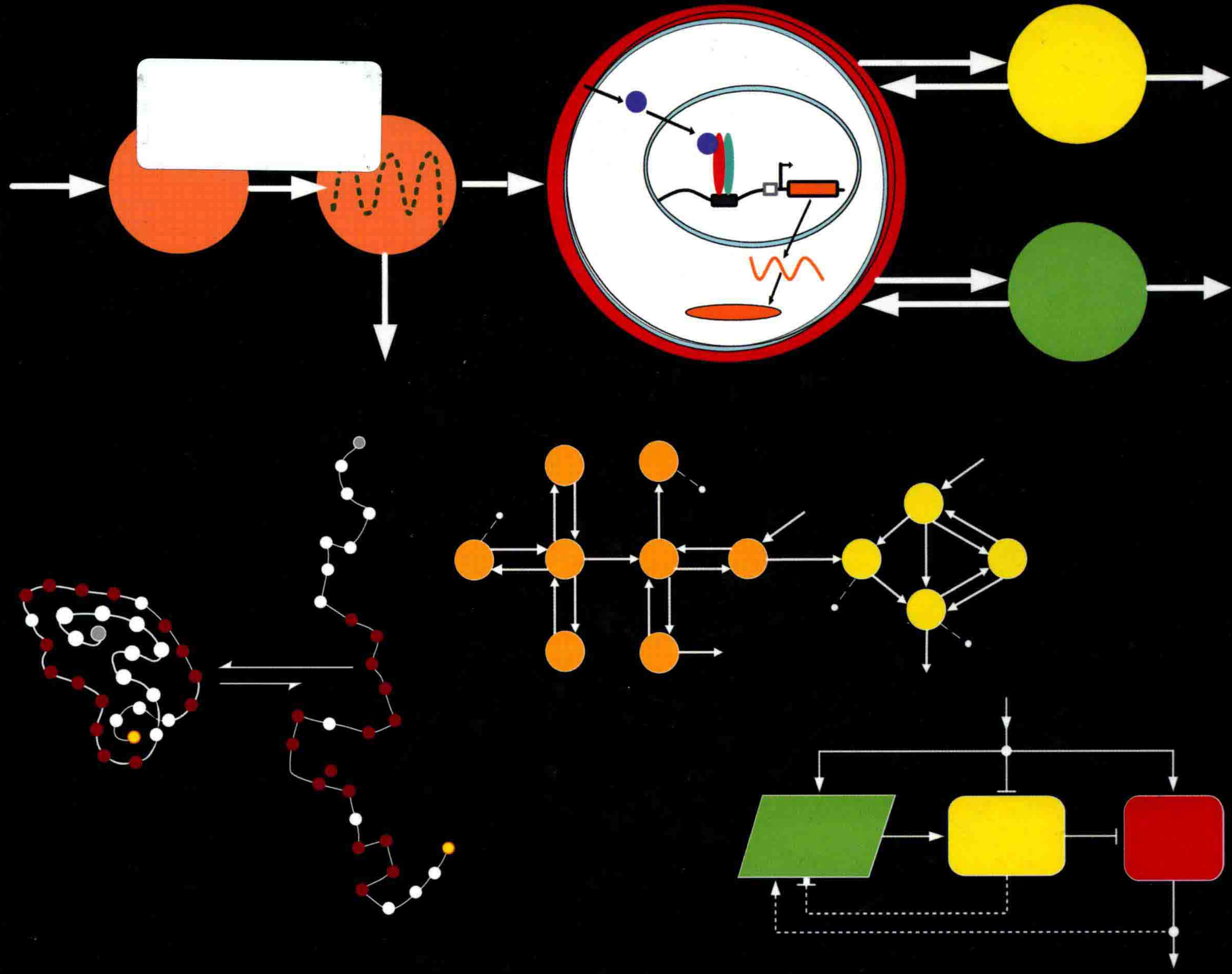

JOSEPH DiSTEFANO III

DYNAMIC SYSTEMS BIOLOGY MODELING AND SIMULATION

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Joseph DiStefano III

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DYNAMIC SYSTEMS BIOLOGY MODELING AND SIMULATION

"For anyone interested in kinetic modeling of substances in physiological systems, Chapter 8 *is a must read. It so elegantly covers the three important areas the reader is likely to encounter in a wider reading of the subject, namely physiologically-based models of organs and whole-body systems, multicompartmental models applied to such systems, and application of noncompartmental models. It is rare to find in one chapter all three elements succinctly explored yet in sufficient depth to allow the reader meaningful insights into their application, pitfalls and limitations. Throughout the chapter the assumptions of system linearity and stationarity underpin much of the mathematical development, and the reader is rightfully cautioned that there are situations encountered, for example in toxicology and pharmacology, where one or more processes is saturable at the applied dose, rendering the system nonlinear, which can often be readily incorporated in the modeling process."*

Malcolm Rowland
Professor of Pharmacy,
