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Editors

Mathematical Modeling and Validation in Physiology

Applications to the Cardiovascular and Respiratory Systems

Springer

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Preface

The focus of this volume is on mathematical modeling techniques essential for studying human physiology and biomedical and clinical problems at primarily the organ and system level. The areas of focus for physiological modeling are the cardiovascular and respiratory systems, central systems which impact all aspects of human physiological function. Particular emphasis is placed on control mechanisms and clinical problems arising from deficiencies in these control mechanisms.

Mathematical modeling of physiological systems is a complicated enterprise. Decisions must be made on model complexity in the context of the problem of acquiring sufficient data for model validation. As a consequence, close collaboration is essential between scientists from the mathematical/engineering side and the physiological/medical side. This requires developing a new perspective based on a common language and common understanding of diverse scientific principles. New research insight and improved research protocols can evolve in response to this merging of several scientific disciplines and the skills, training, and experience of each.

Important state-of-the-art questions are included in this volume. For example, modeling of physiological systems often leads to the design problem that these models have to be detailed enough in order to represent the complex physiological mechanisms acting at various functional levels. Consequently such models usually contain a large number of parameters. Based on these factors, valid models are often difficult to apply in the clinical setting where noninvasive tests and measurements restrict the availability of data from which parameters can be estimated. In addition, interindividual variation in physiological function and in particular the individualized combination of a physiological system's inventory of control responses add further complication to model application for diagnosis and treatment design.

Goal

The goal of this volume is to provide the reader with an understanding of the theory and practice of modeling of physiological control systems with a primary application of studying clinical problems related to the cardiovascular and respiratory control systems.

Scientific Content

The content of this volume is focused on principles of modeling and applications of mathematical methods for model development, model validation, and model application related to important physiological questions and clinical conditions with the focus on application to the cardiovascular and respiratory systems. Cardiovascular and respiratory control mechanisms receive particular attention and represent the vehicle for exemplifying the theoretical ideas presented. The role of time delay in feedback control is also examined theoretically and in terms of clinical manifestations of instabilities induced by delay.

Interdisciplinary Collaboration

A key theme in this volume is the development of interdisciplinary collaboration between mathematicians, engineers, clinicians, and life scientists (both theoretical and experimental). Authors from all these disciplines have contributed to this volume. As a consequence, important mathematical and physiological concepts and perspectives are included and merged into the volume content. In particular significant attention is given to the practical side of modeling, especially in regard to assessing model parameter identifiability as well as insight into problems and methods of experimental design and data collection.

This approach illustrates interdisciplinary research in a concrete way. Model development and experimental design go hand in hand: models must contain the necessary degree of detail to reflect the problem under study but must allow for model validation in the context of the data that can be collected from available measurement tools and experiments. The merging of both the modeling and experimental perspectives and coordinating their contributions can lead to improved adaptation of models to individual patients leading to potential diagnostic and treatment tools.

In the spirit of these observations the text is divided into the following two parts:

- Part I entitled Theory focuses on key concepts and methods needed for the development of models with a special emphasis on the problems of parameter estimation and model validation.
- Part II entitled Practice provides a number of modeling studies which employ the concepts discussed in the Theory part of the volume. These studies also exemplify the parameter identification tools discussed in the theory section such as sensitivity analysis and subset selection. In addition this part seeks to provide insight into data collection and experimental design.

Advancement of knowledge in the focus area of this volume impacts important areas of clinical research including orthostatic intolerance (a key problem in the elderly), hypotension during hemodialysis, the interaction of respiratory and cardiovascular mechanisms in sleep apnea, congestive heart failure, and many other areas.

The book is intended for applied mathematicians, engineers, biophysicists, physicians, physiologist and others interested in learning about mathematical modeling of physiological systems in general and the cardiovascular and respiratory systems, in particular. The reader who has at least a background in differential and integral calculus, ordinary differential equations, can profit from this book. While the application focus is on cardiovascular and respiratory modeling, the more general reader will find these applications accessible and illuminating since important topics such as physiological control mechanisms, feedback delays in such systems, experimental design, model design and development and model parameter estimation are illustrated in the concrete cases examined.

Chapters

Chapter 1 provides an overview of modeling issues and modeling strategies. An overall framework for the topics discussed in the book is presented, including issues of interdisciplinary collaboration.

