to model biological phenomena, understand patterns, and crunch huge amounts of data such as those generated by the human genome project. Today, virtually any advance in the life sciences requires a sophisticated mathematical approach. Characterization of biological systems has reached an unparalleled level of detail, and modeling of biological systems is evolving into an important partner of experimental work. As a result, there is a rapidly increasing demand for people with training in the field of biomathematics.

Training at the interface of mathematics and biology has been initiated in a number of institutions, including Rutgers University, the University of California at Los Angeles, North Carolina State University, the University of Utah, and many others. In 2001, a National Research Council panel found that "undergraduate biology education needs a more rigorous curriculum including thought provoking lab exercises and independent research projects." To improve quantitative skills, faculty members should include more concepts from mathematics and the physical sciences in biology classes. Ideally, the report says, "the entire curriculum would be revamped."[1] As the demand for academic programs that facilitate interdisciplinary ways of thinking and problem solving grows, many of the challenges for creating strong undergraduate programs in mathematical biology have become apparent. The report *Math & Bio 2010: Linking Undergraduate Disciplines* summarizes the results of the project *Meeting the Challenges: Education Across the Biological, Mathematical, and Computer Sciences*[2] and emphasizes that interdisciplinary programs should begin as early as the first year of college education, if not in high school. In one of the articles, an editorial reprinted from the journal *Science* and used in the report, the author Louis Gross specifically underscores the importance of finding ways to "teach entry-level quantitative courses that entice life science students through meaningful applications of diverse mathematics to biology, not just calculus, with a few simple biological examples."[3]

The book that you are about to read, our *An Invitation to Biomathematics*, was conceived and written with this exact goal in mind. This book is meant to provide a glimpse into the diverse world of mathematical biology and to invite you to experience, through a selection of topics and projects, the fascinating advancements made

possible by the union of biology, mathematics, and computer science. The laboratory manual component of the text provides venues for hands-on exploration of the ever-present cycle of model development, model validation, and model refinement that is inherent in contemporary biomedical research. The textbook aims to provide exposure to some classical concepts, as well as new and ongoing research, and is not meant to be encyclopedic. We have tried to keep this volume relatively small, as we see this text used as a first reading in biomathematics, or as a textbook for a one-semester introductory course in mathematical biology. It is our hope that after reading this *Invitation* you will be inspired to embark on a more structured biomathematical journey. We suggest considering a classical textbook, such as Murray's *Mathematical Biology*, to gain a systematic introduction to the field in general. We also encourage you to delve deeper into some of the more specialized topics that we have introduced, or to take additional courses in mathematical biology.

The textbook is divided into two parts. In Part I, we present some classical problems, such as population growth, predator–prey interactions, epidemic models, and population genetics. While these have been examined in many places, our main purpose is to introduce some core concepts and ideas in order to apply them to topics of modern research presented in Part II. Because we also felt that these topics are likely to be covered in any entry-level course in mathematical biology, we hope that this organization will appeal to college and university faculty teaching such courses. A possible scenario for a one-semester course will be to cover all topics from Part I with a choice of selected topics from Part II that is, essentially, modular in nature. The diagram in Figure 1 outlines the chapter connectivity. Table 1 presents brief chapter descriptions by biological and mathematical affiliation.

A committed reader who has had the equivalent of one semester-long course in each of the disciplines of calculus, general biology, and statistics should be able to follow Chapters 1 to 10. With these prerequisites, we believe that the book can be read, understood, and appreciated by a wide audience of readers. Although Chapters 11 and 12 also comply with those general prerequisites, a quality understanding of the fundamental concepts covered there may require a somewhat higher level of general academic maturity and motivation. Thus, although Chapters 11 and 12 can be considered optional in essence, we would like to encourage the readers to explore them to the extent and level of detail determined by their individual comfort level.