University of Manchester, U.K.

*"I am just in awe of your ability to start with simple ideas and use them to explain sophisticated concepts and methodologies in modeling biochemical and cellular systems (*Chapters 6 and 7*). This is a great new contribution to the textbook offerings in systems biology."*

Alex Hoffman
Director of the San Diego Center
for Systems Biology and the UCSD Graduate Program
in Bioinformatics and Systems Biology

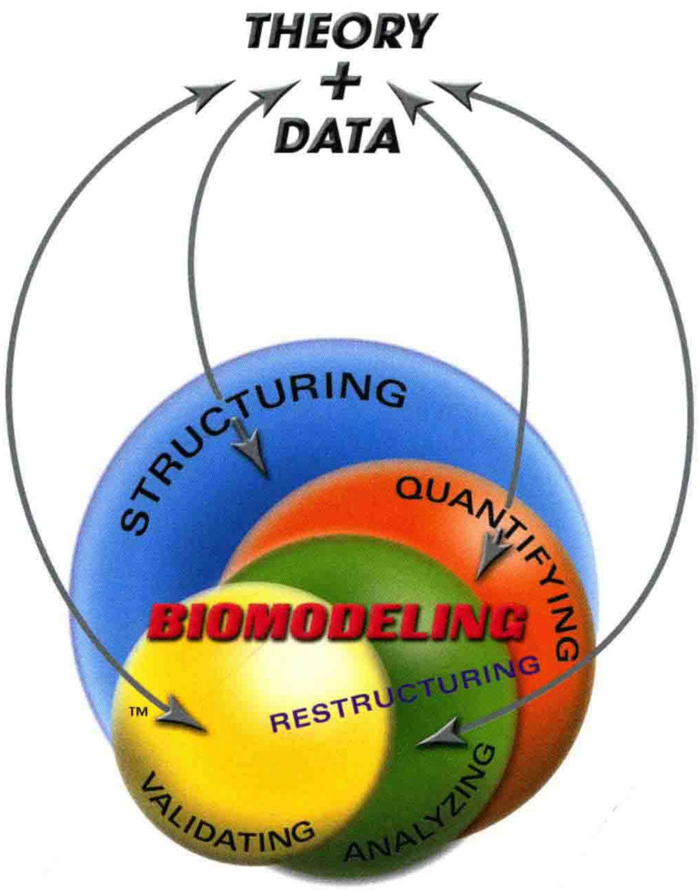
"I found Chapter 1 *to be a marvel of heavy-lifting, done so smoothly there was no detectable sweat. Heavy-lifting because you laid out the big load of essential vocabulary and concepts a reader has to have to enter the world of biomodeling confidently. In that chapter you generously acknowledge some us who tried to accomplish this earlier but, compared to your Chapter 1, we were clumsy and boring. For me, now, Chapter 1 was a "page-turner" to be enjoyed straight through. You have the gift of a master athlete who does impossible performances and makes them seem easy.*
"Your Chapter 9 *– on oscillations and stability – is a true jewel. I have a shelf full of books etc on nonlinear mechanics and system analyses and modeling, but nothing to match the clarity and deep understanding you offer the reader. You are a great explainer and teacher."*

