

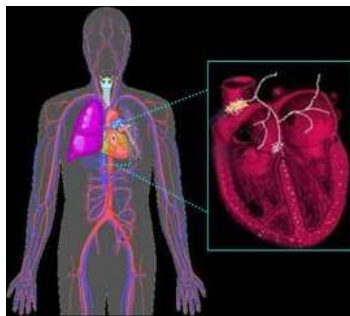
Graz Summer School and Workshop on Biomedical Modeling and Cardiovascular-Respiratory Control: Theory and Practice

organized by the
Mathematics and Medical Physiology Group
of The Institute for Mathematics
and Scientific Computing

University of Graz

Schloss Seggau

July 22 - August 4, 2007



Event Organizers

Mostafa Bachar, Jerry Batzel and Franz Kappel



Fresenius Medical Care



MARIE CURIE ACTIONS



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Organizing Groups

Mathematics and Medical Physiology Group
The Institute for Mathematics and Scientific Computing
University of Graz

The Mathematics and Medical Physiology Group focuses on interdisciplinary research projects combining applied mathematics, physiology and several areas of engineering. It has become widely accepted that techniques from applied mathematics - in particular from the areas of optimization and numerical mathematics - are essential for extending our scientific knowledge about physiological control. The interdisciplinary efforts within the MMPG seek to develop innovative techniques to apply to this area of research.

BioMedMath A Marie Curie Series of Four Events

BioMedMath is the acronym for our program of four school-workshop events entitled **Mathematical Modeling of Human Physiological Systems with Biomedical Applications**. These events are sponsored by the European Union Marie Curie Training Course Initiative with the next events:

- 2007 Graz: Biomedical Modeling and Cardiovascular-Respiratory Control: Theory and Practice.
- 2008 Copenhagen: Stochastic Differential Equation Models with Applications to the Insulin-Glucose System and Neuronal Modeling;
- 2009 Acireale Italy: Parameter Estimation in Physiological Models;
- 2010 Dundee: Mathematical Modeling of Cancer Growth and Treatment.

More information on these events can be found at the web page:

<http://www.uni-graz.at/biomedmath/info.html>

Event Organizers

Mostafa Bachar and Jerry Batzel and Franz Kappel

School Support

- European Union and the Marie Curie Conference and Training Sessions Program
- University of Graz
- European Society of Mathematical and Theoretical Biology
- The Fresenius Corporation

Special thanks to Prof. David Paterson, director of the Cardiac Neurobiology Research Group of Oxford University for use of their human cardiovascular-respiratory system image.

A very special thanks to Summer School Secretary Katharina Nill and Uni-Graz Mathematics Institute Systems Administrator Fabian Tschitschek for their valuable help. **A very very special thanks** to Uni-Graz Mathematics Institute secretary Gerlinde Krois who makes everything work correctly.



Open-Loop Control

General information

- Meals are held as follows:
 - Breakfast 7:15 - 8:15
 - Lunch 12:30
 - Dinner 19:00
- Meals are free for registered students and those staying at Schloss Seggau with the full pension plan. Other guests or day participants are welcome to have lunch or dinner at the conference site. Lunch price about 10 Euro and dinner price also about 10 Euro.
- We will pass around each day a lunch and dinner menu and choice list. Please mark on the choice list whether you want regular or vegetarian. If neither is marked we will assume you will be away for that meal.
- Drinks at meals are not free. Please pay for drinks at the beverage counter. Beverages at class or workshop breaks during morning and afternoon sessions are free.
- The swimming pool is in general open.
- The Schloss Cafe is open approximately from 10:00-23:00.
- It is an easy walk down to Leibnitz (not so easy walk back). There is a path down behind the winery. Ask at the registration office for instructions.
- There are tours and wine tastings at the winery for those interested and also a tour of the castle grounds is available. For tour information ask at the registration desk.
- Posters of the school are available. The cost is 2 Euro.

Social Events

- Monday evening July 23 at 19:00: there will be a Welcome Dinner Buffet.
- A social event is planned for Sunday July 29.
- A Farewell Dinner will be Friday August 3.
- A social event is planned Saturday August 4.