Our rule while writing this book was that the biology problem should lead the mathematics, and that we only present the mathematics on a need-to-know basis and in the amount and level of rigor necessary. As a consequence, very few mathematical theorems are proved or even discussed in the text. We limited ourselves to the minimal
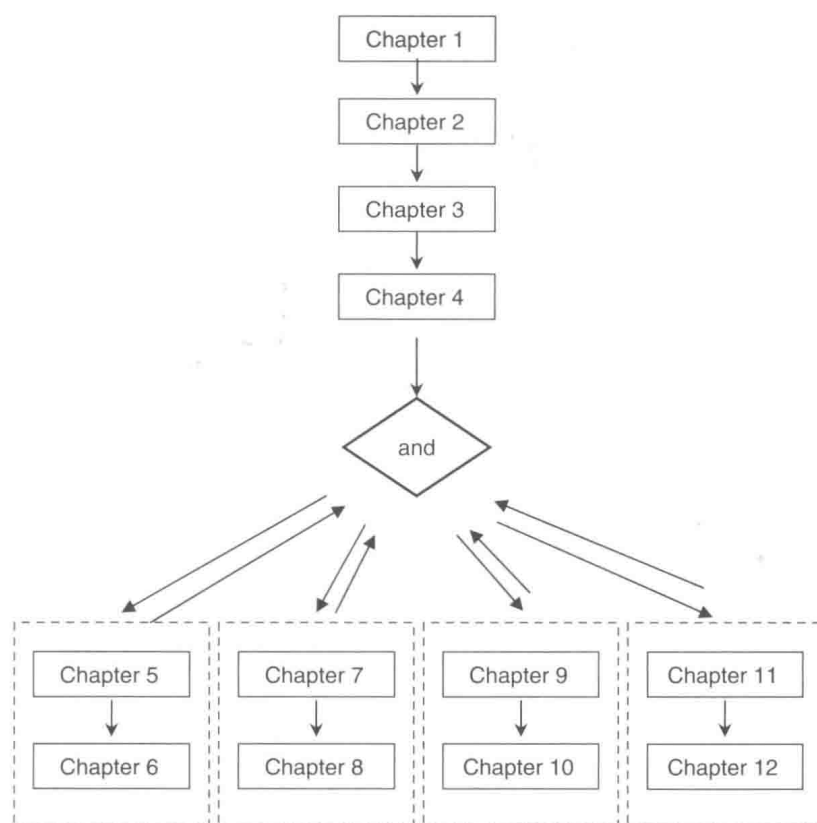
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FIGURE I.

mathematical terminology necessary for understanding, formulating, and solving the problem, relying on the reader's intuition for the rest. We felt that in the interest of showing how the tools of mathematics and biology can blend together and work as one when needed, we should resist the urge for possible generalizations (an urge that is almost second nature for those of us trained in the field of theoretical mathematics). The choice not to explore many of the possible exciting mathematical venues that stem from some of the topics and projects was deliberate, and we apologize to those readers who wish we had included them.

Chapter	Biological topics	Biological subtopics	Mathematical topics
1	Ecology, Conservation Biology, Toxicology	Population growth, harvesting model, drug dosage model	Discrete and continuous dynamical systems, difference equations, differential equations
2	Ecology, Microbiology, Epidemiology	Epidemic model, predator-prey model, competition model	Continuous dynamical systems
3	Genetics	Hardy-Weinberg law, genetic selection, polygenic inheritance	Discrete dynamical systems, probability histograms, Normal distribution, Central Limit Theorem
4	Genetics, Biostatistics	Heritability	Probability distributions, statistics
5	Physiology, Endocrinology	Blood glucose levels, glucose homeostasis	Data transformation, risk function, statistics
6	Physiology, Microbiology	Development, bacterial infections, cardiac function, premature birth	Probability distributions, statistics, approximate entropy
7	Biochemistry, Physiology, Cell Biology	Hemoglobin function, cooperativity, conformational change	Continuous dynamical systems, probability distributions
8	Biochemistry, Physiology	Ligand binding	Numerical solutions of algebraic equations, iterative computational strategies, time series
9	Endocrinology, Physiology, Cell Biology	Hormone pulsatility	Periodic components, FFT, pulse-detection algorithms
10	Endocrinology, Physiology, Cell Biology	Hormone networks	Continuous dynamical systems with delays
11	Physiology, Cell Biology, Molecular Biology	Circadian rhythms	Confounded time series, rhythm analysis
12	Physiology, Cell Biology, Molecular Biology	Gene chips, molecular biology of circadian rhythms	Data normalization, clustering strategies, time series, rhythm analysis

TABLE I.
Chapter topics by biological and mathematical affiliation

You are now invited to turn the page and begin your exploration of biomathematics.

The Authors
July 20, 2007

1. Morgan, A., for the Committee on Undergraduate Biology Education. (2002). *BIO2010: Transforming Undergraduate Education for Future Research Biologists.* Washington, DC: The National Academy Press.
2. Steen, L. (editor). (2005). *Math & Bio 2010—Linking Undergraduate Disciplines.* Washington, DC: The Mathematical Association of America.
3. Gross, L. G. (2000). Education for a Biocomplex Future. *Science*, Vol. 288. no. 5467, p. 807. The author, Louis Gross is a Professor of Ecology and Evolutionary Biology and Mathematics, University of Tennessee, Knoxville, and Past-President of the Society for Mathematical Biology.
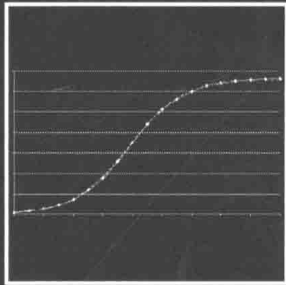
CONTENTS

Chapter 1

PROCESSES THAT CHANGE WITH TIME: INTRODUCTION TO DYNAMICAL SYSTEMS

Life belongs to the living, and he who lives must be prepared for changes.

