Preface

Cells sense their environment largely through the activities of signal transduction networks which regulate diverse aspects of cellular behavior. Signaling outputs are dynamic, extraordinarily complex, and yet highly specific. A comprehensive understanding of how signaling networks behave in space and time to generate specific biological responses is paramount to biology and medicine. Aberrations in signaling networks are associated with many human diseases such as cancer and diabetes. Better understanding of signaling mechanisms can potentially have a major impact on drug design and therapeutics.

Signaling networks are composed of numerous signaling pathways and each has its own intricate component parts. In the past three decades, the molecular biology approach has dominated the field of signal transduction research. Reductionism—with an emphasis on identifying and characterizing the components of each pathway—is the prevailing philosophy underlying much signaling research. The success of this approach has enabled biologists to enumerate a "parts list" for many signaling pathways. Robust molecular techniques and easy-to-standardize protocols researchers can follow have enabled the application of molecular biology techniques to signaling. Automation of these techniques has led to sequencing of the entire genome of many organisms including humans. There has been an explosion of information gathered through genome-wide technologies, such as measurements of gene expression through DNA microarray technology, assays of genome-wide protein–protein interaction maps, and proteomic measurements of posttranslational modifications. As the description of molecular components of signaling systems gets more detailed, it becomes more and more evident that the behaviors of signaling networks amount to more than the sum of their parts.

The ultimate goal of studying signaling networks is to predict cellular responses to external stimuli based on molecular mechanisms. Accurate predictions require quantitative understanding of the interactions of the signaling components. Mathematical and computational modeling techniques are emerging as powerful tools in cellular signaling research. There are several reasons behind the rapid rise in popularity of modeling in biological research. Firstly, the extraordinary complexity of signaling networks calls for the representation of intricate relationships in mathematical terms. Modeling helps to recognize patterns and recurring themes in signaling networks. Secondly, the modeling process requires critical evaluation of different types of biological data to get an integrated view of the system. Thus, modeling promotes critical thinking about the systems in question. Thirdly, once a model is built, it represents a sophisticated hypothesis that can be tested by running simulations and comparing the outputs to experimental data. The relative ease of running simulations can save time (relative to experiments). Finally, modeling can identify possible ways by which molecular mechanisms give rise to higher-order behavior and predict system behavior under conditions that have yet to be experimentally tested.

Despite these obvious advantages of modeling, significant challenges exist in order for experimentalists to adapt modeling into their daily research. Unlike molecular biology, where standard protocols for experimental design and manipulation are readily available from manuals like *Molecular Cloning* or *Current Protocols*, standard protocols that many experimentalists are accustomed to for mathematical and computational modeling are difficult to find. Perhaps this partly reflects the fact that modeling of signaling networks

is still very much in its infancy. This book is written with the intention of helping the experimentalists to ease through this transition, while also enabling mathematical and physical scientists to learn how modeling is currently being applied to research in signaling. By no means will the current book be as comprehensive as manuals like *Molecular Cloning*, but we do hope that this book will serve as a catalyst for achieving this goal.

Chapters 1 and 2 by Iber, Fengos, and coauthors address two related topics in model formulation and analysis. Chapter 1 outlines the basic process that is the bread and butter of many computational systems biologists: it focuses on systems of ODEs and walks through the formulation and analysis of a model. Systems of ODEs are an appropriate model for situations where spatial variation is not important and the numbers of molecules is relatively large. A specific example of a simplified TGF-beta signaling model is used to illustrate the methods. This chapter introduces many useful concepts: in model formulation, they discuss the mathematical representation of some common biochemical reactions, including synthesis, degradation, shuttling, binding, and enzymatic activity (with or without inhibition). In the analysis section, Iber and Fengos discuss a number of useful tools in the analysis of dynamical systems, including nondimensionalization, phase-plane analysis, linear stability analysis, bifurcation diagrams, and sensitivity analysis. Familiarity with these tools of the trade is essential for anyone who wants to work (or understand the research) in this area. Chapter 2 by Geier et al. builds on Chap. 1 to discuss the parameterization of signaling models. This is an important issue that addresses questions ranging from the practical (how does one actually determine parameter values to use in day-to-day work in computational biology?) to the fundamental (how well can one constrain parameter values given limited data? How do uncertainties in the parameters affect conclusions one can draw from the model?).