Chapter 2 provides a detailed examination of the modeling process using the application of the principles developed to the cardiovascular control systems as template.

Chapter 3 provides an in-depth analysis of subset selection, a sensitivity identifiability-based approach introduced in Chaps. 1 and 2. This procedure is applied to assess the parameter estimation problem and improve the parameter estimation results.

Chapter 4 takes a closer look at the process of parameter estimation and provides an application of the Kalman filter to refine the estimation process.

Chapter 5 exemplifies how delays in model equations can arise and be treated in parameter estimation.

Chapter 6 looks at various levels of modeling and perspectives of the modeling process. This chapter acts as a bridge to the second part of the book.

Chapter 7 considers the modeling of the respiratory system illustrating and using a minimal model approach. The chapter provides a concrete example of the stability issues of respiratory control discussed in Chap. 8, namely the important clinical problem of sleep apnea.

Chapter 8 provides a careful explication of the steps involved in deriving a model of the respiratory system from physiological information and principles. This chapter exemplifies many of the concepts described in Part I and illustrates the role of experimental design and data collection in model development.

Chapter 9 is devoted entirely to the experimentation process, examining how physiological information about the baroreflex, a key control of the cardiovascular system, has been derived. This chapter also provides the physiological background for the modeling studies of Chap. 10.

Chapter 10 provides an extensive study of the many issues involved in cardiovascular blood pressure control and how model development proceeds from physiology to the problem of patient-specific model adaptation.

Chapter 11 examines another key component of the cardiovascular control system, namely the quantity unstressed volume, and illustrates how sensitivity analysis and subset selection proceed in studying this control using invasive and noninvasively collected data.

This volume has its origin in a series of combined summer school/workshop events supported by funds from the Marie Curie Training Series. This program involved four events which examined key methods for modeling, data utilization, and clinical application of complex models of important physiological systems. Taken as a whole, the sequence of events spanned four years and represented a multisided examination of mathematical modeling for biomedical application.

The general web page linking and reflecting all four events can be found at:

www.uni-graz.at/biomedmath/info.html

The addresses of the individual web pages for the four events are:

Graz:	www.uni-graz.at/mc_training_schools/graz/summerschool/
Copenhagen:	www.math.ku.dk/~susanne/SummerSchool2008/
Lipari:	www.biomatematica.it/lipari2009/
Dundee:	www.maths.dundee.ac.uk/summerschool2010/

The first event in the series from which the current volume draws its inspiration was held in Graz and was entitled *Biomedical Modeling and Cardiovascular–Respiratory Control : Theory and Practice*. It was held in Schloss Seggau in Leibnitz near Graz. This event consisted of 11 days of summer school followed by a 3-day scientific workshop on the same theme as the school focus. The summer school introduced new researchers (pre to early post doc) to critical mathematical and physiological ideas and methods by experts in both fields. The workshop which followed directly after the summer school was designed to be equivalent to a stand-alone workshop involving current researchers in the field. As part of their training, students from the summer school attended the workshop. In this way, students

introduced to new methods and concepts in the school could apply this knowledge in learning state-of-the-art issues in cardiovascular–respiratory system modeling research.

Acknowledgments

This book would never have existed without the commitment and work of the contributors of this volume and we would like to thank them all for their efforts and for sharing their insights with us. In particular we acknowledge support by the European Commission under Contract MSCF-CT-2006-045961 Biomathtech 07–10. For each chapter at least one contributor also participated in the first event (Graz) of our Marie Curie training event series. We are grateful to all those who helped with organizing the four Marie Curie training events. We wish to also thank all the people who attended the summer school and workshop and especially the teachers and workshop presenters of the summer school/workshop events. We also thank Springer Verlag and especially Ute McCrory for their support during the production of the book.

