Control Theory and Systems Biology

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Preface

Issues of regulation and control are central to the study of biological and biochemical systems. The maintenance of cellular behaviors and the appropriate response to environmental signals can only be achieved by systems that are robust to certain perturbations and sensitive to others. Because these behaviors demand the use of feedback, it is natural to expect that the tools of feedback control theory, which were developed to analyze and design self-regulating systems, would be useful in the study of these biological mechanisms. Indeed, the application of control-theoretic tools to biochemical systems is currently an area of burgeoning interest.

The application of control theory to biological systems has a long history, dating back more than 60 years. The mathematician Norbert Wiener, through his pioneering work on cybernetics, saw a set of problems, common to both "the machine" and "living tissue," centered around questions of communication and control (Wiener, 1948). Subsequent work dealt with attempts to understand human physiology. For example, in their influential 1954 paper, Fred Grodins and colleagues discussed the response of the respiratory system to CO_2 inhalation as a feedback regulator, using electrical circuit analogs. Representative references include Bayliss (1966), Grodins (1963), Kalmus (1966), and Milhorn (1966).

The current spate of research activity differs from previous efforts in a number of respects. First, the focus is on cell physiology. Our understanding of the molecular mechanisms by which a cell operates has advanced dramatically over the last quarter century; we now have a solid characterization of the chemical basis for the cell's ability to regulate its behavior. Second, in recent years, biologists have developed experimental techniques that have opened up new opportunities for investigating cellular behavior. Traditional molecular biology techniques are restricted to measurements of only a few variables at a time. Using new "high-throughput" technologies, researchers can now take hundreds or even thousands of measurements simultaneously, allowing them to investigate system-wide behavior. Moreover, many of these techniques provide quantitative measurements of time-series data—crucial to an understanding of dynamics. These developments have enabled the development of accurate mathematical models of cellular mechanisms based on physicochemical laws and falsifiable by experimentation. It is these experimental developments that have ushered in systems biology as a "new" field devoted to systems-inspired analysis of cellular biology (Ideker et al., 2001; Kitano, 2001, 2002).

This type of interdisciplinary work requires knowledge of the results, tools and techniques of another discipline, as well as an understanding of the culture of an unfamiliar research community.

Our primary objective is to present control-theoretic research in an accessible manner. Although readers are presumed to have some familiarity with calculus and differential equations, they need have no specific knowledge of control theory. We present the necessary concepts from dynamical systems and control theory in chapter 1, which introduces ordinary differential equation–based modeling and should allow theoretically inclined life scientists to follow the rest of the volume. Because it covers standard material, readers from the mathematical sciences may wish to skip this introduction.

The next two chapters introduce alternative modeling frameworks. In chapter 2, Mustafa Khammash introduces stochastic modeling, used to address the probabilistic nature of processes. In chapter 3, Pablo Iglesias introduces partial differential equation–based modeling, used to address dynamic processes where spatial localization is significant.

Chapters 3 through 14 sample a wide variety of applications of control theory to molecular systems biology. In chapter 4, Simone Frey, Olaf Wolkenhauer, and Thomas Millat show how measures of dynamic behavior, central to control engineering, can be used to study cell signaling systems. The next chapters discuss modularity, a key concept in control, with Hana El-Samad demonstrating an analysis of the bacterial heat-shock response as a modular controller in chapter 5, and Domitilla Del Vecchio and Eduardo Sontag presenting a treatment of "retroactivity to interconnections," a feature that threatens our ability to apply modular thinking to cell biology, in chapter 6. David Angeli and Eduardo Sontag adopt a modular approach to dynamics in chapter 7 by applying graph-theoretic and stoichiometric ideas to interpret complex biochemical systems as compositions of dynamically simple building blocks. Further exploring network stoichiometry in chapter 8, Brian Ingalls discusses its implications for sensitivity analysis.

That feedback loops can be used to reduce sensitivity is a foundational concept in control engineering. Harold Black invented the negative feedback amplifier in 1927 as a means of decreasing the sensitivity of the telephone network to nonlinearities in the underlying components. In the 1980s, there was renewed interest in techniques for analyzing the sensitivity of systems and for designing systems that are insensitive or *robust* to uncertainties. Robustness, most often framed in the context of *homeostasis* (Cannon, 1932), is also a central concept in biology. Much of the recent interest in the robustness of biological systems by biologists and control engineers alike was spurred by the theoretical (Barkai and Leibler, 1997) and experimental (Alon et al., 1999) work of Stan Leibler and colleagues. Not surprisingly, the use of control-theoretic tools to study robustness and sensitivity is the topic of several chapters in this volume. In chapter 9, Jason Shoemaker, Peter Chang, Eric Kwei, Stephanie Taylor, and Frank Doyle discuss sensitivity analysis and present a number of techniques, some from robust control theory, for addressing robustness of cellular networks. Reporting on a number of biological case studies in chapter 10, Camilla Trané and Elling Jacobsen further expand on the use of robust control techniques. And in chapter 11, Jongrae Kim and Declan Bates take a robust control approach to the robustness of oscillatory behavior, using oscillations in the social amoeba *Dictyostelium* as an illustrative example.

The final three chapters concern themselves with network identification. In chapter 12, David Thorsley and Eric Klavins take up the analysis of stochastic models, demonstrating a powerful technique for model comparison and model calibration. In chapter 13, Jorge Gonçalves and Sean Warnick then discuss network reconstruction—the derivation of a system "wiring diagram" from input-output data. Finally, Dirk Fey, Rolf Findeisen, and Eric Bullinger consider the closely related task of calibrating model parameters from experimental data, presenting a novel observer-based design, in chapter 14.

We hope these chapters, which range from surveys of established material to presentation of current developments will provide readers with a useful overview of recent control-theoretic studies in systems biology, an appreciation of the biological insights such studies can provide, and perhaps even the inspiration to join us in the continuing task of unraveling the complexities of biological regulation and control.

We want to thank those without whose help this project would not have reached fruition. First and foremost, the contributors for their excellent chapters and for dealing with numerous requests for revisions in a timely manner. Second, Bob Prior at the MIT Press for his phenomenal encouragement. Bob has been a supporter of the systems biology community for more than a decade. It was at his urging that we undertook this work. And last, but most important, we thank our families—Elizabeth, Vicente, Miguel, Angie, Logan, Alexa, Sophia, and Ruby—for the patience they have shown. To them, we dedicate this book.