F. Eugene Yates
Emeritus Professor of Medicine,
Chemical Engineering and Ralph and Marjorie Crump Professor
of Biomedical Engineering, UCLA

"Chapter 4 *covers many aspects of the notion of compartmentalization in the structural modeling of biomedical and biological models – both linear and nonlinear. Developments are biophysically motivated throughout; and compartments are taken to represent entities with the same dynamic characteristics (dynamic signatures). A very positive feature of this text is the numerous worked examples in the text, which greatly help readers follow the material. At the end of the chapter, there are further well thought out analytical and simulation exercises that will help readers check that they have understood what has been presented.*
"Chapter 5 *looks at many important aspects of multicompartmental modeling, examining in more detail how output data limit what can be learnt about model structure, even when such data are perfect. Among the many features explained are how to establish the size and complexity of a model; how to select between several candidate models; and whether it is possible to simplify a model. All of this is done with respect to the dynamic signatures in the model. As in Chapter 4, readers are helped to understand the often challenging material by means of numerous worked examples in the text, and there are further examples given at the end."*

Professor Keith Godfrey
University of Warwick,
Coventry, U.K.

Preface to the First Edition



Pedagogical Struggles

I've been learning and teaching mathematical (abbrev: math) modeling and computer simulation of biological systems for more than 47 years. As a control systems engineering graduate student in the 1960s searching for a research area, I found myself quite attracted by biological control systems. This was an esoteric and lonely direction at the time; the primary alternatives for control systems engineering PhD students in southern California were well-funded military control system projects most of my peers were choosing. Worthy, but not my calling. Biological control system modeling otherwise fit neatly into the realm of my major field. For added value, it also provided living examples for another collaborative writing project (DiStefano III et al. 1967).

There was little integrated pedagogy or support at the time for the subject of *my* calling and I realized I faced a multidisciplinary learning task. I had to learn a great deal of new vocabulary (and jargon), and digest no small amount of new scientific knowledge – in biophysics and biochemistry as well as basic biology and physiology; all this before I could begin to develop models for addressing and helping solve real problems in life sciences. Credible math modeling – in any field – requires deep knowledge in the domain of the system being modeled.

Multicultural aspects of my quest also became evident, as did the varieties of different approaches to modeling science. The *cultures* in which each of these disciplines function are quite different, most different between life sciences and math. In the 1960s, biology was largely empirical – still firmly rooted in observation and experiment – with a highly disciplined "wet-laboratory" culture. Quite foreign to my math-systems-engineering "work-anywhere-anytime" culture. Biology remains much that way and, although this is changing, it's still very much reductionist. The other sciences and engineering rely on more theory, as well as empiricism, in the extreme often functioning successfully as "solo" (research) performances – no need for a culture!

I minored in physiology as a PhD student and followed an early path studying physiological systems and mathematical and systems engineering-inspired methods for best modeling them. Biomodeling in those days was done primarily at macroscopic and whole-organism levels. Not any more. As technological breakthroughs in measurement technologies have burgeoned in the last half-century, the spatial and temporal scales over which biological systems knowledge is unfolding has generated a need for deeper understanding of molecular and cellular biology, biochemistry and neurobiology at more granular levels. In lieu of specializing in all these areas, interdisciplinary scientists have typically "picked-up" the needed knowledge along the way, as I did. Modern biomedical engineering programs now include the bio-basics. This means courses with substantive content in molecular and cellular biology as well as physiology and biochemistry.

After earning my PhD in 1966, I began teaching modeling and simulation of dynamic biological systems via an *ad hoc* interdisciplinary major called "biocybernetics." This developed later into a formal PhD field, as well as the moniker of my laboratory at UCLA. I've been wrestling with optimizing my pedagogical path ever since, adjusting it continually along the way, with the goal of communicating it ever-better, and upgrading it as new approaches and discoveries have emerged.