Closed-Loop Control

Summer School Teachers

- Modeling Theory
 - H. Thomas Banks (North Carolina State University) Pg. 13
 - Franz Kappel (University of Graz) Pg. 15
- Physiological Theory
 - John M. Karemaker (Univ. of Amsterdam) Pg. 16
 - John Remmers (University of Calgary) Pg. 17
- Parameter Estimation Theory and Practice
 - Spiros Courellis (University of Southern California) Pg. 18
 - Hien T. Tran (North Carolina State University) Pg. 19
- Modeling Techniques and Applications for the CVRS
 - James Duffin (University of Toronto) Pg. 20
 - Thomas Heldt (Massachusetts Institute of Technology) Pg. 24
 - Zbigniew Topor (University of Calgary) Pg. 25
- Long Term CVRS Control
 - Vito Starc (University of Ljubljana) Pg. 26

Workshop Presenters

- Theo Arts (University of Maastricht)
- Clive M. Brown (University of Fribourg)
- Eugene N. Bruce (University of Kentucky)
- Silvio Cavalcanti (University of Bologna)
- Michael Chappell (University of Warwick)
- Gilbert Chauvet (University of Angers)
- John W. Clark (Rice University)
- Roberto Furlan (University of Milan)
- Mats Gyllenberg (University of Helsinki)
- Patrick Hannaert (University of Poitiers)
- Vera Novak (Harvard University)
- Shigehiko Ogoh (University of North Texas)
- Johnny T. Ottesen (Roskilde University)
- M. Pennacchio (The National Research Council (CNR), Italy)
- C.S. Poon (Massachusetts Institute of Technology)
- W. Wang (Queen Mary, University of London)

Daily Schedule Notes

- July 22 is a day for arrival and registration. We plan a welcome dinner for 19:00 on Monday July 23 and a Farewell dinner on August 3.
- First day of class is July 23 and classes end with the workshop on August 4.
- Classes will be divided into morning and afternoon sessions with each class given as a 45 minute lecture separated by short breaks and with one coffee break each session. Supplemental class notes will be published on the internet at the web page and book references also given. Courses have two or more teachers and classes may be distributed among the two weeks.
- Workshop days will be similarly structured. See the daily schedule sample below and the total schedule in your book bag.
- On the enclosed daily schedule, courses are referenced by teachers. Course areas and teachers are given below. The schedule of workshop presentations is also given below.

Typical Daily Schedule

Time	Talk
7:15-8:15	Breakfast
8.30 – 9:15	Unit Lecture
9.20 – 10:05	Unit Lecture
10:05 - 10: 40	Break
10:40 – 11:25	Unit Lecture
11:30 – 12:15	Unit Lecture
12:30-15:00	Lunch Break
15:00 – 15:45	Unit Lecture
15:50 – 16:35	Unit Lecture
16:35 – 17:10	Break
17:10 – 17:55	Unit Lecture
18:00 – 18:45	Unit Lecture
19:00	Dinner

Summer School Course Outlines

(I) Modeling Techniques

H.T. Banks

An Introduction to Statistical Methodology in Inverse Problems

Outline of Lectures

1. Introduction to statistical models and probability review
2. Statistical models and inference: asymptotic sampling distributions
3. Inverse problem methodology summary
 - (i) Parameter estimation (MLE, OLS, GLS), standard errors and confidence intervals
 - (ii) Model comparison techniques and significance tests for improvements in models

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- [16] G. A. F. Seber and C. J. Wild, *Nonlinear Regression*, John Wiley & Sons, Inc., New York, 1989.
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Franz Kappel

Basic Concepts in the Methodology of Mathematical Modeling

The objective of this course is to introduce the student to important concepts and methods needed for developing complex models of physiological control mechanisms at the organ and system level. In particular, parameter estimation will be a primary focus. A key issue in such research is that models that have sufficient complexity to allow for new insights about complex interactions often leads to the problem that such models contain many parameters but data for identification is limited. This is certainly an issue for models intended for application in the clinical setting where non-invasive testing generates only a restrictive set of data. Furthermore, the inter-individual variation in a physiological system's inventory of control responses adds further complication to model application for diagnosis and treatment design. These problems represent an important challenge to current research and shape, to a large extent, the approach to model design.

Topics for this module include:

1. Key concepts in model design and the validation of the design;
2. How control issues enter the model design;
3. Approaches to linear and nonlinear control design:
 - (a) Optimal control;
 - (b) Receding horizon control;
4. The need for innovative methods of parameter estimation and the definition of the mathematical setting;
5. An application: cardiovascular modeling;
6. Numerical issues and problems in model implementation.