Johann Wolfgang von Goethe (1749–1832)

According to *Encyclopædia Britannica*, a *mathematical model* is defined as "either a physical representation of mathematical concepts or a mathematical representation of reality." Physical mathematical models, such as graphs of curves or surfaces defined by analytic equations or three-dimensional replicas of cylinders, pyramids, and spheres, are used to visualize mathematical terms and concepts. Such models present realistic depictions of abstract mathematical definitions. In contrast, a mathematical representation of reality uses mathematics to describe a phenomenon of nature. There are many mathematical tools that can be used in this process, including statistics, calculus, probability, and differential equations. Different methods may provide insights to different aspects of the problem, and there is often much debate about what approach is preferable. Mathematical models that represent reality are the subject of this text.

Building a good mathematical model is a challenging task that requires a solid understanding of the nature of the system being modeled, as well as the mathematical tools being used to describe it. Because mathematical models are quite diverse, it is difficult to specify a process that would apply to all problems. However, there are fundamental principles that facilitate and guide the creative process. They are:

1. Initially, a model should be simple.

2. It is crucial to test the model under as many conditions as reasonable.

3. If the model seems to be successful in some ways but fails in others, try to modify the model rather than starting over.

In this chapter, we discuss how biological models of one variable change over time. The first model we study is growth of a population. Our initial attempt is based on numerical data. Later, we build the model based on conjectures about "how populations should grow." Both models yield essentially the same result, and although these constructions are successful in the short term, both are flawed because the long-term behavior they predict is

unrealistic. We then look at the long-term growth of a yeast culture to build a more believable model.

The first models we construct are of exponential growth. Later in the chapter, we study related models describing exponential decrease in the concentration of drugs in the bloodstream. These exponential growth/decay models are derived from the hypothesis that the time rate of change (i.e., the derivative with respect to time) of a quantity is proportional to the amount present.

We begin with a problem popularized in the late eighteenth century by Thomas Robert Malthus—the growth of human populations.

I. USING DATA TO FORMULATE A MODEL

Contemporary research is hypothesis-driven and is based on experimental evidence. A properly designed experiment can corroborate a hypothesis, prove it false, or produce inconclusive data. An experiment can also suggest new hypotheses that, in turn, will need to be tested. This leads to an ever-repeating cycle of collecting data, formulating hypotheses, designing new experiments to attempt to corroborate them, and collecting new data. It should be emphasized, however, that ultimately the validity of a hypothesis can never be proved. Karl Popper gives the following very instructive example: If somebody sees one, two, or three white swans, he or she may hypothesize, "All swans are white." Each white swan seen corroborates the hypothesis but does not prove it, because the first black swan would invalidate it completely. This demonstrates the necessarily close interdependence between hypothesis and experiment.

In this section, we explore the process of creating mathematical models that describe the growth (or decline) in the size of populations of living organisms. We would like to express the size as a mathematical function of time. Although one model will not work for all species, there are certain fundamental principles that apply almost universally. Our first goal is to identify some of these principles and determine the best way to express them mathematically. We begin by considering U.S. census data for 1800–1860 (U.S. Census Bureau [1993]). Table 1-1 presents the figures for the population of the United States over these 6 decades.

Examining the data plot is always a good idea, as it may suggest certain relationships. Letting $t = 0$ be the year 1800 and one unit of time $= 10$ years, we present the data plot in Figure 1-1. Unfortunately, the conventional plot of the data is not very illuminating. It is evident that the growth is nonlinear, but it is not possible to determine the type of nonlinear dependence by mere observation. There are many mathematical functions that exhibit similar growth patterns. For example, if $P(t)$ represents the U.S. population as a function of the

Year	U.S. Population (millions)
1800	5.3
1810	7.2
1820	9.6
1830	12.9
1840	17.1
1850	23.2
1860	31.4

TABLE 1-1.
Population of the United States from 1800 to 1860.
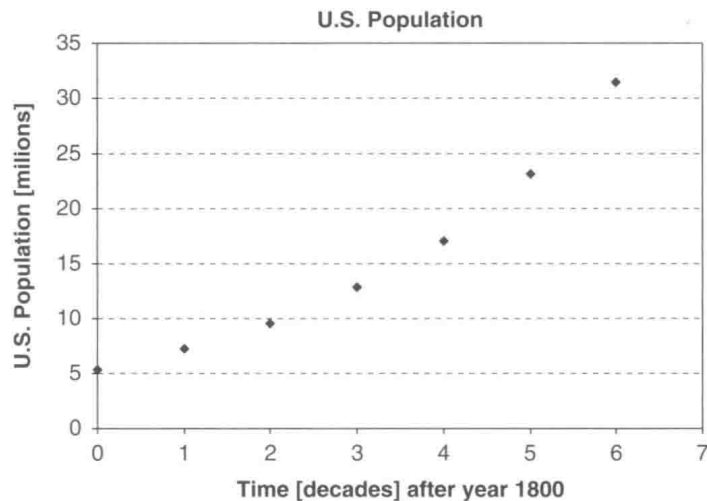
U.S. Population