Crystallizing and Focusing – My Way

MODELING, as such, can stand alone as a mature discipline, but it is done somewhat differently across the multidisciplinary spectrum of its practitioners, and has a history of being studied and developed on an "as-needed" basis, especially in the life sciences. There is, however, a substantial common core of methodologies for dynamic biosystem modeling widely disseminated in journals and books. Much of it is developed or described for different applications, or for single *scales* (e.g. molecular-cellular, organ-system, or population levels), using a variety of (and sometimes ambiguous) nomenclature. One of my goals as a teacher has been to help crystallize and unify the substance and language of this core of material – to make it more accessible to a larger audience – at the same time exposing and clarifying the ambiguities in some concepts and tools.

I've been drawing from and merging aspects of the several classical disciplines involved with math modeling in biology into a *unified subject matter*, maximally comprehensible to undergraduates (and graduates) in any of these sciences or engineering. This textbook codifies this process. It offers a basics-to-intermediate-level treatment of modeling and simulation of dynamical biological systems, focused on classical and contemporary multiscale methodologies, consolidated and unified for modeling from molecular/cellular, organ-system, on up to population levels. It will undoubtedly be of interest to individuals from a variety of disciplines, probably with widely varying degrees of mathematical as well as life science training. It is intended primarily as an upper division (advanced undergraduate), graduate level or summer program textbook in biomedical engineering (bioengineering), computational biology, biomathematics, pharmacology and related departments in colleges and universities.

The text material is written in a maximally tutorial style, also accessible to scientists and engineers in industry – anyone with an interest in math modeling and simulation (computational modeling) of biological systems. One or 2 years of college math are prerequisite and, for those with minimum preparation, the needed math (differential and difference equations, Laplace transforms, linear algebra, probability, statistics and stochastics topics, etc) is included either in methods development sections or in appendices.

My approach to biomodeling is drawn in large part from my dynamic systems engineering and control theory viewpoint and training (the theory). But my 30 years of "wet-lab" research (the data) – closely integrated with and guided by biomodeling – plays an equal role. The two have motivated each other, first serendipitously, and then by design. Much of the book pedagogy is a distillation and consolidation of my own and my students' modeling efforts and publications over half a century, including novel and previously unpublished features particularly relevant to modeling dynamic systems in biology. These include qualitative theory and methodologies for recognizing dynamical signatures in data, using structural (multicompartmental and network) models, and no small amount of algebra and graph theory for structuring models, discovering what they are capable of revealing about themselves – from data – and designing experiments for quantifying them from data.

Approaches to biomodel formulation by various practitioners – interdisciplinary scientists with basic training in a diversity of fields – have many common features, for example, as found in references like (Rashevsky 1938/1948; Jacquez 1972; Carson et al. 1983; Murray 1993; Edelstein 2005; Palsson 2006; Alon 2007; Klipp et al. 2009; Voit 2012). I've made every effort to maintain the best of these developing features as they morph into our communities' best traditions – toward developing a culture of its own. Following the practice of most expositions of modeling biological systems, the biology, biochemistry and biophysics needed to comprehend context, goals and biomodeling domain details are included within the chapters. Some of this supporting and complementary material is in the text proper, some is in footnotes – as much as needed and space considerations allow. Abundant citations to supplementary and advanced topics are included throughout.[1]

The chapters include exercises for students and solutions will be available for teachers on the book website. Ancillary material, including computer code and program files for many examples and exercises (*Matlab, Simulink, VisSim, SimBiology, Copasi, SBML, Amigo* model code, etc) also are included on the book website.

1 All citations in the text are formatted by name and year, instead of potentially distracting numbers, to facilitate reading without wondering about the origins of textual statements.