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(II) Cardiovascular-Respiratory System Physiology

John M. Karemaker

Control of the cardiovascular system

1. Autonomic nervous system (in relation to the cardiovascular system)
2. Body fluid & blood pressure regulatory mechanisms
3. Heart as an electric driven pump
 - (a) Action potential generation & propagation
 - (b) Rhythm generation
 - (c) Electrocardiogram, chest wall projection, forward & backward
 - (d) Excitation-contraction coupling
 - (e) Ventricular stiffness in diastole & systole
 - (f) Ventricular 'function curves'; description & 'contractility'
4. (Left) ventriculo-vascular coupling; function of aorta and elastic vessels
5. Vascular bed, pulse wave transfer & reflection
6. Microvasculature; fluid & solutes exchange; NO & cytokines signaling
7. Venous system; depot function, elastic recoil, 'unstressed volume', venous return, cardiac filling
8. Right ventricle & Pulmonary system; specialized low pressure circulation for oxygen uptake & CO₂-delivery
9. Mechanisms of respiratory control; respiratory - cardiovascular interaction (with a special note on sleep-apnea)
10. Analysis & interpretation of cardiovascular variability
11. Effects of posture on heart & circulation & pulmonary function
12. Regulation of flow in special areas, in particular cerebral blood flow.

John Remmers

Respiratory System Physiology

1. The first unit will relate to Neurogenesis of Respiratory Rhythm, providing a review of the various types of rhythm generators and exploring in some detail the coupled respiratory oscillators that underlie the generation of inspiratory activity.
2. In the second unit Control of the Upper Airway Muscles and Pharyngeal Patency will be evaluated. The effects of the interaction of passive properties and pharyngeal dilators during inspiratory flow limitation will be outlined.
3. The third unit will examine the behavior of chemoreceptors in controlling breathing. The location and mechanisms for peripheral and central chemoreceptions will be evaluated.
4. In the fourth unit Chemoreflex Control of Breathing will be reviewed and the overall behavior of the system with two chemoreflex loops will be considered. The importance of relative delay involved in the two chemoreflexes will be explored.
5. In the fifth unit an exposition of sleep as a global phenomenon will be presented. In addition, the importance of REM and nonREM sleep as well as specific alterations in chemoreflex control will be described.
6. In the final two units both central and obstructive sleep apnea will be considered. Each will be described as classically presented and, as well, common pathogenic factors will be explored. These phenomena will be related to more detailed understanding derived from the Topor model.

(III) Modeling Validation and Parameter Identification and Applications

Spiros Courellis

Neural Networks with Physiological Applications

The course will focus on various traditional and emerging neural network topologies and their application to solve problems in physiology and medicine. The audience need not have any prior knowledge of Neural Networks, as an introductory session will be dedicated to basic neural network concepts (e.g., neuron types, connectivity, learning rules, and so on) and architectures (e.g., feed-forward, recursive, feed-forward with lateral inhibition, and so on). Subsequently, focus will shift on specific Neural Network concepts and topologies associated mainly with Multi-Layer Perceptrons (MLPs), Hopfield Networks, Self-Organizing Maps (SOMs), Cellular Neural Nets (CNNs), Radial Basis Function Neural Networks (RBFNNs), Support Vector Machines (SVMs), Bayesian Neural Networks (BNNs), and Spiking Neural Networks (SNNs). The category of applications each topology addresses and guidelines in selecting and adjusting the size of a network and in establishing good training and testing protocols will be discussed throughout the course. Case studies will be presented and discussed from a number of areas in physiology and medicine including neurophysiology (with emphasis in neuroprosthetics), cardiology, vision, biosensors, and so on. The course will involve the participants in individual and group class activities. Several class activities will involve running software (demo and simulation tools) distributed during class. Bring your laptop, install, and take with you most of the software we will use in class.

Hien Tran

Parameter Estimation Techniques and Model Validation

Outline of Lectures

1. Parameter Estimation in General
 - (a) Basic concepts and examples
2. An Overview of Probability and Statistics
3. Sensitivity Identifiability
4. Nonlinear Least Squares Estimation
 - (a) Gauss-Newton method
 - (b) Subset selection and reduced-order estimation
 - (c) Sampling optimization algorithms
5. Kalman Filter Based Estimation

References

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- [2] M. Burth, G. C. Verghese, M. Velez-Reyes, "Subset selection for improved parameter estimation in on-line identification of a synchronous generator", *IEEE Trans. On Power Systems*, Vol. 14, No. 1, 218-225, 1999.
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(IV) Cardiovascular-Respiratory System Modeling and Applications

James Duffin

Respiratory System Modeling and Applications

Introduction

This series of talks is intended to provide students with the necessary physiological knowledge and a practical approach to constructing models simulating the control of breathing. Clinical examples that use these modeling concepts are presented as appropriate. The talks begin with an introduction to simulation programming and then develop a conceptual graphical model of the chemoreflex control of breathing in the steady state. The experiments that produced the model and the parameter estimation from those experiments are reviewed next.

