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Introduction to the Special Issues: Short-term Cardiovascular–Respiratory Control Mechanisms

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Abstract

This and the following issue of Cardiovascular Engineering are special issues reflecting research discussed during an interdisciplinary focused workshop entitled *Short-term Cardiovascular–Respiratory Control Mechanisms.* The workshop was organized by Mette Olufsen and Hien Tran at the Department of Mathematics at North Carolina State University, Jerry Batzel and Franz Kappel at the Institute for Mathematics and Scientific Computing, University of Graz, and Vera Novak at the Department of Gerontology at Harvard Medical School, and hosted by the American Institute of Mathematics (AIM), Palo Alto, California, October 9–13, 2006. The workshop was co-sponsored by AIM and the National Science Foundation.

Workshop Topics and Issues

The overall objectives of this workshop were (i) to identify physiological mechanisms involved in short-term cardiovascular–respiratory regulation, (ii) to develop mathematical models that can improve understanding, diagnosis, and treatment of clinical problems related to short-term cardiovascular–respiratory regulation, (iii) to discuss the methodological and computational framework for adapting complex mathematical models to clinical applications, and (iv) to develop new projects/collaborations. To tackle these objectives the organizers brought together a mixed group of world-renowned experts and young, promising researchers, with expertise in physiology, mathematics, clinical sciences, and statistics.

One of the main challenges in bringing together mathematicians and medical experts is to ensure effective communication between these diverse groups of scientists. This requires that mathematicians learn about medical terminology, and that medical experts become exposed to mathematical thinking. This type of communication is typically not facilitated at big, special topics conferences that are targeted towards one of the two groups. Hence, a

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small workshop that can bring these two groups together is an ideal venue to initiate new collaborations. To promote undergraduate research, the workshop organizers invited faculty members from undergraduate institutions who have potential to mentor projects at their institutions.

The main mechanisms involved in short-term cardiovascular–respiratory control include auto-regulation of vasculature, control of cerebral blood flow, autonomic nervous system regulation of heart rate, vascular resistance, and capacitance, and regulation of oxygen (O_2) and carbon dioxide (CO_2) concentrations in the brain and other tissues. These mechanisms involve multiple organ systems and act to stabilize blood pressure and ensure adequate tissue blood flow, in particular cerebral blood flow. The interactions between these regulatory mechanisms are complex, transient, and often nonlinear, and are not well understood. In healthy young people short-term regulation adapts quickly, but in elderly people and in people with cardiovascular diseases these regulation mechanisms are delayed, and responses are often diminished and/or impaired. Thus, as the population demographics move toward a higher proportion of elderly, clinical problems such as orthostatic intolerance will become more prevalent.

Clinical manifestations of diminished short-term control capacity include orthostatic hypotension, dizziness, and syncope leading to falls, and these effects can be caused by several biological mechanisms that impact short-term cardiovascular–respiratory regulation. The falls that result from these manifestations produce injuries that are the leading causes of morbidity and mortality in elderly people. Unfortunately these manifestations of reduced control are difficult to predict and prevent given the complexity of the control interactions. Therefore, modeling short-term interactions among cardiovascular, respiratory, and other system control mechanisms addresses important clinical issues and may provide insights into the impairment of these mechanisms that cannot be well understood using traditional physiological methods.

An important focus of the workshop was the application of mathematical models to the clinical setting. A key topic of discussion during the workshop centered on issues of model validation using only clinical data. A number of ordinary and delay differential equation models have been developed to study aspects of short-term regulation. Most of these models are fairly complex, none of them include all regulatory mechanisms, and few have been adapted to and tested using clinical data. Thus, practical applications of such models in the clinical setting was a central issue for the workshop and a fundamental reason for the interdisciplinary background of the participants. It was the general workshop consensus that as new mathematical approaches are developed for parameter estimation, and as advances are made in the measurement of state variables and patients specific parameters, new possibilities will be constantly emerging for model application in the clinical setting. The manuscripts presented in these two special issues address some of these questions and it is our hope that this work can provide inspiration for future studies.

Workshop Design

This workshop had several features that distinguished it from standard workshops or conferences. For example, even before the workshop began, participants were asked to contribute topics and issues for consideration. Hence the workshop contained a degree of flexibility and openness that encouraged the emergence of a set of issues for examination that were of fundamental interest to the participants and also of central scientific significance. Each day was centered on a primary topic. In the morning 2–3 plenary talks introduced various aspects of that topic followed by an open discussion. Topics included both areas of mathematical techniques in modeling and clinical issues where modeling could

be applied. A number of focused working groups were established that met in the afternoons to discuss different aspects of problems related to the topic under consideration that day. At the end of each day a summary was given and open discussion on points developed in the working groups was carried out involving the entire group. This is the workshop-format recommended by the AIM coordinators. The participants felt that the workshop had an excellent format for stimulating discussion and encouraging participant involvement by both senior and junior researchers. At the end of the workshop, reports from each working group were developed. The manuscripts presented in this issue reflect the main topics examined in the workshop and in some cases the manuscripts reflect results of work initiated at the workshop. Some of the manuscripts are co-authored by several workshop participants, and some results in the manuscripts directly represent insights that emerged during the workshop. Several new collaborations have been formed since the workshop, and it is our hope that more research results will be published in future manuscripts.

Workshop Support and Funding

The host of this workshop was The American Institute of Mathematics (AIM): http://www.aimath.org/. AIM is a nonprofit organization, founded in 1994 by Silicon Valley businessmen John Fry and Steve Sorenson, longtime supporters of mathematical research. The motivation of AIM is to expand the frontiers of mathematical knowledge through focused research projects, through sponsored conferences, and through the development of an on-line mathematics library.