FIGURE 1-1.
Plot of U.S. population versus time. A graph of the data shown in Table 1-1.

time t, the data points in Figure 1-1 may have come from sampling the function $P(t) = at^2$ or $P(t) = at^3$, where $a > 0$ is a constant, or some other power law. It may also be that the data follow an exponential law of increase with the general form $P(t) = ae^{bt}$ where $a > 0$ and $b > 0$ are constants. To determine the specific nonlinear function that provides the best fit for the data, we examine the *change* in U.S. population per decade; that is, the *rate of change*. In our example, they appear to be growing with time—the population change is 1.9 million from 1800 to 1810 but 8.2 million from 1850 to 1860 (more than four times as large). Thus, the rate of population growth increases as the U.S. population increases.

These observations lead to two different ways of plotting the data: (1) The change in population size per decade versus time, and (2) the change in population size per decade versus population size at the beginning of decade. While the graph in Figure 1-2(A) is still not very telling, the one in Figure 1-2(B) is strikingly *linear*. Is this a mere coincidence, or are
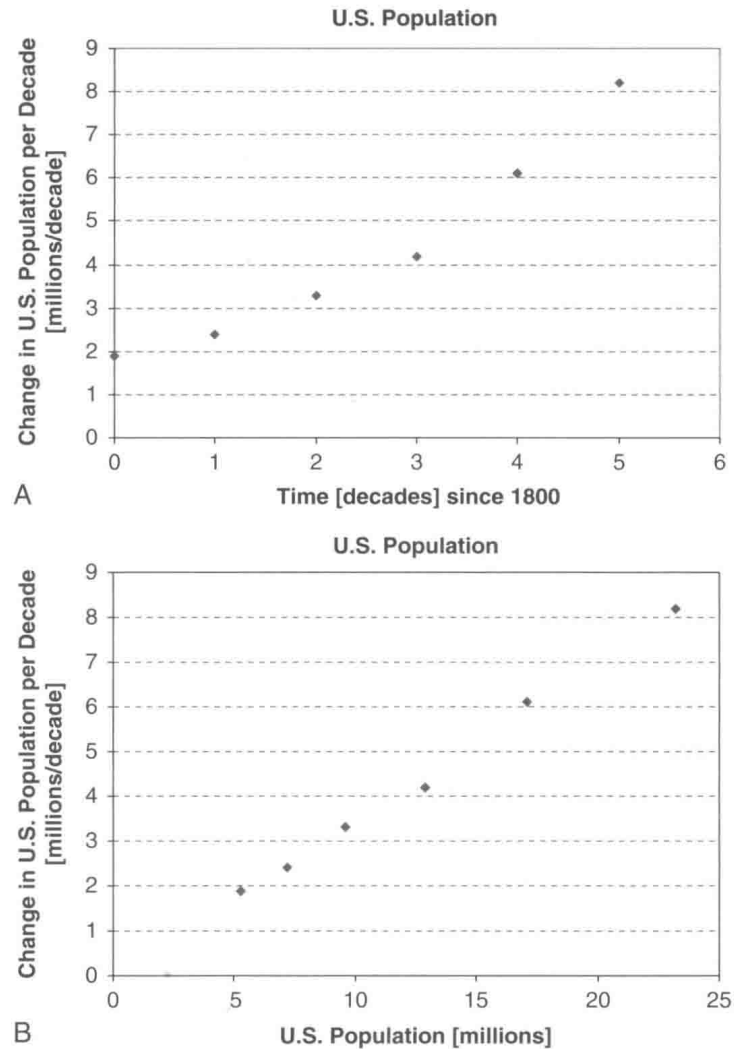
FIGURE 1-2.

Comparison of rate of change versus time to rate of change versus population size. Panel A: Population rate of change versus time; panel B: Population rate of change versus population size.

we on to something important? Observing the data prompts us to make the following conjecture:

There is a linear dependence between the rate of change in population size and the population size itself.

We now have a hypothesis. How should we proceed in order to corroborate or reject it? In general, the process involves the following major components, presented here in their natural order:

1. *Solicit expert opinion.* In this case, discuss the conjecture with population biologists. If they cannot dismiss the hypothesis right away by providing examples that clearly contradict it, it merits further investigation.