Preface

Efforts in modeling cardiovascular and respiratory control have been ongoing for a number of years. These efforts include seminal work by A. C. Guyton and coworkers and F. Grodins and coworkers in the 1950's and 1960's. In particular, over the last decade there has been a rapid increase in modeling activities in this area as technology has advanced both for simulation and for data collection. It is now possible to consider a wide range of features from the cellular level to the macroscopic level as well as the complex interaction of control processes and ask harder questions concerning interdependencies between systems. Indeed, as a consequence of these capabilities, the Physiome Project (see Section 5.3) was recently formed to coordinate knowledge about such issues. Often, asking the right question or focusing on a crucial physiological mechanism is more important than utilizing sheer computational power to simulate and capture data behavior.

Control mechanisms provide the basis for maintaining homeostasis at various levels in living systems. Such processes tend to have their own local operational goals and yet physiological systems are interdependent and interact. However such interaction could conceivably diminish overall performance. Nevertheless, these critical control systems seem to be well coordinated and to function complementarily. This raises very interesting evolutionary and organizational questions. The range of control processes involved in the effective regulation of human cardiovascular and respiratory systems includes a number of global and local mechanisms. Modeling efforts are certainly required to elucidate these complex interdependencies. As a consequence of the progress in relevant mathematical disciplines and the availability of increasingly powerful computing tools, models are becoming more realistic which allows for the adaptation to individual persons in the clinical setting and thereby making possible the development of diagnostic and therapeutic tools. This book does not aim to exhaustively examine all research efforts in this field but to selectively develop some important themes and modeling strategies.

The cardiovascular and respiratory control systems represent an important focal point for developing physiological control theory given the complexity of the control mechanisms involved, the important modes of interaction between cardiovascular and respiratory function, as well as their importance in many clinical situations. The modeling of physiological control systems has resulted in numerous research monographs written over the years. In this volume we will bring together contemporary mathematical and control methodologies to study these problems. We will highlight a number of analytical techniques and ideas from optimal control theory, systems theory, and parameter estimation to give the reader an appreciation of how these tools can be utilized to better understand the regulation processes in the cardiovascular and respiratory systems. Modeling efforts are arranged around specific questions or conditions such as exercise or sleep transition and generally are based on physiological mechanisms rather than on formal description of input-output behavior. We make an effort to emphasize open questions relevant to medical and clinical applications. More specifically, the context for questions will be on elucidating underlying themes of physiological control organization such as optimization of some process, minimization of quantities such as energy, and possible critical state values which seem to drive the control design such as maintaining pH levels in a narrow band. Another goal is to highlight important questions to be resolved and areas where knowledge is lacking. Throughout the book, we seek to uncover or explain physiological relationships through a first principle based modeling approach and, in particular, through the analysis of feedback control regulation.

This monograph is intended for researchers in this field but is also written in such a way as to be accessible to graduate students in biomedical engineering, life sciences, and applied mathematics, as well as to scientists interested in beginning research in this area. Topics are organized around specific questions of control interactions and physiologically based modeling approaches. The primary goals of this volume are: (i) to provide an overview that highlights the complex nature of control processes and interactions between the cardiovascular and respiratory systems; (ii) to describe state-of-the-art developments in modeling the control processes of the cardiovascular and respiratory systems; (iii) to illustrate and develop some basic underlying principles of physiological control organization; and finally (iv) to point out the direction of future research arranged around natural analytical questions. In summary, we strive to provide insight into organizational principles of cardiovascular and respiratory control and a clear and workable picture of research efforts in this area and possible areas of medical applications.

The material presented in this monograph is organized into five chapters and three appendices. Each chapter provides physiologically relevant background as well as physiologically based approaches to modeling. In addition, analytical issues associated with the mathematical model are also discussed. Chapter 1 introduces basic elements of cardiovascular modeling including key physiological concepts, some analytical tools and the application of optimal control to model the baroreceptor loop. To illustrate the modeling philosophy used in this book and the applicability of the model, the transition of the cardiovascular system from rest to ergometric exercise is given as an example. In a similar way Chapter 2 presents the basic elements of the respiratory control system and the development of a mathematical model with the same level of complexity as the cardiovascular model of the first chapter. Time delays play an important role in respiratory control. Such delays are included in the model and their influences on the dynamics of the respiratory system is discussed. A number of important clinically relevant applications are also provided. In Chapter 3 the models developed in Chapters 1 and 2 are integrated into a model for the cardiovascular-respiratory system. Aspects of control theory, steady state analysis, and state dependent delays are discussed in the context of this more complex model. Furthermore, interaction of respiratory and cardiovascular control is discussed in great detail. Clinically relevant applications are given which also illustrate how models can be extended to cover new situations. These applications include congestive heart failure which was already discussed in Chapter 2 as well as new applications to orthostatic stress and basic reactions of the cardiovascular-respiratory system to hemorrhage. Chapter 4 gives a thorough discussion on how the venous system and blood volume control influence the cardiovascular system. This role of the venous system is often underestimated, partly because the arterial system parameters and control mechanisms such as the arterial baroflex have been more accessible to measurements. These issues play an important role in hemodialysis which is given as a modeling application. Chapter 5 provides a detailed evaluation of the state of the art in areas related to the themes of developed in this book. In particular, important questions are raised the answers to which should have an impact on the further development of the field. This includes some well-accepted principles which are currently being re-examined.

The appendices provide detailed computations that would interrupt the presentation in the chapters and also short descriptions of important analytical topics which can be pursued in greater detail using the references provided. In particular, Appendix A gives an introduction to generalized sensitivity analysis. Appendix B provides background on nonlinear feedback control. In Appendix C we present basic facts and ideas on delay equations which, in particular, are used in Chapters 2 and 3.

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