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Graz and Riyadh
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Contents

Part I Theory

1 Merging Mathematical and Physiological Knowledge: Dimensions and Challenges 3
Jerry J. Batzel, Mostafa Bachar, John M. Karemaker, and Franz Kappel
1.1 Introduction 4
1.2 The Problem Setting 4
1.2.1 Conceptual Models 4
1.2.2 Mathematical Models 5
1.2.3 Interdisciplinary Research 7
1.2.4 Overcoming Barriers to Collaboration 7
1.3 Aspects of Parameter Estimation and Model Validation 8
1.3.1 Model Outputs and Measurements 9
1.3.2 Parameter Estimation, Least Squares Formulation 11
1.3.3 Sensitivity Analysis 12
1.3.4 Generalized Sensitivities 14
1.3.5 Experimental Design 16
1.4 Model Validation 17
1.5 A General Validation Protocol 18
References 19

2 Mathematical Modeling of Physiological Systems 21
Thomas Heldt, George C. Verghese, and Roger G. Mark
2.1 Introduction 21
2.2 Simulation 23
2.3 Exploration of Hypotheses 26
2.4 Model Identification 31
2.4.1 Non-linear Least-Squares Estimation 32
2.4.2 Subset Selection 35
2.5 The Case for Structured Model-Order Reduction 37

2.6 Conclusions 38
References 38

3 Parameter Selection Methods in Inverse Problem Formulation 43
H.T. Banks, Ariel Cintrón-Arias, and Franz Kappel
3.1 Introduction 44
3.2 Statistical Models for the Observation Process 45
3.3 Subset Selection Algorithm 49
3.4 Models 51
3.4.1 A Mathematical Model for HIV Progression with Treatment Interruption 51
3.4.2 A Model for the Reaction of the Cardiovascular System to an Ergometric Workload 55
3.5 Results and Discussion 58
3.5.1 The HIV-Model 58
3.5.2 The CVS-Model 65
3.6 Concluding Remarks 70
References 70

4 Application of the Unscented Kalman Filtering to Parameter Estimation 75
Adam Attarian, Jerry J. Batzel, Brett Matzuka, and Hien Tran
4.1 Introduction 76
4.2 The Unscented Kalman Filter 78
4.3 Parameter Estimation 82
4.3.1 Dual Estimation 83
4.4 Estimation Examples 84
4.4.1 A Hard Nonlinear Spring Model 84
4.4.2 An HIV Model 85
References 87

5 Integrative and Reductionist Approaches to Modeling of Control of Breathing 89
Chung Tin and Chi-Sang Poon
5.1 Introduction 89
5.2 Reductionist View of Biological Modeling 90
5.2.1 The Physiome Project and Multiscale Model 91
5.3 Engineering and Physics View of Integrative Modeling 92
5.4 Top-Down (Integrative) vs Bottom-Up (Reductionist) Approach to Biological Modeling 93
5.5 Criteria of a Good Mechanistic Model 94
5.6 Control of Breathing: Reductionism vs Integration 94
5.6.1 Limitations of Classical Reflex Models: A Case for Sensorimotor Integration 94
5.6.2 Optimal Sensorimotor Integration in Respiratory Control 95

5.6.3 Hebbian Feedback Covariance Learning Model of Respiratory Motor Control 97
5.6.4 Cheyne–Stokes Breathing: Three Different Engineering Control Perspectives 100
References 102

6 Parameter Identification in a Respiratory Control System Model with Delay 105
Ferenc Hartung and Janos Turi
6.1 Introduction 105
6.2 Model Equations 106
6.3 Numerical Approximation 108
6.4 Parameter Estimation 109
6.5 Conclusions 117
References 117

Part II Practice

7 Experimental Studies of Respiration and Apnea 121
Eugene N. Bruce
7.1 Introduction 122
7.2 "Black-box" Models of Chemoreflex Control of Ventilation 123
7.3 A Model for Predicting Brain Tissue Oxygen Tensions 125
7.4 Conclusions 129
Appendix 130
References 131

8 Model Validation and Control Issues in the Respiratory System 133
James Duffin
8.1 Introduction 133
8.1.1 The Respiratory Control System 133
8.1.2 The Central Chemoreceptors 136
8.1.3 The Peripheral Chemoreceptors 136
8.2 Modeling the Chemoreflex Control System 137
8.2.1 Measurement Techniques 137
8.2.2 Chemoreflex Model Parameter Estimation 139
8.3 Modeling Acid-Base Relations 141
8.4 The Chemoreflex Control System Model 141
8.4.1 The Central Chemoreflex 141
8.4.2 The Peripheral Chemoreflex 142
8.4.3 The Complete Chemoreflex Control System Model 142
8.4.4 The Graphical Model of the Chemoreflex Control of Breathing 143
8.5 Chemoreflex Control System Stability 146