To convert the model to handle the effects of acid-base changes on respiratory control, models of oxygen and carbon dioxide carriage in blood are presented after reviewing the relevant physiology. The Stewart approach to modeling acid-base is presented and the steady state chemoreflex control of breathing and acid-base is developed. This model is incorporated into a dynamic simulation of the chemoreflex control of breathing and acid-base. If time permits, the Campbell diagram approach to modeling pulmonary mechanics will be discussed as a possible approach to simulating the action of ventilators on patients. The last talk will focus on a current modeling challenge; the control of breathing during exercise, detailing current theories.

The topics covered are as follows:

1. Programming Simulation Models with LabVIEW
 - (a) Basic ideas
 - (b) Simulation solutions
 - (c) Material balance equations
 - (d) Time delays
 - (e) The state-machine approach to programming
 - (f) An example program step-by-step
2. The Chemoreflex Control of Breathing (Steady State)
 - (a) System physiology

- (b) Chemoreflex feedback
 - (c) The central chemoreflex
 - (d) The peripheral chemoreflex
 - (e) The controlled system
 - (f) Graphical steady state model
 - (g) System stability
 - (h) Clinical Example (Mahamed et al., 2005)
3. Measuring the Chemoreflex Parameters
- (a) Rebreathing method
 - (b) Rebreathing results
 - (c) Parameter estimation (Duffin et al., 2000)
 - (d) Model assumptions
 - (e) - Chemoreflex model equations
4. CO_2 & O_2 carriage and Acid-Base
- (a) Physiology of CO_2 and O_2 carriage in blood
 - (b) O_2 dissociation curve models (Lobdell, 1981; Chiari et al., 1997; Longobardo et al., 2002)
 - (c) CO_2 carriage equation (Douglas et al., 1988).
 - (d) The Stewart approach to acid-base balance (Stewart, 1983)
 - (e) The Stewart-Watson equations. (Watson, 1999)
 - (f) CO_2 dissociation curve model.
 - (g) Modelling the steady state chemoreflex control of breathing and acid-base (Duffin, 2005).
 - (h) Clinical Example
5. The Chemoreflex Control of Breathing (Programming a Dynamic Model)
- (a) Overview
 - (b) Blood flow control
 - (c) Pulmonary ventilation
 - (d) Pulmonary gas exchange
 - (e) Tissue gas exchange
 - (f) Chemoreflexes

- (g) Determining default values
 - (h) Demonstration
6. Pulmonary Mechanics: the Campbell diagram
- (a) Introduction (Moscovici da Cruz et al., 2002)
 - (b) Simple conceptual models
 - (c) Lung and thoracic wall compliances
 - (d) Two compliance graphical model
 - (e) Airway resistance
 - (f) The Campbell diagram
 - (g) Work of Breathing
 - (h) Model equations
 - (i) Demonstration
7. Exercise: a modeling challenge
- (a) The human system as an endurance athlete (Noakes, 2006)
 - (b) The respiratory control system
 - (c) The response to exercise
 - (d) Exercise drives to breathe
 - (e) Central command and afferent feedback measurement (Bell, 2006)
 - (f) Sine wave exercise experiments (Wells et al., 2007)
 - (g) Vascular distension theory (Haouzi, 2006)
 - (h) The drive to breathe in heavy exercise (Mateika and Duffin, 1995)
 - (i) The possible role of carotid chemoreceptors

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Thomas Heldt

Cardiovascular System Modeling and Applications.

The topics covered are as follows:

1. Modeling the peripheral circulation (2 units). Taking a Guytonian viewpoint, I will introduce the concept of the venous return curve and how its shape can be modeled with a simple lumped-parameter model of the peripheral circulation. Particular attention will be paid to the concept of a Starling resistor to model the plateau of the venous return curve at low filling pressures. (2 units).
2. Modeling the heart-lung pumping unit. Similar to the above, I take again a Guytonian viewpoint to introduce the concept of the cardiac output curve. Particular attention will be paid to the non-linear nature of the pulmonary vasculature, the end-diastolic pressure-volume limit of the right and the left ventricles, and the fact that under normal circumstances, cardiac output is limited by the right heart. (2 units)
3. Modeling the short-term cardiovascular control mechanisms. Particular attention will be paid to modeling the action of the sympathetic and parasympathetic control of heart rate, vascular resistance, venous tone, and cardiac contractility. I will review the basic physiology of autonomic control and the time delays involved. I will also touch upon various implementations of these reflex mechanisms. (2 units)
4. Putting everything together. In the final two units allocated to me, I will give a survey of different types of models and control system implementations, their purposes, applications, pitfalls, and strengths.