In Other Words... & Other Didactic Devices

The substance and style of my teaching and writing developed from my experience in the classroom – typically populated by students from mixed subject backgrounds. Indubitably,[2] interdisciplinary material typically needs *more* explanation, of one disciplinary sort or another. So, with major emphasis on being tutorial, exposition and development of biomodeling methods and applications in this text range from simple introductory material – understandable by any science student with high school math, some physics or chemistry, and maybe some biology – to fairly complex, requiring intermediate-level math skills. There may be more information than perhaps desired by one target group (e.g. the mathematicians) or the other, and I apologize for this necessity in advance. But that same target group should appreciate extra verbiage, examples or redundancy, when the extras are about what *they* know little about (e.g. cell biology). (So, maybe I should take back the apology?) In any case, such 'distractions' have been minimized, or isolated for purposes of ignoring them as desired – as I explain below.

For mathematical exposition (all *applied* math), I've aimed for a relatively low level of formality, or rigor, without sacrificing accuracy, and I provide very few proofs – only when it is instructive of the modeling point at hand. Most math beyond the basics is developed as needed in the chapters, with some developed more completely in appendices, detailed in item 3 below. The reference citations and bibliography provide additional theory. On the other hand, my expository style is methodical, with the purpose of providing foundations for comprehension and for developing these modeling methodologies further. I've used several devices in organizing the chapters and their content to simplify use of this book in different settings, and for students or readers having different backgrounds. These include:

1. Every chapter has a detailed table of contents of its own, an overview or introductory section describing its purpose and content, and a final section summarizing the main points of the chapter and providing readers with some guidance on the content of subsequent chapters relative to that in the present one.

2. This book has a "logo family" associated with it, depicted in its primary (parent) form at the beginning of this *Preface* and on the back cover. It depicts the rather circular nature of the overall process and steps in biomodeling, and their intimate connections with theory and data – a fundamental theme of the book – all as explained in Chapter 1. The logo is repeated in slightly different forms (the children) as the chapters progress, each one depicting the focus of that chapter.

3. Several more traditional math or engineering topics pertinent to modeling dynamic biological systems are developed further or presented concisely in separate *appendices*. These topics have been studied elsewhere by many, and therefore might distract from the main exposition. Alternatively, these topics may be new or not so well-known – and are thus included for gaining depth of understanding, for completeness, or as a refresher or for separate study. They include pertinent extracts of subjects like Laplace transform and transfer function methods

2 The famous comedic actor Jimmy Durante often used this word in his films and TV appearances – instead of the less efficient "without a doubt." It always made me smile, so I'm sharing this with you here.

(***Appendix A***); linear algebra and matrices basics (***Appendix B***); some advanced systems and control theory – like model *equivalence* and model *reduction*; statistical methods and algorithms, and other topics useful for some biomodeling developments (***Appendices C – F***).

4. To highlight additional explanatory remarks following more difficult concepts, mathematical developments, or less well-known biology, I've included numerous *Footnotes, Remarks, Caveats* and also some special remarks called *In Other Words*... Hopefully, these will suffice to clarify denser or more complex material.

5. Numerous examples are included – from simple to moderately complex – many being published and unpublished biomodels developed from real biodata and used in real applications. These serve to put a practical face on the whole process. Some "simple" examples are carried forward to subsequent chapters, where they are used to build on and illustrate the additional methodologies and concepts therein.

6. ***Notation***: I use *italics* to highlight (and emphasize) words or phrases; **boldface** to designate definitions and their synonyms or variants; and ***boldface italic*** for strongest emphasis or for special headers. For the math, I've tried to stay as close as possible to the conventional and accepted terminology and symbology of applied math, for example in defining matrices and vectors as typically done in linear algebra – because it's standardized and imminently logical. This is invariably a little more difficult for specific modeling topics, e.g. compartmental modeling, because areas developed within different fields typically have their own pet jargon. But I've chosen the terminology I believe is most acceptable and consistent with applied math symbology.

7. Modeling is done in a variety of ways in the sciences, at the most obvious level with different nomenclature, jargon and the like. Pharmacology, physiology, molecular biology, biochemistry, physics and engineering all have their modicum of modeling distinctions and distinguishing features. These include some ambiguities and disagreements on nomenclature, definitions and other more or less important details. As a central theme throughout this book, I make every attempt to bridge these cultural differences, with additional explanations and information.

