

Book Review

Computational Modeling of Genetic and Biochemical Networks

Edited by James M. Bower and
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'Computational Modeling of Genetic and Biochemical Networks' arose from a graduate course taught by the editors in the California Institute of Technology in 1998. The aim of the book is to provide instruction in the application of modelling techniques in molecular and cell biology to graduate students and postdoctoral researchers. It is also intended as a primer in the subject for both theoretical and experimental biologists.

The preface discusses the interplay between experiments, theory and modelling by addressing two important questions: Why is modelling necessary and what type of modelling is appropriate? It also explains the structure and organization of the book, as well as how it should be used. The book is divided into two parts: Modeling Genetic Networks (Chapters 1–5) and Modeling Biochemical Networks (Chapters 6–10). The book concludes with a chapter on multiscale modelling (Chapter 11).

The first part of the book deals with models of gene regulation. Chapter 1, 'Modeling the Activity of Single Genes' by Michael Gibson and Eric Mjolsness, is an introduction to modelling gene regulation. It is perhaps one of the best tutorials I have seen in the different modelling techniques for gene activation and inhibition. In Chapter 2 'A Probabilistic Model of Prokaryotic Gene and its Regulation', Michael Gibson and Jehoshua Bruck focus exclusively on the stochastic modelling of gene regulation. It was a wise decision to dedicate a chapter to the stochastic modelling of gene regulation. At the molecular level, random fluctuations and

stochastic modelling are inevitable due to the small number of molecules in a cell [1]. These intrinsic noise effects have been measured in gene expression using fluorescent probes [2, 3]. Chapter 3, 'A Logical Model of *cis*-Regulatory Control in Eukaryotic Systems' by Chiou-Hwa Yuh and others, builds up on the theoretical framework introduced in Chapter 1 and presents a detailed characterization of a developmental biology gene network with a large number of regulatory factors. Chapters 1–3 deal with individual gene regulations. Eric Mjolsness introduces and reviews computational techniques, such as neural network approaches, to study gene networks in Chapter 4 'Trainable Gene Regulation Networks with Application to *Drosophila* Pattern Formation'. Special emphasis is made in the activity patterns during the fruit-fly development. High-throughput experimental assays play a major role in the current shift from reductionist to systems biology approaches. The data sets generated by these experiments promise to identify the components and interactions of biochemical networks. We increasingly require computational approaches suited to the analysis of these data sets, in particular techniques which require little prior knowledge of the interactions involved [4]. In Chapter 5, 'Genetic Network Inference in Computational Models and Applications to Large-Scale Gene Expression Data', Roland Somogyi and others review a number of potentially useful techniques for uncovering the structure of gene networks and also present several studies that used these methods.

The second part of the book deals with the modelling of biochemical networks. The editors have considered these networks as the interactions among the proteins produced by genetic regulation. It starts with Chapter 6 'Atomic-Level Simulation and Modeling of Biomacromolecules' by Nagarajan Vaidehi and William Goddard. This chapter deals with the molecular dynamics techniques that help us to predict the structure of molecules and understand the interactions between them. It also presents a few examples of drug design and discovery. Although, the molecular dynamics techniques are the closest to

reality, they are very computationally expensive [5] and frequently require parameters which are not easy to acquire from experiments. For this reason, the chapter also provides a justification for the phenomenological modelling approaches typically employed in chemical kinetics, which are used in the rest of the book. Chapter 7 'Diffusion' by Guy Bormann and others shows how diffusion often has a crucial impact on modelling. The reader should not underestimate the importance of this chapter. Historically, researchers working in the modelling of biochemical networks have disregarded diffusion. However, it is now well-known that diffusion processes have a profound effect on the reactions by affecting their local rates. Unfortunately, this chapter does not make reference to the classic book by James Murray 'Mathematical Biology' [6, 7] and Keener & Sneyd's 'Mathematical Physiology' [8]. These two references have excellent textbooks with standard applications of diffusion process to biology and physiology. A similar omission occurs in Chapter 8 'Kinetic Models of Excitable Membranes and Synaptic Interactions'. Alain Destexhe looks at the transport of molecules across the cell membranes, focusing on the mechanisms of ion transport channels, and their stochastic modelling. This chapter does not refer readers to the 'Mathematical Physiology' book [8], which is a standard text in physiological modelling and deals quite well with the transport of molecules across the membranes. Despite leaving out such a reference, this chapter briefly discusses the importance of the integration of ion channels modelling with intracellular biochemical processes. I am very pleased that the author has pointed out this. It is a subject of great importance in biochemistry, physiology and developmental biology, where biochemical pathways are closely linked to the electrophysiology of the ion channels. Type 2 diabetes mellitus is an exciting problem in which this multiscale linking occurs [9]. In Chapters 2 and 8, stochastic modelling techniques were introduced for modelling gene regulation and the mechanisms of ion channels. Carl Firth and Dennis Bray in Chapter 9, 'Stochastic Simulation of Cell Signaling Pathways', revisit stochastic modelling techniques in a different context: to simulate bacterial chemotaxis pathways. The intracellular medium has a high macromolecular content. When the concentration of obstacles becomes large, molecules get easily isolated into compartmentalized regions; under such conditions, the number of reacting molecules is presumably much smaller than

