Preface

OVERVIEW

Let's begin our journey into systems biology by comparing complex diseases to a firing squad. While working as a postdoc at the California Institute of Technology, I had the opportunity to know a talented biologist and a well-read Russian who convinced me to read Tolstoy's *War and Peace.* One thrilling highlight of that masterpiece finds the protagonist, Pierre, in front of a firing squad in Moscow. Tolstoy describes the wild thoughts ringing in Pierre's mind as he faces the guns, wondering how he had come to this point. "Who was it that had really sentenced him to death?" As Pierre looks into the nervous eyes of the young soldiers, he realizes that they are not to blame, for "not one of them had wished to or, evidently, could have done it."

So, who was responsible? In all the chaos of the scene and his imminent death, Pierre has a moment of clarity. He realizes that it was *no one.* Rather (and I have added italics for emphasis), "It was a *system*—a concurrence of circumstances. A *system* of some sort was killing him—Pierre—depriving him of life, of everything, annihilating him."

As I read this passage, I could not help but think about the many patients with complex and untreatable diseases that feel virtually the same way as Pierre. What is it that has really sentenced them to death? When they read the newspapers or watch television, they see headline after headline about "the cancer gene" or "the Alzheimer gene," but if these genes truly exist, then why have cures to these diseases eluded us?

I take my answer from Pierre: Such diseases do not depend on any one gene, but on a "concurrence of circumstances"—a system. A *Science* commentary on complex diseases emphasizes this point:

> The most common diseases are the toughest to crack. Heart disease, cancer, diabetes, psychiatric illness: all of these are "complex" or

> "multifactorial" diseases, meaning that they cannot be ascribed to mutations in a single gene or to a single environmental factor. Rather, they arise from the combined action of many genes, environmental factors, and risk-conferring behaviors. One of the greatest challenges facing biomedical researchers today is to sort out how these contributing factors interact in a way that translates into effective strategies for disease diagnosis, prevention, and therapy. (From Kiberstis, P. and Roberts, L. *Science*. 2002, **296**(5568): 685. Reprinted with permission from AAAS.)

Put simply, our ability to tackle complex diseases is limited by our ability to understand biological systems. We need ways to explain organismal behaviors in terms of cellular components and their interactions. Even a small number of components can interact in nonintuitive ways; thus, systems-level research requires mathematical and computational strategies.

We are at the cusp of a revolution in understanding the systems-level mechanisms that underlie human disease. However, before the revolution can achieve its full potential, we first must grasp the systems-level behavior of molecules, pathways, and single cells. Vast progress has been made toward this goal in the past 30 years, but much exciting research remains to be completed before the power of these systems-level investigations can be turned to the elucidation and eradication of human disease.

This book seeks to empower you, the student, by aiding you to develop the tools, techniques, and mindset to directly engage in primary research yourself. Whether you are interested in microbes, organs, whole organisms, diseases, synthetic biology, or just about any field that investigates living systems, the intuition that you will develop through the examples and problems in this book will critically contribute to your success at asking and answering important scientific questions.

This book focuses on the use of computational approaches to model, simulate, and thereby better understand complex molecular and cellular systems, research that is often called "systems biology." This field has grown rapidly: There is now an Institute for Systems Biology in Seattle, a new Department of Systems Biology in various institutions (notably Harvard Medical School and Stanford University), a Nature/EMBO (European Molecular Biology Organization) journal, *Molecular Systems Biology*, and an International Conference on Systems Biology that draws over 1,000 people each year. The field has drawn together researchers from nearly every scientific domain. For example, students from biology, bioengineering, computer science, chemistry, biomedical informatics, chemical and systems biology, aeronautical engineering, chemical engineering, biophysics, electrical engineering, and physics have all participated in the systems biology class that I teach at Stanford University.

