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Analysis, Simulation, and Estimation

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To

Pam, Bryant, and Mason
and in memory of
John H. K. Khoo

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Preface

Control mechanisms provide the basis for the maintenance of homeostasis at all levels of organization in the hierarchy of living systems. As such, one's knowledge of the workings of a given biological system is incomplete unless one can arrive at some understanding of the regulatory processes that contribute to its natural operating characteristics. In order to attain this understanding, a conceptual model of the various interacting processes involved is necessary—but not sufficient. To determine whether one's model reflects the underlying reality, one has to make predictions with the model. However, more often than not, the factors in play are complex and dynamic, and the behavior of the model may depend strongly on the numerical values of certain key parameters. Under such circumstances, the rigorous framework provided by a quantitative approach becomes indispensable. Indeed, some of the most notable advances in the physiological sciences over the past several decades have been made through the application of quantitative models. Physiological control modeling also has been critical, directly or indirectly, for the development of many improved medical diagnostic techniques and new technological therapeutic innovations in recent times.

Because of its importance, the study of physiological control systems is generally incorporated, in one form or another, into the typical undergraduate biomedical engineering curriculum. Some programs offer courses that deal explicitly with physiological control systems, whereas in others, basic control theory may be incorporated into a course on quantitative physiology. Numerous high-quality research volumes on this subject have been published over the years, but there exist only a few books that most instructors would consider suitable for use as a comprehensive text in an upper-level undergraduate or first-year graduate course. Milsum's *Biological Control Systems Analysis* and Milhorn's *The Application of Control Theory to Physiological Systems* are two classic examples of possible texts, but these and the handful of other alternatives were published in the 1960s or early 1970s. The present book is aimed at filling this void. In addition to the classical methods that were covered in previous texts, this book also includes more contemporary topics and methodologies that continue to be employed in bioengineering research today.

The primary goals of this book are to highlight the basic techniques employed in control theory, systems analysis, and model identification, and to give the biomedical engineering student an appreciation of how these principles can be applied to better understand the processes involved in physiological regulation. The assumption made here is that the book would be used in a one-semester course on physiological control systems or physiological systems analysis taken by undergraduates in the junior or senior year. The book and its accompanying programs may also prove to be a useful resource for first-year biomedical engineering graduate students, as well as interested life science or clinical researchers who have had little formal training in systems or control theory. Throughout this book, I have emphasized the physiological applications of control engineering, focusing in particular on the analysis of feedback regulation. In contrast, the basic concepts and methods of control theory are introduced with little attention paid to mathematical derivations or proofs. For this reason, I would recommend the inclusion of a more traditional, engineering-oriented control theory course as a supplement to the material covered in this volume.