Zbigniew Topor

Respiratory System Modeling and Applications

The topics covered are as follows:

1. The first topic will be dedicated to a historical review of most important models of the respiratory control system. For each model one characteristic feature will be emphasized to illustrate a gradual progress in our understanding of the respiratory control and translation of this knowledge into the computational realm
2. Development of a modern, Grodins' type model of the respiratory control system will be presented. Special attention will be given to plant description and derivation of controller's equations from a steady state experimental data.
3. In the third unit I will present a typical approach to model validation including selection of experimental data against which model's predictions will be tested and some aspects of sensitivity analysis.
4. System identification technique will be introduced as an alternative to the descriptive modeling based on time-delayed differential equations. I will demonstrate how one technique can benefit the other by providing necessary insights and assessing possible changes introduced into the system by pathology.
5. This unit will be dedicated to the stability analysis of the respiratory control system during sleep. I will introduce a concept of the chemosensitivity plane as an intuitive graphical method used to elucidate complex interaction between central and peripheral chemoreflex loops.
6. Model based analysis of sleep disordered breathing in congestive heart failure will be presented. I will demonstrate how the model and other introduced earlier techniques may be used to explain the mechanism of central sleep apnea in patients with congestive heart failure.
7. As a final topic I will discuss how expansion and refinement of the introduced earlier concept of the chemosensitivity plane may lead to the development of a new clinical treatment for central sleep apnea based on transient intervention.

(V) Long-term Control **and Applications**

Vito Starc

Long Term CVS Control

Introduction

This course is divided into two parts. The purpose of the first one is to introduce basic elements of the cardiovascular system and their properties, necessary for the mathematical description of the short-term and long-term regulation of blood pressure. The second part will be focused on the current understanding of the essential hypertension, describing possible pathophysiologic mechanisms using the basic elements from the first part, though with more phenomenological than mathematical description.

The topics covered are as follows:

1. Basic elements of the cardiovascular system and their properties;
 - (a) The heart as a pump, cardiac output and its determinants (preload, afterload, heart rate and contractility), description in the pressure volume diagram and in the flow pressure diagram.
 - (b) Vessels, vessel resistance, and compliance and its control: local (autoregulation, endothelium dependent vasodilatation) and central (nervous and endocrine).
 - (c) Valves
2. Modelling of the CVS elements (heart models, vessel models);
 - (a) how to relate geometric properties to the function (lumped parameter models, distributed models; cavity pressure-wall stress and cavity volume -wall strain relationships).
3. Closed CVS and its properties, distribution of fluid in the CVS (stressed volume, unstressed volume), contribution of the vascular system (venous return curves), and the heart (cardiac function curves) to the circulation.
4. Extracellular volume homeostasis,

- (a) Distribution of fluid between the extracellular (EC) and intracellular space (basic concepts of the transcellular fluid and electrolyte exchange), and between the EC and vascular space (transcapillary fluid exchange).
 - (b) The kidney and the role of renal sodium handling in the retention of body water, pressure natriuresis
5. Short term CVS control;
- (a) Cardiovascular reflexes (baroreflex and its influences).
 - (b) The role of the 'central command' as a baroreflex modulator in regulation of blood pressure, the concept set-point and its necessity in the blood pressure regulation.
 - (c) The 'central command' model based on the demand-supply mechanism.
6. Long term control
- (a) Endocrine control of the CVS: renin-angiotensin-aldosterone system, NO, endothelin.
 - (b) Mechanisms of sodium retention in the essential hypertension.
 - (c) Cardiovascular system remodeling as an adaptation to increased blood pressure and increased flow.
7. Essential hypertension: what do epidemiologic data and the related risk factors (diet factors: high sodium, low potassium and calcium intake), and genetic data suggest on possible mechanisms of the long term CVS regulation.

Workshop Presentation Titles and Topics

Speaker	Title
T. Arts	Patient-specific modeling of hemodynamics and cardiac mechanics using rules for adaptation to mechanical load
C. M. Brown	Mechanisms and assessment of cerebral autoregulation in health and disease
E. N. Bruce	Mechanisms and consequences of sleep apnea: insights from modeling of chemoreflex control of ventilation
S. Cavalcanti	Computer model for the analysis of pressure response to hemodialysis-induced hypovolemia
G. Chauvet	Working in Integrative Physiology (circulation): the PhysioMatica system
M. Chappell	Structural Identifiability Analysis: A Tool for Biomedical Systems Modelling
J. W. Clark	A Human Cardio-Respiratory Model: Applications in Care Medicine
R. Furlan	Relationship among respiratory activity, cardiovascular variables and their variability in health and disease: a focus on the neural autonomic control of cardiovascular system as assessed by power spectrum analysis methodologies and muscle sympathetic nerve activity direct recording
M. Gyllenberg	Topic: Validation of models for the cardiovascular and respiratory systems
P. Hannaert	SAPHIR - a multiscale, multiresolution modeling environment targeting blood pressure regulation and fluid homeostasis: current progress
V. Novak	Flow-pressure regulation in cerebrovascular disease