Zi contributed the modeling tutorial in Chap. 3. This chapter is recommended for those new to the field who want an entry-level description of how to approach modeling of signaling pathways. Zi explains the differences between top-down approaches (using high-throughput data) and bottom-up approaches (using modeling). With a focus on ODE modeling of signaling pathways, the tutorial explains the commonly used types of kinetics (the law of mass action, the Hill equation, Michaelis–Menten kinetics) and explains how to go from a reaction to writing down an ODE. For the development of more complex models, Zi includes discussion of signal transduction steps including production/degradation of mRNA and protein, phosphorylation, and dephosphorylation, feedback, and signaling inputs. The chapter wraps up with a discussion of initial conditions and parameter estimation by least squares, and includes a workflow that goes through all the steps required in development and analysis of a model.

Chapter 4, Anderson, Liu and Ferrell discuss several important concepts critical for understanding and characterizing dynamical systems, including steady state, stability, reversibility, ultrasensitivity, bistability, bifurcations, and hysteresis. Using an example of a well-studied signaling pathway, they illustrate the use of purely graphical methods to determine the plausibility of two network behaviors, bistability and irreversibility.

In Chap. 5, Stites and Ravichandran explain the development and analysis of their model of Ras signaling using mass-action kinetics and ODEs. This chapter shows how the basic modeling techniques can be applied to address an important scientific question. The goal is to predict cellular levels of RasGTP, a key oncogenic protein. They use this signaling network as a prototype for a tutorial on the development, validation, and analysis of a mathematical model. The chapter gives a clear explanation of how the model was constructed, addressing the questions they wished to investigate, how they chose how much

of the pathway to include, simplifications made in developing the model, and the parameter values used. They validated the model using predictions for experiments and sensitivity analysis. They conclude with new predictions for experiments and insight into possible mechanisms that affect RasGTP levels.

Chapter 6, by Lai, Wlkenhauer, and Vera, addresses the role of micro RNAs (miRNA) in regulating signaling. This work shows how experiments and modeling can be integrated in a single study, as well as a pedagogical explanation of different types of feedback in signaling networks. The chapter focuses in particular on the signaling module involving p53, Sirt1, and the micro RNA miR-34a, and investigates different silencing mechanisms of miR-34a on Sirt1. It is known that miRNAs can be involved in different types of feedback loop, including simple negative feedback, positive feedback involving an intermediate protein, and negative feedback involving an intermediate protein. Lai et al. develop an ODE model with rate equations based on power law terms, which also includes time delays; they discuss parameter estimation for their model. They explicitly consider 4 different models for repression of Sirt 1, including enhanced degradation of mRNA, reversible deactivation of mRNA, translation inhibition, and transcription inhibition. The model predictions are used to design an experiment that can distinguish the different proposed mechanisms; the comparison to experimental results suggests that translational repression seems the most likely mechanism.

In Chap. 7, authors Bandara and Meyer discuss a novel but increasingly important approach to modeling: how to use modeling to plan experiments. The chapter discusses three specific problems: first, parameter estimation—fitting a model to data to estimate the parameters of the model. Second, they discuss model discrimination—using models to design an experiment to determine which of two models is correct. Here the basic idea is to design an experiment that will make the difference between two model predictions very obvious—this can be done by maximizing a function that describes the difference between the two model predictions. The third problem is experimental design for model parameterization—the design of an experiment that will make the parameter estimation problem easier. Each of these problems is addressed in the context of least-squares fitting (minimizing the sum of squared errors between two variables). Optimization of an objective function based on the model predictions and data is the goal in all cases.

Chapter 8, by Maiwald, Eberhardt, and Blumberg, is a tutorial on using the software system PottersWheel. The focus of this software is ODE models, and PottersWheel is integrated with Matlab as a Matlab toolbox. The authors use the JAK/STAT pathway as a tutorial example and focus their discussion on model discrimination, parameter estimation, and experimental design. They walk through a series of steps in their tutorial, focusing on model creation, data import, fitting the model to the data, assessing goodness of fit, model refinement, analysis and model prediction, and design of new experiments. Some interesting features of PottersWheel may make it particularly attractive to those in the field. For example, models can be entered either with a GUI "model designer" or a text file. The software is designed to easily integrate experimental data; data from text or excel files can be loaded into the model.

In Chap. 9, Sekar and Faeder give a tutorial on rules-based modeling using the BioNetGen (BNG) language. The language is designed to handle combinatorial complexity in ODE-based signaling models, which occurs when the number of possible states and reactions becomes large. In this case, writing out every state and reaction by hand is tedious. Rules-based software packages based on BNG can start with a shorter list of reaction rules and generate the model states and equations automatically. Sekar and Fedar take a

pedagogical approach, which will be useful for readers new to this type of modeling, and focus their discussion on how to deal with common challenges and potential pitfalls in constructing a rules-based model. The discussion of what a rules-based model is, how to represent the model in BNG syntax, and how to write model rules is useful for getting started with this approach and includes numerous examples. The tutorial on receptor–ligand interactions works through every step of the construction and analysis of an example model of the EGF receptor. More advanced topics are addressed in the sections on compartmental modeling and parameterization. Examples of rules written to describe common mechanisms in signaling pathways are included. The chapter concludes with some best practices for good modeling.

