

Preface

This book is an exploration of mathematics as applied to physiological systems. It is not a mathematics textbook *per se*, nor is it designed to provide a self-contained background in physiology. It is specifically aimed at the interface between these fields, and in particular is intended to address the question: why should I bother with a nonlinear-systems analysis of my physiological system, and how should I go about this analysis? The material, especially in the first 14 chapters, is essentially mathematical. Physiological applications are presented as case studies in later chapters.

It is important to appreciate the role of mathematics in the analysis of physiological systems. In too many cases, mathematical tools (Fourier analysis, nonlinear dynamical analysis, computer modeling) have become so easy to use that they are easily misused¹. All mathematical tools are based on assumptions, and at the very least the investigator should be aware of these assumptions when using the tools. (The use of statistical *t*-tests with data drawn from non-normal distributions is a pertinent example from another context.) This book will attempt to provide sufficient mathematical background so that the reader can avoid major mistakes in applying the tools presented here, while keeping the level of rigor firmly in check.

The mathematical approach taken here can be summarized by two well-known quotations. The first is from renowned physicist Richard Feynman: “The next great era of awakening of human intellect may well produce a method of understanding the qualitative content of equations.

¹ RM May (2004) Uses and abuses of mathematics in biology. *Science* 303:790-793.

Today we cannot see that the water flow equations contain such things as the barber pole structure of turbulence that one sees between rotating cylinders. Today we cannot see whether Schroedinger's equation contains frogs, musical composers, or morality - or whether it does not."² In fact it is this type of qualitative understanding that is stressed in this book, most obviously through the visualization of system trajectories in state space, and measurements based on these trajectories. The second quote is from mathematician and computer scientist Richard Hamming, in his book on numerical methods: "The purpose of computing is insight, not numbers"³. It will be good to bear this in mind, as some of the computational techniques presented here can produce numerical values which might give a false sense of confidence. The field of computational nonlinear dynamics is still at a stage where many of the numerical results should be viewed as estimates, best interpreted as relative values to be compared across conditions or across populations.

The text will also provide some appropriate historical background from time to time. In the vast majority of undergraduate, and even graduate, education, material is presented in the form of revealed truths. Instructors often present the subject matter in a way that makes it seem as if it should be obvious to one and all, if only the student would take the time to think about it for a few minutes. Alas, this is not the way science works. It proceeds in fits and starts, there are debates about what the crucial questions are, there is contention as to the best approaches, and there is often little agreement even when solutions are proposed. This is a human endeavor, and although the end product is extremely reliable, having passed the tests of peer review and trial by fire, the process of getting there is not always straightforward. It is helpful to have a sense of how even today's most "obvious" scientific truths were once muddled in the fog of battle.

This is not solely to indulge the author's personal interest in the history of science. The more important goal is to provide for the reader

² RP Feynman, RB Leighton, M Sands (1964) *The Feynman Lectures on Physics*, Vol. II. Reading MA: Addison-Wesley.

³ RW Hamming (1962) *Numerical Methods for Scientists and Engineers*. New York: McGraw-Hill.

(especially young students) a sense of the evolution of ideas, the dead ends and unproductive paths, the overall somewhat haphazard nature of the development of a scientific field. This imbues a crucial perspective for anyone considering a career in research. First, it shows (hopefully) the excitement and grand adventure of the research endeavor, and indicates why many of us consider it a true privilege to be a member of the international community that engages in this mad pursuit. Second, it demonstrates that in any scientific field (and especially in one that is new, such as nonlinear dynamics in the life sciences), the research literature must be read with a critical eye, until consensus is developed as to the important problems and the legitimate approaches to them. (Of course such consensus is subject to later upheaval, but most of us must for practical purposes be constrained by these limits for a time⁴.) Third, the historical perspective should provide some solace to the beginning researcher who feels overwhelmed with the mass of information already available, and must face the feeling that everyone else is faster, smarter, or at least better-funded. Even if these esteemed goals are not met, at least I hope that the occasional historical background will be enjoyable.