Speaker	Title
S. Ogoh	Static and dynamic modeling of the operating point of the arteial baroreflex
J. T. Ottesen	Modelling feedback mechanisms regulating the cardiovascular system- on the track of syncope induced by orthostatic stress.
M. Pennaccio	Multiscale Modeling and Numerical Methods for the Bioelectric Activity of the Heart
C. S. Poon	Homeostasis of exercise hyperpnea and optimal sensorimotor integration: The internal model paradigm
W. Wang	Cutaneous Microcirculation and Tissue Oxygenation

Workshop Presentation Abstracts

Theo Arts

Patient-specific modeling of hemodynamics and cardiac mechanics using rules for adaptation to mechanical load

In modeling the dynamics of heart and circulation patient-specifically, information about geometry, myofiber structure, tissue properties and hemodynamics is lacking. Measurement of these parameters is often cumbersome, and not realistic in clinical practice.

In heart and blood vessels, geometry and structure is known to adapt to mechanical load. In stead of performing detailed geometric measurements, we estimate geometry and structural parameters by using adaptation rules. Stresses and strains determine tissue orientation and geometry. Myocytes (heart) and smooth muscle cells (blood vessels) are 'glued' at the optimal working range within the passive matrix. Thus, adaptation rules for ventricles, atria and blood vessels appear quite similar, albeit parameters values are different for the different types of tissues.

In a trial, patient-specific modeling has been focused on non-invasive quantification of the complete pressure-volume loop of the left ventricle. For that purpose the CircAdapt model (Am J Physiol, 2005) has been developed, simulating whole heart and circulation dynamics.

In 11 patients with and without cardiac overload (4 hypertension, 3 mitral regurgitation, 4 control), we made patient-specific fits of whole circulation hemodynamics using CircAdapt modeling. To this aim, we identified a novel smart combination of measured 2-dimensional- (2DE) and Doppler echocardiographic parameters, and armcuff-measured blood pressure. Peak systolic (range 115-161 *mmHg*) and end-diastolic *LV* pressures (range 4-18 *mmHg*) agreed within $\pm 8\%$ and $\pm 15\%$ (sd) with the invasively measured pressures during cardiac catheterization in the same patients, respectively, showing the reliability of CircAdapt. With CircAdapt, systolic and diastolic myofiber stress could also be obtained (55 ± 14 kPa and 2.7 ± 1.2 kPa, respectively). In conclusion, measuring global hemodynamics, adaptation rules were used to determine the most likely cardiovascular geometry and hemodynamic status. Using non-invasive techniques only, dynamic pressures and flows and wall stresses and strains can be simulated realistically. Bringing measured information together in a comprehensive model renders more accurate assessment than the separate measurements would do.

Clive M. Brown

Mechanisms and assessment of cerebral autoregulation in health and disease.

The cerebral circulation is regulated in a complex manner by mechanisms that tend to oppose changes in cerebral perfusion pressure in order to maintain cerebral blood flow near constant. Neurogenic, myogenic, neurohormonal, metabolic and local factors probably contribute to cerebral autoregulation.

Variations in systemic and cerebral perfusion pressure represent a considerable challenge to cerebral autoregulation. For example during orthostatic stress there is a substantial increase in spontaneous fluctuations in blood pressure which must be dampened by the cerebral resistance vessels to maintain a near-constant cerebral blood flow. In situations where there are rapid changes in gravitational stresses, such as those encountered on board a high performance aircraft, there may be a deterioration in cerebral autoregulation, requiring specific protective measures to be taken by the pilot. Physical exercise represents another situation in which the ability to maintain a constant cerebral perfusion is challenged.

Several methods are available for assessing cerebral autoregulation in humans. To test the dynamics of cerebral autoregulation the immediate response of the cerebral blood vessels to a rapid change in blood pressure can be evaluated. Stimuli such as the Valsalva manoeuvre, rapid deflation of a leg cuff or squatting can be used to induce a rapid change in blood pressure. Cerebral autoregulation can also be determined in a more static situation by application of sustained orthostatic stress such as lower body negative pressure. Spectral analysis techniques can determine the extent of transfer of blood pressure oscillations onto cerebral blood flow.