8.6 The Cerebral Blood Flow Control System 147
8.6.1 Interaction with the Chemoreflex Control System 147
8.6.2 The Cerebral Blood Flow Control System Model 147
8.7 Dynamic Simulation of the Chemoreflex and Cerebral Blood Flow Control Systems 148
8.7.1 Concluding Remarks 150
Appendix 151
References 160

9 Experimental Studies of the Baroreflex 163
Clive M. Brown
9.1 Introduction 163
9.2 Physiological Relevance of the Baroreflex 164
9.3 Baroreceptor Denervation Studies 164
9.4 Do Baroreceptors Have a Role in the Long Term Control of Blood Pressure? 165
9.5 Testing Baroreflex Sensitivity in Humans 166
9.5.1 Mechanical Methods of Assessing Baroreflex Function 166
9.5.2 Pharmacological Methods of Assessing Baroreflex Function 168
9.5.3 Spontaneous Techniques 169
9.6 Baroreflex Responses in Posturally-Related Syncope 170
9.7 Role of Cardiopulmonary Receptors 171
9.8 Conclusions 172
References 172

10 Development of Patient Specific Cardiovascular Models Predicting Dynamics in Response to Orthostatic Stress Challenges 177
Johnny T. Ottesen, Vera Novak, and Mette S. Olufsen
10.1 Introduction 177
10.2 Methods 181
10.2.1 Experimental Design 181
10.2.2 Modeling Strategy 182
10.2.3 Mathematical Models 184
10.2.4 Parameter Estimation and Model Validation 195
10.3 Discussion 201
10.3.1 Open Loop Model 201
10.3.2 Closed Loop Model 203
10.3.3 Syncope 207
10.4 Conclusion 210
References 211

11 Parameter Estimation of a Model for Baroreflex Control of Unstressed Volume 215
Karl Thomaseth, Jerry J. Batzel, Mostafa Bachar, and Raffaello Furlan
11.1 Introduction 215
11.2 Stressed and Unstressed Vascular Volume 216
11.3 Model Structure 217
11.3.1 Mass Balance Equations 218
11.3.2 Control Equations 221
11.3.3 Control Responses: Unstressed Volume and Systemic Resistance 221
11.4 Data 222
11.5 Model Identification 224
11.6 Sensitivity Identifiability: A Subset Selection Approach 224
11.6.1 Parameter Identification Framework 225
11.6.2 Reduced Rank Subspace Selection Using Singular Value Decomposition 228
11.6.3 Effective Dimensions of Estimated Parameter Vectors 230
11.7 Results 232
11.8 Sensitivity Identifiability: A General Strategy 235
Appendix 238
References 245

Glossary 247

Index 251

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Acronyms

AIC	Akaike's Information Criterion
ANOVA	Analysis of variance
CBF	Cerebral blood flow
COPD	Chronic obstructive pulmonary disease
CSF	Cerebral spinal fluid
CVP	Central venous pressure
CVS	Cardiovascular system
ECG	Electrocardiogram
EKF	Extended Kalman filter
EPCA	Equations with piecewise constant argument
G + W	Whole brain
GLS	Generalized least squares
GM	Grey matter
GRV	Gaussian random variables
GSF	Generalized sensitivity function
HIV	Human immunodeficiency virus
HR	Heart rate
HUT	Head up tilt
LBNP	Lower body negative pressure
LQP	Least squares problem
LTP	Long term potentiation
M	Muscle
MIMO	Multiple-input-multiple-output
MLE	Maximum likelihood estimator
MSNA	Muscle sympathetic nerves activation
NIRS	Near infrared spectroscopy
NLWLS	Nonlinear weighted least squares
NM	Non-muscle
NMDA	*N*-methyl D-aspartate
NREM	Non-REM sleep
ODE	Ordinary differential equations

OLS	Ordinary least squares
PDE	Partial differential equation
PI	Protease inhibitor
RTI	Reverse transcriptase inhibitor
SID	Strong ion difference
SISO	Single-input-single-output
SMC	Sequential Monte Carlo
STS	Sitting to standing
SVD	Singular value decomposition
TSF	Traditional sensitivity function
UKF	Unscented Kalman filter
UT	Unscented transformation
WM	White matter