Some readers may remember the intense enthusiasm generated in the past with the rise of interest in such areas as neural networks and expert systems in artificial intelligence. There was a great flurry of interest in each of these fields, associated with what we might graciously call “over-enthusiastic claims.” In each case, there was great temptation to believe that all existing computational/cognitive/modeling problems could be solved imminently, if only enough support and attention would be devoted to that particular field of endeavor. I recall that in the 1980s the case was made for the creation of distinct Neural Networks Departments in research universities, in order to make clear the separation from electrical engineering and the other progenitor fields. Things have calmed down considerably since that time, and now each field can be seen within a broader perspective. The shortcomings and difficulties of each have become more apparent, and their place in the wider intellectual landscape is both more certain and more circumscribed.

⁴ TS Kuhn (1996) *The Structure of Scientific Revolutions*, 3rd edition. Chicago: University of Chicago Press.

And so it is with the topic of this book. In its early years (late 1970s to early 1980s), the promise of the “new” field of nonlinear dynamical systems (more correctly, the re-discovery of computational approaches to nonlinear dynamics) was often vastly overstated. Widely known as “chaos theory” at the time, many in the field were motivated by a mad rush to demonstrate chaotic behavior in a favorite system. With the passage of time, the difficulty of this specific task has become very clear, while at the same time its importance has been called into question. As reflected in the preferred designation of “nonlinear dynamics,” the field has attained a broader perspective, improved its techniques, refined the scope of its inquiries, and moderated its rhetoric. In parts of this book this journey will be clear.

The approach taken in this book is based almost solely on analysis of system trajectories in state space. By this I mean that we will consider properties of system behavior that can be derived from these trajectories. This is different from approaches based more directly on time-series analysis or bifurcations of dynamical equations. In particular this is not a mathematics text, nor is it a collection of articles from the research literature. Rather I have tried to tie together the various tools and techniques that have proven most useful to date, and to present the physiological results in a way that emphasizes the system not the tools.

The computational techniques that form the heart of the book are recent by the standards of linear systems theory, but they may appear rather dated in light of the rapid development of nonlinear dynamical analysis. Nevertheless, the methods are by no means outdated. The emphasis on these techniques is deliberate, and based on several factors. First, these techniques are the most firmly established ones, especially for physiological analysis. Second, they serve as good illustrations of the underlying concepts and principles. Third, they are not very difficult to understand and are therefore appropriate for teaching and for developing intuition and insight. Fourth, more recent developments have almost invariably built upon these basic methods. Fifth, they are the methods that I have found to be the most useful in initial dynamical studies of the oculomotor system.

Following on this last point, in many places throughout the text (and most notably in Chapter 5 on dimension estimation), practical

suggestions for implementation and interpretation of the computational tools are provided. This information is based on both published recommendations and personal experience. These passages provide the essence of a “user’s guide” to some of the tools, which will hopefully make readers more comfortable in attempting their use.

Deciding on the organization of the book was a difficult task. Coverage includes mathematical review material, advanced and recent techniques for analysis of systems and signals, and a review of progress in several different fields of physiology and life sciences. An obvious approach would have been to include pertinent physiological examples in association with the description of each computational technique. The problem with this is that many of the physiological systems have been analyzed with several techniques, and of course each technique has been applied to several different fields of physiology. I have therefore taken a different approach. Part I (Chapters 1-3) introduces basic concepts in signal processing, dynamics, and linear systems. In part II (Chapters 4-14), each chapter is devoted to a single computational technique or dynamical concept; each computational tool is introduced and elucidated with appropriate examples. Then, in part III (Chapters 15-21), different physiological systems are addressed in turn as a set of case studies, and the range of techniques applied to each system can be shown together in a single chapter. This has allowed me to emphasize the physiological interpretations in part III rather than the tools themselves.