I teach the material in this book to advanced undergraduate and beginning graduate students over 10 weeks, with two 90-minute lecture sessions per week. Both my class and this textbook are divided in half. The first half, "Building Intuition," focuses on learning the computational tools that underlie systems biology using a simple autoregulatory feedback element as the subject of study. Without grasping these fundamental concepts, you will have great difficulty in forming intuition about the systems-level behavior of molecules and cells, intuition that will strongly contribute to the effectiveness of your systems biology research. The concept of biological feedback and the circuit itself are introduced in Chapter 1, which is followed by five chapters that describe various methods to model this circuit's behavior. Chapter 2 concerns Boolean logic models, Chapters 3–5 focus on ordinary differential equation-based solutions (using analytical, graphical, and numerical methods, respectively), and Chapter 6 describes how to perform stochastic simulations.

The second half of the text, "From Circuits to Networks," applies the tool kit developed in Section 1 to study and model three of the most important and interesting biological processes: transcriptional regulation (Chapter 7), signal transduction (Chapter 8), and metabolism (Chapter 9). Finally, Chapter 10 describes the methods for integrating these diverse modeling approaches into integrated hybrid models using the same techniques that recently led to the creation in my lab of a whole-cell model, the first of its kind.

LEARNING FEATURES

Prerequisites

The material in this book represents a substantial convergence of thought, expertise, and training. Although I believe that this interdisciplinary aspect is one of the most exciting aspects of the field, it also presents a teaching challenge because student backgrounds can be so varied. I therefore encourage students who have never gone beyond high school biology either to take a class or to review a book such as *Molecular Biology of the Cell* (Alberts et al., 2007). I recommend that the biologists at least be acquainted with ordinary differential equations before tackling this material. In addition, I highly recommend that all students have some experience in mathematical programming. Many of the problems within and at the end of each chapter give hints about potentially useful MATLAB® functions, but this help will not be sufficient if the student has never programmed previously. Sample code appears in the chapters and Practice Problems, end-of-chapter Problems, and their solutions (solutions available online).

Learning Objectives

My goal in writing this textbook is to give you a hands-on, behind-the-scenes tour of this exciting field. After working through this book, I expect that you will

- appreciate the importance of studying biological systems as a whole, rather than as isolated parts;
- be proficient with a broad range of modeling methods relevant to systems and computational biology;
- understand several important studies in the field; and
- apply systems biology approaches to your own research someday!

Specific learning objectives for each chapter are listed at the beginning of the chapter.

Practice Problems

Each chapter contains Practice Problems that explore concepts that may be new to you. The solutions to these problems model how to implement the mathematics described in the text (for example, in MATLAB), how to effectively present quantitative results, and how to conceptualize the biological behavior that underlies our measurements, calculations, and simulations.

Sidebars

Chapters 1, 3, and 8 contain sidebars that delve further into the details or background of concepts presented in the text.

Glossary

Within the text, I have highlighted critical terms that may be unfamiliar to systems biology, biology, biochemistry, or engineering novices. The glossary contains definitions of those terms that focus on our implementations in the text.

Chapter Summaries

Each chapter ends with a few paragraphs that summarize the major concepts and methodologies of the chapter. The summaries also highlight the most critical assumptions, equations, and mathematical treatments that you explored in that chapter.

Recommended Reading

Citations to primary research articles, textbooks, websites, and popular-science works that are directly related to each chapter appear at the end of each chapter. I hope that students will "follow the citations" as they formulate their own research interests—and perhaps discover new ones.

Problems

Finally, each chapter ends with a selection of problems that are intended to give you hands-on experience with computational systems biology. You will explore MATLAB code, practice a variety of modeling techniques, and start developing an intuition for biological systems that will provide the foundation for future scientific endeavors. I provide a few hints to help you along (especially hints to help you navigate MATLAB). The solutions to these problems are provided in a separate solutions manual that will be available to instructors.

RECOMMENDED READING

Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., and Walter, P. *Molecular Biology of the Cell* (5th edition). New York: Garland Science, 2007.

Kiberstis, P. and Roberts, L. It's not just the genes. *Science* 2002. **296**(5568): 685.

Moore, H. *MATLAB for Engineers* (3rd edition). Englewood Cliffs, NJ: Prentice Hall, 2011.