8. "Systems biology" software tools based in new biochemistry and cell biology languages are becoming widely available via the Internet, with user groups to support and further develop them. I illustrate the utility of some representative ones in modeling examples and do my best to clarify and bridge differences between older and newer nomenclature employed in these programs.

9. Not all published quantitative modeling methodologies applied to biological systems are included in this book. Instead, the focus is on primary ones I've found most useful in my research and teaching, those I believe are likely to persist as major sustainable approaches over the longer term. This should not be interpreted as any sort of judgement on the importance of any not included. Both space and, in some cases, mathematical complexity, have been the main motivators for limiting coverage. There are many other fine textbooks out there that cover what I've left out.

How to Use this Book in the Classroom

The ordering of the material covered here is my best compromise toward systematically organizing the material in increasing complexity, for both teaching purposes and maximum comprehension. In part, it accounts for what I believe most university students in the sciences and engineering learn first, second and so on about the basic science and math that underlies modeling concepts. But it's only one way of presenting the subject matter. I've designed (and redesigned) the chapters with this in mind, so it can be used in multiple settings.

As such, the book can be taught in its entirety in a year of coursework – two semesters in most universities, or 3 quarters in those, like UCLA, on the quarter system. The chapters are laid out so this could be done sequentially. Ideally, in a year-long 2-semester sequence, chapters 1–9 are doable in the first semester and 10–17 in the second. In a 3-quarter modeling sequence of courses, chapters 1–5 can be covered more deeply in the first quarter, 6–11 in the second, and 12–17 in the third.

The even-numbered chapters (2, 4, 6, . . .) include the basics of the different modeling topics covered throughout the book. With the exception of Chapter 3, on simulation methodology, the odd-numbered chapters provide extensions of the material in the even-numbered chapter that precedes it. Some teachers (or individual readers) might thus consider using the even-numbered chapters as the basis for initial course development of their own.

For a single course (or for a summer program), much of Chapters 1–9 can be covered selectively – with choices dependent on the student audience and their backgrounds; and it should include basic material on quantifying models, selected from Chapters 10–12. Advanced material – usually designated as such – with asterisks – can be skipped over in short courses.

Acknowledgements

So many former and current students, colleagues, friends and family have helped me with the book and deserve my heartfelt appreciation. They have assisted with producing it, critiquing it, contributing to it, motivating it, or have supported it in other important ways. Thank you: Celine Sin, Marisa Eisenberg, Robyn Javier, Thuvan Nguyen, Pamela Douglas, Greg Ferl, Sharon Hori, Nik Brown, Long Nguyen, Olivera Stajic, Rotem ben Shacher, Natalia Tchemodanov, Christine Kuo, Bill Greenwald, Patrick Mak, Gene Yates, Tom Chou, Van Savage, Elliot Landaw, Alan Garfinkle, Malcolm Rowland, Matteo Pellegrini, Marc Suchard, teD Iwasaki, Chris Anderson, Walter Karplus, Keith Godfrey, Nikki Meshkat, John Novembre, Mary Sehl, Fiona Chandra, Pep Charusanti, Eva Balsa-Canto, Alex Hoffmann, Paul Lee and Todd Millstein.

My daughter Allegra DiStefano contributed the beautiful original graphics. My wife Beth Rubin provided key criticism along the way – as well as infinite patience and loving support. My immediate progenitors, Joe and Angie, provided me *every* opportunity to learn. They put

the pen in my hand early on and gently and firmly encouraged me to use it creatively and constructively.

I also thank the people of the State of California for supporting the great University of California educational system. For nearly half a century, it has granted me virtually complete academic freedom and support for my intellectual pursuits. It has promoted my interests in biomedical research and in teaching and honing great minds. Teaching and learning from students continues to be an honor for me – the reason I remain employed full-time at UCLA. I wrote this textbook for my students, past, present and future; and I dedicate it to them.

Los Angeles, California, July 4, 2013

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Contents