The material selected for the case studies consists of examples chosen primarily for their didactic nature. These chapters do not contain comprehensive reviews in a given area of physiology, which would be unwieldy and quickly dated. Rather, they were selected for clarity in application and interpretation, and in some cases novelty and originality. Also note that the methods selected for presentation in the case-study chapters are not necessarily those that have the most promise for future research, or even those that have been most widely embraced, but those that can be understood and appreciated by the intended readers of this book.

Associated with the book’s organization is its anticipated appeal to a wide range of readers. The book is suitable as a text for graduate students or advanced undergraduates in such fields as biomedical engineering and

neuroscience. However, my hope is that others who wish to acquire a feel for this relatively new approach to physiology will also find the book useful, as a reference for the computational tools, as a primer on the types of physiological questions that can be addressed with these tools, and as an introduction to some key findings in a few physiological systems. These readers might be researchers in a specific field, or those wishing to survey recent advances in nonlinear dynamics. Those specialists interested in a specific physiological system may find the corresponding chapter in section III to be of particular use.

To summarize, my main goal with this book is to provide a volume for reference and review, which can also help to develop intuition on how to approach nonlinear problems in physiology. The book will introduce computational techniques, and show through examples what can be done with them by life-science researchers. My hope is that this combination of reference material and applications will give the reader the background to make use of the material in his or her own research, and the confidence and insight that will be useful for further exploration and invention of new techniques.

I recall vividly the day, when I was in graduate school, when my close friend and fellow student Dan Merfeld came into the lab shortly after reading the book *Chaos: Making a New Science*, by James Gleick. This popular book for non-specialist readers describes the modern rise of computational approaches to nonlinear systems (by and large the material covered in the present book), and gives a taste of some of these approaches. He said, “after reading this, I’m convinced that there are things in our data that we are missing.” After reading the book myself, I felt the same way, and my hope is that after reading the book you are holding, you will feel the same way, and in addition will be armed with some of the tools with which to begin your investigation.

In closing, I would like to express my thanks to the many scientific colleagues over the years who have inspired and encouraged me, in particular David Zee, David Robinson, Peter Trillenberg, Larry Young, and Chuck Oman. Dan Kaplan has been most generous in answering my questions on nonlinear dynamics. The students at Johns Hopkins who have taken my course on nonlinear dynamics over the years, and who have asked probing and insightful questions, have helped me greatly in

clarifying this material in my own mind. Those deserving of special mention include Scott Molitor, David Scollan, Sarah Plymale, Josh Csyk, Chris Gross, Nabeel Azar, Olga Telgarska, Wilsaan Joiner, and Faisal Karmali. My dynamical systems research over the years has been supported by several organizations, to whom I am greatly indebted: NASA, The Whitaker Foundation, NSF, NIH (National Eye Institute, National Institute on Deafness and other Communication Disorders, National Institute of Biomedical Imaging and Bioengineering), and the Department of Otolaryngology – Head & Neck Surgery of The Johns Hopkins University School of Medicine.

Thanks are also due to World Scientific for their help in the production of this volume, and Dan Shelhamer for proofreading portions of the manuscript. Portions of section 13.4 are reprinted from the journal *Biological Cybernetics*, volume 93, “Sequences of predictive eye movements form a fractional Brownian series - implications for self-organized criticality in the oculomotor system” (M. Shelhamer), pages 43-53, copyright Springer-Verlag 2005, with kind permission of Springer Science and Business Media. Some material in several other chapters, Chapter 15 in particular, is reprinted from *Journal of Neuroscience Methods*, volume 83, “Nonlinear dynamic systems evaluation of ‘rhythmic’ eye movements (Optokinetic Nystagmus)” (M. Shelhamer), pages 45-56, copyright 1998, with permission from Elsevier. Portions of chapter 15, including Figures 15.1.1, 15.1.3, and 15.1.6, are reprinted from the journal *Biological Cybernetics*, volume 76, “On the correlation dimension of optokinetic nystagmus eye movements: computational parameters, filtering, nonstationarity, and surrogate data” (M. Shelhamer), pages 237-250, copyright Springer-Verlag 1997, with kind permission of Springer Science and Business Media.

M. Shelhamer
Baltimore MD
March 2006