Preface

The field of systems biology encompasses scientists with extremely diverse backgrounds, from biologists, biochemists, clinicians and physiologists to mathematicians, physicists, computer scientists and engineers. Although many of these researchers have recently become interested in control-theoretic ideas such as feedback, stability, noise and disturbance attenuation, and robustness, it is still unfortunately the case that only researchers with an engineering background will usually have received any formal training in control theory. Indeed, our initial motivation to write this book arose from the difficulty we found in recommending an introductory text on feedback control to colleagues who were not from an engineering background, but who needed to understand control engineering methods to analyse complex biological systems.

This difficulty stems from the fact that the traditional audience for control textbooks is made up of electrical, mechanical, process and aerospace engineers who require formal training in control system *design methods* for their respective applications. Systems biologists, on the other hand, are more interested in the fundamental concepts and ideas which may be used to analyse the effects of feedback in evolved biological control systems. Researchers with a biological sciences background may often also lack the expertise in physical systems modelling (Newtonian mechanics, Kirchhoff's electrical circuit laws, etc.) that is typically assumed in the examples used in standard texts on feedback control theory. The type of "control applications" in which a systems biologist is interested are systems such as metabolic and gene-regulatory networks, not aircraft, robots or engines, and the type of mathematical models they are familiar with are typically derived from classical reaction kinetics, not classical mechanics.

Another significant problem for systems biologists is that current undergraduate books on control theory (which introduce the basic concepts at great length) are uniformly restricted to linear systems, while nonlinear systems are usually only considered by specialist postgraduate texts which require advanced mathematical skills. Although it will always be appropriate to introduce basic ideas in control using linear systems, biological systems are in general highly nonlinear, and thus a clear understanding of the effects of nonlinearity is crucial for systems biologists.

To address these issues, we have tried to write a text on feedback control for systems biologists which

- is self-contained, in that it assumes no prior exposure to systems and control theory;
- focuses on the essential ideas and concepts from control theory that have found applicability in the systems biology research literature, including basic linear introductory material but also more advanced nonlinear techniques;
- uses examples from cellular and molecular biology throughout to illustrate key ideas and concepts from control theory;
- is concise enough to be used for self-study or as a recommended text for a single advanced undergraduate or postgraduate module on feedback control in a course on biological science, bioinformatics, systems biology or bioengineering.

During the time we have spent preparing this book we have also been struck by the constantly increasing interest among control engineers in biological systems, and thus a second goal of this text has been to provide an overview of how the many powerful tools and techniques of control theory may be applied to analyse biological networks and systems. Although we do assume that the reader has some familiarity with basic modelling concepts for biological systems, such as mass-action and Michaelis–Menten kinetics, we have provided introductory descriptions of many of the biological systems considered in the book, in the hope of enticing many more control engineering researchers into systems biology.

The book is made up of eight chapters. Chapter 1 provides an introduction to some basic concepts from feedback control, discusses some examples of biological feedback control systems and gives a brief historical overview of previous attempts to apply feedback control theory to analyse biological systems. Chapters 2 and 3 introduce a number of fundamental tools and techniques for the analysis of linear and nonlinear systems, respectively. Fundamental concepts such as state-space models, frequency domain analysis, stability and performance are introduced in the context of linear systems, while Chapter 3 discusses more advanced notions of stability for nonlinear systems, and also provides an overview of numerical optimisation methods for the analysis of complex nonlinear models. Chapter 4 focusses on the role of negative feedback in biological processes, and introduces notions of robustness, integral control and performance tradeoffs. Chapter 5 considers the rich variety of dynamics which arise due to positive feedback, and introduces tools such as bifurcation diagrams, monotone systems theory and chemical reaction network theory, which can be used to analyse bistable and oscillatory systems. Chapter 6 focusses on the issue of robustness, and provides an overview of the available robustness analysis methods, such as sensitivity analysis, μ-analysis, sum-of-squares polynomials and Monte Carlo simulation, which may be used to assist in validating or invalidating models of biological systems. A range of techniques for the reverse-engineering of biological interaction networks is described in Chapter 7. These techniques, which are rooted in the branch of control engineering known as system identification, appear to have huge potential to complement and augment the statistical approaches for network inference which currently dominate research on biological interaction networks. Finally, Chapter 8 provides an introduction to the analysis of stochastic biological control systems, and points out some exciting new research directions for control theory which are directly motivated by the particular dynamic characteristics of biological systems.

A key feature of the book is the use of biological case studies at the end of each chapter, in order to provide detailed examples of how the techniques introduced in the previous sections may be applied to analyse realistic biological systems. Each case study starts with an introductory section which provides a simple explanation of the relevant biological background, so that readers from the physical sciences can quickly understand the key features of the chosen system.

By its very nature, this book cannot pretend to provide an exhaustive treatment of all aspects of control theory. It does, however, represent a first attempt to arrange in a pedagogical manner the methods and applications of control theory that pertain to systems biology. Our aim has been to pinpoint the most important achievements to date, provide a useful reference for current researchers, and present a sound starting point for young scientists entering this exciting new field.

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Carlo Cosentino and Declan Bates
Catanzaro and Exeter