that in free solution and hence stochastic effects are important [3]. Dennis Bray is one of the world leaders in chemotaxis, and is one of the first researchers to recognize the importance of modelling stochastically reactions occurring in the intracellular environment. Chapter 10 entitled 'Analysis of Complex Dynamics in Cell Cycle Regulation' uses numerical simulations and dynamical system techniques to study the complex dynamics regulating the cell cycle. Among the authors of this chapter, we find John Tyson and Bela Novak. Both have made fundamental contributions to the understanding of the cell cycle dynamics through modelling. The final chapter 'Simplifying and Reducing Complex Models' by Bard Ermentrout (Chapter 11) deals with a scaling technique, known as averaging, to reduce complex models. The complexity of biological models does not permit us to carry out a proper analysis to understand the parameter controlling the system under consideration. Scaling is one of the strategies available to mathematicians to reduce the complexity of biological models, and has been effectively applied in numerous instances by the author, and many other people working in mathematical biology. Lee Segel, who has recently passed away, is a pioneer in this area. One of the most important messages of Segel's work is that in the use of scaling techniques it is difficult to identify the scales; thus the reduced systems may not be a valid approximation of the phenomenon studied [10–12]. I would like to have seen some of Segel's contribution to scaling mentioned in the discussion and caveats section of the last chapter.

The structure of each chapter is homogeneous in the book. Each chapter begins with an overview of the biological phenomenon under consideration. Attention is paid to the modelling approaches, but some of the chapters do not give full details on computational and mathematical modelling techniques. While exercises are not given, chapters are extremely useful to advance students and scientists who are interested in initiating research in the area: they are very well-written from a pedagogical point of view with extensive references and examples carefully cited. In addition, there are many internal cross-references and comparisons. References are provided at the end of the each chapter and the book includes an extensive index.

The book has been well-received in the community. I have seen open copies of the book in the offices of several of my colleagues. This is the

first text introducing such a diversity of modelling approaches of genetic and biochemical networks. However, it is not the first book published in the topic. Reinhart Heinrich and Stefan Schuster published [13] perhaps one of the finest introductions to the deterministic mathematical modelling of biochemical networks. Eberhard Voit [14] gives an excellent introduction to the mathematical and computational modelling of genetic and biochemical networks using S-systems. Michael Savageau [15] wrote the first textbook available in the literature on the topic. These authors are pioneers in the modelling of genetic and biochemical network. I could only find a citation to one of Michael A Savageau's papers in Chapter 1. Reinhart Heinrich's and Eberhard Voit's work is not cited in the book, and it is unfortunate that readers are not encouraged to consult their books. These are references helpful for students and researchers interest in learning more about some of the techniques presented in the book.

The book can also be used as a reference in which it is only necessary to read the editors' introduction to understand the structure of the book, the reader can then study the subject of his interest in its corresponding chapter. I have used it in this manner with very successful results: I have published a number of papers using techniques which I initially learned from this book. The latter point clearly illustrates one of the values of this book: it is worth its weight in gold!

Despite my criticisms, the book is to this date the best starting point for students as well as researchers who wish to learn how to build models using mathematical and computational techniques to study genetic and biochemical networks. Also, it is very useful to become familiar with the modern modelling approaches in genetic and biochemical networks. The editors have done an extraordinary and remarkable work summarizing a broad field in one volume. This book fills a very special niche and deserves a place on the bookshelf of anyone interested in modelling genetic and biochemical pathways.

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References

1. Turner TE, Schnell S, Burrage K. Stochastic approaches for modelling *in vivo* reactions. *Computational Biology and Chemistry* 2004;**28**:165–78.
2. Elowitz MB, Levine AJ, Siggia ED, Swain PS. Stochastic gene expression in a single cell. *Science* 2002;**297**:1183.
3. Blake WJ, Kaern M, Cantor CR, *et al.* Noise in eukaryotic gene expression. *Nature* 2003;**422**:633–7.
4. Crampin EJ, Schnell S, McSharry PE. Mathematical and computational techniques to deduce complex biochemical reaction mechanisms. *Progress in Biophysics and Molecular Biology* 2004;**86**:77–112.
5. Rottler J, Magg A. Local molecular dynamics with coulombic interactions. *Physical Review Letters* 2004;**93**:170201.
6. Murray JD. *Mathematical Biology. I. An Introduction* 3rd edn. New York: Springer, 2002.
7. Murray JD. *Mathematical Biology. II. Spatial Models and Biomedical Applications* 3rd edn. New York: Springer, 2003.
8. Keener J, Sneyd J. *Mathematical Physiology*. New York: Springer, 1998.
9. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. *Nature* 2004;**414**:799–806.
10. Segel LA. Simplification and scaling. *SIAM Review* 1972;**14**:547–71.
11. Li CC, Segel LA. Mathematics applied to deterministic problems in the natural sciences, *Classics in Applied Mathematics*. Philadelphia: SIAM, 1988.
12. Segel LA, Slemrod M. The quasi-steady-state assumptions: A case study in perturbation. *SIAM Review* 1989;**31**:446–77.
13. Heinrich R, Schuster S. *The Regulation of Cellular Systems*. New York: Chapman and Hall, 1996.
14. Voit EO. *A practical guide for biochemists and molecular biologists. Computational analysis of biochemical systems*. Cambridge: Cambridge University Press: UK, 2000.
15. Savageau MA. *Biochemical systems analysis. A study of function and design in Molecular Biology*. Reading, MA: Addison-Wesley, 1976.