This presentation will focus on introducing some of the concepts of cerebral autoregulation and various methods of its assessment. Pathophysiological conditions in which cerebral autoregulation are affected will be discussed. Finally some controversies in research into the regulation of cerebral blood flow will be addressed.

Eugene N. Bruce

**Mechanisms and Consequences of Sleep Apnea: Insights from
Modeling of Chemoreflex Control of Ventilation**

With regard to the genesis of periodic breathing and apneas, the use of physiologically-based computational models of chemoreflex control of breathing has provided general insights into the roles of specific mechanisms involved in the feedback control of ventilation. Our early studies utilized formal mathematical approaches to simplify complex models of this type so that their behaviors could more easily be predicted from various combinations of physiological and environmental parameters. Because it is difficult to apply such models to individual patients, we subsequently pursued a "black-box" approach in which the objective was to characterize the dynamic properties of the system for individual subjects, then relate these properties to physiological and environmental parameters. By stimulating ventilation through pseudorandom variations in inspired CO_2 (or O_2) level, we estimated input-output models, both open-loop (i. e., from end-tidal PCO_2 to ventilation) and closed-loop (i. e., from inspired CO_2 to ventilation). We have shown that the dynamic properties of the resulting models differ between normal subjects and both sleep apnea patients and heart failure patients. We also demonstrated in normal subjects that the closed-loop model does not change between wakefulness and quiet sleep, even though the gain of the openloop (or controller) model decreases. To explore the mechanistic basis for these findings using a detailed, physiologically-based, chemoreflex model, we felt it necessary to enhance the typical model of this type by improving the representation of O_2 transport and distribution beyond the usual, single lumped-compartment, approach. In our new model, brain and muscle tissue each comprise two subcompartments with intercompartmental diffusion and arterio-venous shunting, as well as O_2 binding to myoglobin in muscle. We are using this model to predict changes in brain tissue PO_2 during sleep apnea.

Silvio Cavalcanti

Computer model for the analysis of pressure response to hemodialysis-induced hypovolemia.

Acute hypotension is the most frequent intratreatment complication of chronic hemodialysis, with an incidence still reported to be around the 20-30% of treatments [1]. Apart from patient discomfort, acute hypotension also leads to a less effective treatment, especially in terms of body water removal. Sessions complicated by hypotension often end without achieving the correct dry body weight and the repetitive hypotensive episodes yield a chronic hydro-electrolytic derangement that promotes critical cardiovascular side-effects. Several factors have been ascribed to the pathogenesis of this complication. The first determinant of the hypotensive event is the hemodialysis-induced intravascular hypovolemia due to plasma-water ultrafiltration. To prevent excessive hypovolemic stress, the online monitoring of circulatory blood volume reduction is rapidly gaining acceptance in clinical practice [2]. However, for a given hypovolemic stress, a stable pressure response requires the adaptation of cardiovascular functions [1]. To characterize patient's reactivity to hypovolemia, a novel method, based on computer-model simulation has been proposed [3, 4, 5]. The model-based method constituted a quantitative framework useful for giving a coherent explanation of the experimental observations. In the lecture, the model will be presented and some relevant applications will be discussed.

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Michael J. Chappell

Structural Identifiability Analysis: A Tool for Biomedical Systems Modelling

For biomedical systems the mathematical models that are generated invariably include state variables that cannot be directly measured and associated model parameters, many of which may be unknown and which also cannot be measured. For such systems there is often limited access for inputs or perturbations. These limitations cause immense problems when investigating the existence of hidden pathways or attempting to estimate unknown parameters and this can severely hinder model validation. It is therefore highly desirable to have a formal approach to determine what additional inputs and/or measurements are necessary in order to reduce, or remove, these limitations and permit the derivation of models that can be used for practical purposes with greater confidence.

Structural identifiability arises in the inverse problem of inferring from the known, or assumed, properties of a biomedical or biological system a suitable model structure and estimates for the corresponding rate constants and other parameters. Structural identifiability analysis considers the uniqueness of the unknown model parameters from the input-output structure corresponding to proposed experiments to collect data for parameter estimation (under an assumption of the availability of perfect, noise-free data). This is an important, but often overlooked, theoretical prerequisite to experiment design, system identification and parameter estimation, since estimates for unidentifiable parameters are effectively meaningless. If parameter estimates are to be used to inform about intervention or inhibition strategies, or other critical decisions, then it is essential that the parameters be uniquely identifiable. Numerous techniques for performing a structural identifiability analysis on linear parametric models exist and this is a well-understood topic. In comparison, there are relatively few techniques available for nonlinear systems (the Taylor series approach, similarity transformation based approaches and differential algebra techniques) and significant computational problems can arise, even for relatively simple models.

