CHEMICAL BIOPHYSICS

Quantitative Analysis of Cellular Systems

Simulation and analysis of biochemical systems is at the heart of computational and systems biology. This textbook covers mathematical and computational approaches to biochemical systems based on rigorous physical principles. Written with an interdisciplinary audience in mind, this book shows the natural connection between established disciplines of chemistry and physics and the emerging field of systems biology, enabling the reader to take an informed approach to quantitative biochemical systems analysis.

Organized into three parts, introducing the student to basic biophysical concepts before applying the theory to computational modeling and analysis through to advanced topics and current research, this book is a self-contained treatment of the subject.

- Background material – this part introduces kinetics and thermodynamics of biochemical networks, providing a strong foundation for understanding biological systems and applications to well-conceived biochemical models.
- Analysis and modeling of biochemical systems – topics covered include enzyme-mediated reactions, metabolic networks, signaling systems, biological transport processes, and electrophysiological systems.
- Special topics – explores spatially distributed systems, constraint-based analysis for large-scale networks, protein–protein interaction, and stochastic phenomena in biochemical networks.

Featuring end-of-chapter exercises, with problems ranging in scope from straightforward calculations to small computational simulation projects, this book will be suitable for advanced undergraduate or graduate level courses in systems biology, computational bioengineering, and molecular biophysics.

DANIEL A. BEARD is Associate Professor in the Department of Physiology and the Biotechnology and Bioengineering Center, Medical College of Wisconsin.

HONG QIAN is Professor of Applied Mathematics and Bioengineering at the University of Washington.

There is a growing number of physicists, engineers, mathematicians, and chemists who are interested in joining the post-genomics party and addressing cutting-edge problems in molecular and cell biology. The barrier to entry can be high and prohibitive. This marvelous new book opens the door for the quantitively inclined. Beard and Qian, in an accessible and clear style, present fundamental methods that can be used to model and analyze an array of biomolecular systems and processes, ranging from enzyme kinetics to gene regulatory networks to cellular transport. This book will appeal to autodidacts as well as professors looking for course texts.

J. J. Collins, Professor of Biomedical Engineering and MacArthur Fellow, Boston University

This is one of the most useful and readable accounts of biochemical thermodynamics that I have seen for a long time, if indeed ever. It is very definitely a book that I shall want to have on my shelves and to refer others to, because it contains a considerable amount of information not easy to find elsewhere.

Athel Cornish-Bowden, Directeur de Récherche, CNRS, Marseilles

Dan Beard and Hong Qian's *Chemical Biophysics: Quantitative Analysis of Cellular Systems* is a masterful portrayal of a critically important new area of science. The success of genomics now makes it imperative to understand the relationships between proteomics, biochemical systems behavior, and the physiology of the intact animal or human. This book provides the path. Its clarity of description, making the complexities seem simple by adhering to fundamental principles, avoiding cluttering detail while painting the broad picture to great depth, makes it a pleasure to read and a treasure to study. It's a must for scientists and scholars working to understand integrative biology.

James B. Bassingthwaighte, Professor of Bioengineering, Biomathematics and Radiology at the University of Washington, Seattle

This wonderful book will be indispensable to specialists in the fields of systems biology, biochemical kinetics, cell signaling, genetic circuits and quantitative aspects of biology, and also to undergraduate and graduate students. It presents a systematic approach to analyzing biochemical systems. The complex subjects are described in a clear style, with carefully crafted definitions and derivations. This unique book is an important step in the development and dissemination of systems biology approaches.

Aleksander S. Popel, Professor of Biomedical Engineering, Johns Hopkins University

As computational biology moves into a more integrative and multi-scale phase, to provide the quantitative framework for linking the mass of experimental data generated by molecular techniques at the subcellular level to tissue- and organ-scale physiology, it is vitally important that models are based on quantitative approaches that incorporate, wherever possible, thermodynamically constrained biophysical mechanisms. This new book *Chemical Biophysics: Quantitative Analysis of Cellular Systems* by Dan Beard and Hong Qian does a wonderful job of formulating models for metabolic pathways, gene regulatory networks, and protein interaction networks on the well-established principles of physical chemistry. Topics include enzyme-catalyzed reactions, reaction–diffusion modeling, membrane transport, the chemical master equation, and much more. This book will be of lasting value to computational biologists and bioengineers.

Professor Peter J. Hunter, Auckland Bioengineering Institute at the University of Auckland

Metabolic modeling often contains simplified assumptions to achieve convergence of equations and these sometimes violate principles of solution physical chemistry. Readers of this remarkable monograph will no longer find those approaches satisfactory because Beard and Qian elucidate the principles of kinetics and thermodynamics of electrolyte solutions relevant to metabolic modeling and computational biology. They show how these principles are essential for molecular modeling of cellular processes most of which involve ionized molecules and macromolecules in the cytoplasm. Their exposition is rigorous. The chapters have an enormous scope and depth that present clear derivations, explanations, and examples. Beard and Qian set the bar very high for future metabolic modeling yet show how the details involved can be managed well and correctly. Analyses at this level of detail are necessary before more complex concepts of molecular crowding and intracellular compartmentalization can be considered. I expect this monograph will become a landmark in computational and systems biology and will be read thoroughly by all scholars in these fields.