In Chap. 10, Prasad uses the example of the kinetics of thymocyte selection—the positive and negative selection of T cells based on the affinity of TCR–pMHC interaction—to illustrate the process of modeling, analysis of a model, and generating predictions for experiments. The author discusses basic reaction types, the steady state assumption and when to make it, basic reaction kinetics, and stochastic modeling. The example of thymocyte selection is a detailed, well-explained example. The chapter discusses how the model was formulated and the choice of simplifying assumptions. The discussion of equilibria of ODEs and bifurcation analysis is illustrated using the thymocyte kinetic model as an example. The discussion of the stoichiometric matrix, combinatorial complexity and rule-based simulation, and parameter sensitivity will be useful guides for others undertaking this analysis.

In Chap. 11, Song and You focus on modeling spatiotemporal dynamics using a synthetic bacterial ecosystem as an example. As the only chapter in this volume to include spatial variation in modeling, this chapter is a useful introduction to this large area. Song and You discuss model development for a PDE model, parameter estimation, and pattern formation. They discuss the use of finite element methods and comsol for numerically solving PDEs. The chapter works through the modeling process in detail using the example of a synthetic ecosystem, consisting of two engineered *E. coli* populations that act as predator and prey and communicate through quorum sensing. For low prey density, the predator cells die, while at high predator densities the preys die. The authors explain how they constructed their PDE model, with transport of a drift-plus-diffusion form with the drift determined by chemotaxis. They explain how to quantify biodiversity in their model and experimental system using the modified Simpson's biodiversity index.

Chapter 12, by Saadatpour and Albert, focuses on discrete (Boolean) modeling, giving a useful overview of this modeling approach with example models of the abscisic acid signal transduction in plants and the T-cell-survival signaling network in humans. The authors first address the advantages of discrete models, which are particularly valuable when qualitative results are acceptable and many model parameters are unknown. The authors walk through the steps in modeling, including (1) reconstructing the network from the literature; (2) identifying Boolean functions, which addresses how to turn the experimental information into logical rules; (3) implementing time, whether to use synchronous or asynchronous updates; (4) analyzing the dynamics of the system; (5) testing the validity and robustness of the dynamic model; and (6) analyzing the effect of node perturbations, by simulating experimental perturbations such as knockout or overexpression.

The Boolean approach to modeling is illustrated with two examples. The abscisic acid signal transduction network in plants is important in changing the size of holes in the outside of leaves, controlling how rapidly water is lost by transpiration. The other example is the T-LGL leukemia survival signaling network, which addresses a type of leukemia of cytotoxic T lymphocytes.

Chapter 13, by Walczak, Mugler, and Wiggins, is a useful complement to simulation-based approaches to modeling signaling networks: in this chapter, Walczak et al. review analytic approaches for stochastic models. Stochastic approaches are important when the numbers of molecules considered are relatively small, so that the inherent randomness of the dynamics is important. (By contrast, a deterministic model considers the average number of molecules only, and neglects fluctuations.) The methods discussed are a lightning tour of the three classic equations of stochastic modeling: the master equation, the Fokker-Planck equation, and the Langevin equation. The authors demonstrate a variety of methods for solving these equations, both analytic and numerical. Walczak et al. beautifully illustrate how understanding analytic approaches can inform numerical simulation, by allowing the construction of efficient simulation schemes. They use specific simple examples of models of production/degradation of a protein to illustrate general analytic methods. The authors start with a very simple model of production and degradation of a single protein, then add twists to describe self-activation or inhibition, transcriptional or translational bursting, and interaction of two genes. This chapter is a useful introduction to more mathematically sophisticated techniques in stochastic modeling and their application to signaling.

We thank the contributors of this book for their time and efforts devoted to share their state-of-the-art procedures and methods employed in their laboratories. We wish to express our deep appreciation for Dr. John Walker who inspired us to take on this project and supported us during its development.

Boulder, CO, USA

Xuedong Liu, Ph.D.
Meredith D. Betterton, Ph.D.



http://www.springer.com/978-1-61779-832-0

Computational Modeling of Signaling Networks
Liu, X.; Betterton, M.D. (Eds.)
2012, XIV, 327 p., Hardcover
ISBN: 978-1-61779-832-0
A product of Humana Press