AIM together with additional support from NSF fund highly focused workshops, with each workshop organized around a specific important mathematical topic bringing together mathematicians and in some cases other scientists to work collaboratively on important mathematical problems (Fig. 1).

We share with AIM the view that solutions to complex problems frequently require techniques from several areas of mathematics and other disciplines and, hence, can be greatly facilitated by input from a diverse group of researchers. We wish to acknowledge the generous financial support from AIM and NSF and the hospitality provided by AIM that make the workshop not only a successful but also an enjoyable experience. We also thank the contributors for their time and efforts in this endeavor. The editors and contributors to these two special issues hope that these articles will help to stimulate further discussion on the research questions explored during the workshop and eventually leading to improve understanding, diagnosing, and treatment of short-term cardiovascular and respiratory regulation for the elderly.

Finally, we are most appreciative of the opportunity provided by Springer to have these articles published in Cardiovascular Engineering, and we express our special thanks to the Editor, J. Li, for his support and advice in this project.

Workshop Organizers

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Workshop Participants

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- Madalena Costa, Beth Israel Deaconess Medical Center, Harvard Medical School
- Dwain Eckberg, Departments of Medicine and Physiology, Hunter Holmes McGuire Department of Veterans Affairs, Medical Center and Medical College of Virginia at Virginia Commonwealth University
- Laura Ellwein, Department of Mathematics, North Carolina State University
- Martin Fink, Department of Physiology, Anatomy and Genetics, University of Oxford, UK
- Ben Fitzpatrick, Mathematics Department, Loyola Marymount University
- Kathleen Fowler, Division of Mathematics and Computer Science, Clarkson University
- Ary Goldberger, Beth Israel Deaconess Medical Center, Harvard Medical School
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Volume 1

Volume one focuses on cardiovascular control. Four articles consider aspects of baroreflex control while two articles are related to autoregulation:

Baroreflexes and Autonomic Control—D. L. Eckberg provides a review discussing mechanisms essential to include when modeling cardiovascular interactions in *Arterial baroreflexes and cardiovascular modeling.*

M. Mutsaers, M. Bachar, J. J. Batzel, F. Kappel, S. Volkwein apply the design and implementation of a receding horizon control to represent the baroreceptor loop in *Receding horizon controller for the baroreceptor loop in a model for the cardiovascular system*.

J. M. Karemaker and K. H. Wesseling review key features of baroreflex design including evolutionary aspects as well as the importance of variability in blood pressure and noisiness in the baroreflex in *Variability in cardiovascular control: the baroreflex reconsidered.*

M. C. K. Khoo introduces the application of various versions of a minimal model to sleep disordered breathing (SDB) and compares this modeling approach in detecting abnormalities in autonomic cardiovascular control in SDB to univariate analysis of heart rate variability or blood pressure variability in the article *Modeling of autonomic control in sleep-disordered breathing*.

Autoregulation—R. B. Panerai provides a review of a number of methods for studying cerebral autoregulation in the article *Cerebral autoregulation: From models to clinical applications*.

K. Hu, C. K. Peng, M. Czosnyka, P. Zhao, V. Novak discuss a new method relating arterial blood pressure and cerebral blood flow velocity to assess cerebral autoregulation. This is done in the manuscript *Nonlinear assessment of cerebral autoregulation from spontaneous blood pressure and cerebral blood flow fluctuations*

Volume 2

Volume two focuses on heart rate dynamics and model validation. Two articles discuss heart rate modeling from two different points of view and four articles address parameter estimation using sensitivity analysis and associated statistical models.

Heart and Heart Rate—M.S. Olufsen, A.V. Alston, H.T. Tran, J.T. Ottesen, V. Novak examine a model predicting heart rate regulation during sit-to-stand and during head-up tilt in *Modeling heart rate regulation—Part I: Sit-to-stand versus head-up tilt.*

M.D. Costa, C-K. Peng, A.L. Goldberger use multiscale entropy and multiscale time irreversibility to extract information from cardiac inter-beat interval time series, which may be useful in diagnostics, risk stratification and detection of toxicity of cardiac drugs in *Multiscale analysis of heart rate dynamics: Entropy and time irreversibility measures*.

Parameter Estimation—L.M. Ellwein, H.T. Tran, C.L. Zapata, V. Novak, and M.S. Olufsen apply sensitivity analysis to a model to identify those parameters that have potential to be estimated given limited data and discuss how the model complexity can be reduced in *Sensitivity analysis and model assessment: mathematical models for arterial blood flow and blood pressure*.

K.R. Fowler, G.A. Gray, M.S. Olufsen consider and analyze two optimization methods, the implicit filtering and genetic algorithm, that can be used for parameter estimation of a heart

rate model in *Modeling heart rate regulation—Part II: Parameter identification and analysis*.

M. Fink, J.J. Batzel and H.T. Tran compare various approaches to detect and analyze the identifiability of certain key respiratory control parameters using clinical data normally available from non-invasive measurements in *A respiratory system model: Parameter estimation and sensitivity*.

B. G. Fitzpatrick discusses important aspects of statistical features for comparing the difference between model and experiment in *Statistical considerations and techniques for understanding physiological data, modeling, and treatments*.

Fig. 1.
AIM's "castle" conference venue under construction and modeled after the famous Moorish Alhambra palace in Spain