Martin J. Kushmerick, Professor of Radiology, Bioengineering, Physiology and Biophysics at the University of Washington, Seattle

Chemical Biophysics: Quantitative Analysis of Cellular Systems by Daniel Beard and Hong Qian fills a significant niche. The text is a concise yet clear exposition of the fundamentals of chemical thermodynamics and kinetics, aimed specifically at practitioners of the new science of systems biology. It is marvelously illustrated with biochemical examples that will aid those who aim to analyze and model the workings of biological cells.

David Eisenberg, Director UCLA-DOE Institute for Genomics & Proteomics, University of California, Los Angeles, Investigator, Howard Hughes Medical Institute

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Cambridge Texts in Biomedical Engineering provides a forum for high-quality accessible textbooks targeted at undergraduate and graduate courses in biomedical engineering. It will cover a broad range of biomedical engineering topics from introductory texts to advanced topics including, but not limited to, biomechanics, physiology, biomedical instrumentation, imaging, signals and systems, cell engineering, and bioinformatics. The series will blend theory and practice, aimed primarily at biomedical engineering students but will be suitable for broader courses in engineering, the life sciences, and medicine.

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To our wives
Katie and Madeleine

and children
Henry and Isabelle

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Preface

The life sciences have strong traditions as quantitative disciplines. In several fields quantitatively minded research was at a zenith in the 1960s and 1970s. Flick through, for example, chapters of the American Physiological Society's *Handbook of Physiology* that were published in this era (and even into the 1980s) and one will see physiology revealed as an engineering science, applying the tools of chemical, mechanical, and electrical engineering to measure, analyze, and simulate biological systems. A great deal of biochemical research in the 1960s and 1970s was focused on the kinetics, thermodynamics, and generally physical chemistry of biochemical systems. From this work emerged an interdisciplinary field sometimes called *biophysical chemistry*, which encompasses a collection of physical and mathematical methods for analyzing molecular structure and dynamics.

This great era of quantitative physiology and biochemistry was temporarily sidetracked by revolutions in molecular biology and molecular genetics, which, at risk of oversimplification, are focused on the question of what is there (inside a cell) rather than how it works. In the 1980s and 1990s much of the physically oriented quantitative research in biology was similarly focused on isolated molecules. In the 1990s the term *molecular biophysics* arose as a popular name of new departments combining experimental techniques with theory and simulation, emphasizing physicochemical approaches to studying biological macromolecules.

Nowadays, with several genomes sequenced and large amounts of data available on what molecules are present in what quantities and inside what sorts of cells, attention is shifted to the question of how it all works. The new focus is sometimes called *systems biology*. Whatever we call it, although a number of recent publications would have the reader believe that *systems biology* is an entirely new endeavor, the basic idea of pursuing quantitative mechanistic-based understanding of how biological systems function is a shift back to the philosophy of a previous era.

Of course we should not imply that progress in biological systems analysis ever ceased or that the current trend calls for a wholesale abandonment of reductionist approaches in favor of integrative systems analysis. Yet it is obvious to even the casual browser of the headlines of the science magazines that, in some form or another, systems analysis in biology is in the spotlight for now and at least the foreseeable future. At the heart of a systems approach to biology is a recognition of the importance of dynamic behavior (and function) of a system (a cell, an organ, or an organism) emerging from the interaction of its components. Moreover, computational modeling and simulation is centrally important to analysis of such systems.

While it is in the context of this newfound attention on quantitative and computational biology that we hope this book is useful, some readers may find some of the content old fashioned. A student planning a career in systems biology may wonder whether our emphasis on the physical chemical basis of natural phenomena looks backward or forward. This text represents an attempt to do both in synthesizing a basic foundation in *chemical biophysics* for analysis and simulation of cellular systems. The title of the book, yet another permutation of phys-, chem-, bio-, and related syllables, arises from this desire to continue the rigorous tradition while at the same time define something new.

We are fortunate to have been mentored by a number of leading scientists, including James Bassingthwaigthe, Elliot Elson, Carl Frieden, John Hopfield, James Murray, John Schellman, and Tamar Schlick. In particular we have both benefited a great deal from our long-time association with Jim Bassingthwaigthe. His advice and inspiration is at the root of much of what we have endeavored to do, including writing this book. In addition, we owe a particular debt to Athel Cornish-Bowden who gave us advice, both specific and general, and encouragement on the text. His book on enzyme kinetics sets the standard for clarity that we can only strive for. These two books, perhaps together with one that emphasizes molecular biophysics, could provide appropriate material for a year-long sequence on biophysical chemistry, from macromolecules to biochemical systems. On its own, this book has been used for a semester-long course on computational biology.

Many others provided feedback on the text, discovered typos and errors, and suggested improvements. We are grateful particularly to Xuewen Chen, Ranjan Dash, Ed Lightfoot, Clark Miller, Luis Moux-Dominguez, Feng Qi, Rebecca Vanderpool, Kalyan Vinnakota, Fan Wu, and Feng Yang.