The book begins with a presentation of some historical perspectives, a discussion of the differences between technological and physiological control systems, and an introduction to the basic concepts of systems analysis and mathematical modeling. The subsequent five chapters cover classical control theory and its application to physiological systems. These begin in Chapter 2 with a tutorial on linear modeling. Here, we discuss generalized system properties, model analogs, lumped-parameter versus distributed-parameter models, and the utility of employing time-domain and frequency-domain descriptions of linear systems. In Chapter 3, we explore the techniques for steady-state analysis of physiological closed-loop systems. These problems traditionally have relied on graphical solution, as exemplified by the classic cardiac output–venous return analyses of Guyton and coworkers. Here, we also explore a decidedly more "modern" approach—that of employing computer analysis to solve the problems. Chapter 4 covers the transient response analyses of simple linear open-loop and closed-loop systems. We discuss the effect on system dynamics of "closing the loop," as well as changing the type of feedback from proportional to integral or derivative. In Chapter 5, we present the major methods for representing the frequency response of linear models, and also discuss the relationship between time-domain and frequency-domain approaches. Chapter 6 deals with the topic of stability, an issue of critical importance to physiological regulation. We discuss a range of techniques for assessing stability under conditions in which the assumption of linearity can be made. Chapter 7 addresses the problem of system identification, particularly in systems that operate under closed-loop conditions. Previous texts on physiological control have paid little attention to this important topic in spite of the fact that every bioengineering researcher has had to confront this problem at some point or other. In this chapter, we also discuss the related issues of parameter identifiability, sensitivity to noise, and input design. In Chapter 8, we move on to the application of "modern" control theory to physiological systems: these methods are based on the principle of optimization. We end this chapter with a brief exposition of how adaptive control theory may be applied in practice to regulate spontaneous fluctuations in a physiological signal. Chapter 9 presents a survey of some of the more common nonlinear analysis methodologies employed for investigating physiological systems. We recognize that this limited coverage, due to space constraints, does not do justice to the many other important nonlinear techniques and applications that have appeared in the research literature in the past two decades. Nevertheless, we believe we have included sufficient material to give the student a good "feel" of this area of study. Finally, we conclude the book in Chapter 10 with an examination of the potential mechanisms that could give rise to complex dynamic behavior in physiological control systems. These include spontaneous variability arising from structural nonlinearity in the system—the phenomenon of "chaos," interactions between different control systems, and nonstationarity in the system parameters. Throughout the book, I have attempted to include models of a wide range of physiological systems, although I cannot deny that there is somewhat of a bias towards my own favorite area of interest: cardiopulmonary control.

The ubiquity of personal computers among today's college students and the widespread use of MATLAB® and SIMULINK® (The Mathworks, Natick, MA) for systems analysis and simulation in the vast majority of engineering curricula have presented us with the opportunity to add a more "hands-on" flavor to the teaching of physiological control systems. As such, almost all chapters of the book include physiological applications that have accompanying MATLAB/SIMULINK simulation models. These, along with the computer exercises that accompany the end of each chapter, should aid the learning process by allowing the student the opportunity to explore "first-hand" the dynamics underlying the biological mechanisms being studied. This feature of the book is nonexistent in previous texts on physiological control systems. However, in incorporating this feature, we make the implicit assumption that the reader has some basic familiarity with MATLAB and/or SIMULINK. For the reader who has not used MATLAB or SIMULINK, it is fortunate that there are currently many "primers" on the subject that can be easily found in any academic bookstore. Appendix II lists and explains the MATLAB/SIMULINK functions used in the examples presented in this book, along with the names of the files that contain the model simulation/analysis programs discussed in the text. Details of how one can obtain these program files through the Internet are also given in the appendix.

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Acknowledgments

The "birth" of this book took place some two and one-half years ago when Dr. Metin Akay, the editor in chief of this series of monographs, first encouraged me to submit a proposal to the IEEE Press. It has been a long, arduous journey since that moment—indeed, there were times when it felt as if the end would never be in sight. I thank Metin for his faith in me and for his continual support throughout the entire process. I am also thankful to John Griffin and Linda Matarazzo at IEEE Press for their assistance and cordiality. The anonymous reviewers who had to suffer through the drafts of various chapters in this book have my deepest gratitude for pointing out errors and for giving me valuable feedback. The collegial environment provided by my faculty colleagues, the staff, and students of the Biomedical Engineering Department at the University of Southern California (USC) has been an essential ingredient in the development of this book. I would be remiss if I did not mention my eternal indebtedness to the late Professor Fred Grodins, who was always my role model of what a true bioengineer should be like. Much of the intellectual stimulation that has led to the writing of this book is drawn from my own research work in the modeling of neurocardiorespiratory control, an activity sponsored by the National Institutes of Health through the Biomedical Simulations Resource (BMSR) at USC. I thank my colleagues and codirectors of the BMSR, Professors Vasilis Marmarelis and David D'Argenio, for their encouragement and support over the years. Finally, this endeavor certainly would not have been possible if I had not been blessed with the environment of love, joy, and understanding created so generously by those closest to me. My deepest feelings of appreciation go deservedly to my wife, Pam, and my sons, Bryant and Mason. It is to them that I dedicate this book.

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