In this talk an introduction to structural identifiability analysis will be provided demonstrating the application of the techniques available to both linear and nonlinear systems. This will culminate with an example where a structural identifiability analysis was successfully applied to a large-scale nonlinear mathematical model (43 state variables and 81 parameters) of a highly complex biomedical system.

Gilbert Chauvet

**Working in Integrative Physiology (circulation): the
PhysioMatica system.**

Abstract

The objective of this talk is to present a new integrative system, *PhysioMatic*TM, which leads to integrating any biological system of the organism. The cardiovascular system is presented as an element of this integrative software. It is considered as resulting from multiple cardiovascular subsystems (e.g. receptors, capillary beds), each one being described by a mathematical model in the framework of the MTIP (Mathematical theory of Integrative Physiology) already published.

The MTIP is based on: 1) a *representation*, constructed in terms of functional interactions. In this representation, the biological system is viewed as a set of hierarchical physiological functions, each level being defined by their time scale, which result in functional organization. Each function is represented in the structural organization in terms of space scales, and functional interactions propagate at each level through the structural units (e.g. neurons, receptors) that are points in abstract spaces of units. 2) a formalism, the S-propagators, that allows for the functional interactions to traverse levels of structural organization. An illustration is given with the central nervous system which shows the minimal number of couplings between different networks like neurons, astrocytes, capillaries and their connection with the cardiovascular system.

Finally, the computing system written in the MTIP framework appears as a time and space multiscale system that allows us to optimize the mathematical integration of large, non-linear and very complex dynamical systems.

John W. Clark

A Human Cardio-Respiratory Model: Applications in Critical Care Medicine

We present an overview of a composite human cardio-respiratory (C-R) model, integrating hemodynamics, whole-body and cerebral gas exchange, and baro- and chemoreceptor reflexes, and simulating the complex cardio-respiratory interactions occurring during the Valsalva maneuver, thigh-cuff deflation and apnea. Parameters of the modeled systemic and pulmonary circulatory subsystems have been adjusted to fit input impedance data. This provides an excellent description of the output loading conditions for the ejecting ventricles. The model can mimic inlet tricuspid and mitral flow velocity waveforms often used in diagnosing congestive heart failure using echocardiography. We describe an application in critical care medicine, namely left ventricular diastolic dysfunction (LVDD). Diagnosis of LVDD customarily uses a combination of invasive pressure recordings and non-invasive Doppler flow velocity recordings from the inlet valves of the heart. Three flow velocity patterns are of interest in LVDD: Incomplete Relaxation (IR) (evident during early rapid filling of the LV); the Restrictive (R) pattern (evident in late diastole particularly with atrial contraction); and the Pseudonormal (P-N) pattern (putatively a mixed pattern). The C-R model allows study of the inlet flow patterns of both normal and diseased left ventricles (LVDD), giving insight into the mechanisms underlying these differences. Our normal human C-R model serves as control, and simple changes in two parameters of the LV mechanics subsystem can mimic many features of LVDD. Assessing the effect of these changes within the context of the larger C-R model allows prediction of their more global effects manifested in the major symptoms of congestive heart failure: lowered cardiac output and mean arterial blood pressure, elevated heart rate, increased left atrial blood volume and pressure, pulmonary hypertension and altered A-V O_2 and CO_2 differences across different vascular beds (lung, brain, skeletal muscle).

Raffaello Furlan

Relationship among respiratory activity, cardiovascular variables and their variability in health and disease: a focus on the neural autonomic control of cardiovascular system as assessed by power spectrum analysis methodologies and muscle sympathetic nerve activity direct recording.

Abstract

From the functional standpoint, the cardiovascular neural control can be modeled as a dual feed-back system. Excitatory positive feed-back mechanisms depend on sympathetic afferents projecting to the neural cord and efferent fibers innervating, among the different organs, the heart and vessels. Inhibitory negative feed-back mechanisms rely on baroreceptors and vagal afferents and efferent neural fibers connecting the bulbar structures with the heart. A further crucial modulation is exerted by cortical structures and respiratory activity. As a result of the instantaneous relationship between excitatory sympathetic and inhibitory vagal influences on the sinoatrial node activity, the heart period oscillates on a beat by beat basis. Similarly, arterial pressure is characterized by spontaneous, neurally mediated, oscillations with a periodicity of 10 seconds.

1. The differential control of the mean value of heart rate, blood pressure and muscle sympathetic nerve activity (MSNA) and the frequency content of their spontaneous variability. Physiological conditions characterized by a sympathetic excitation such as the morning wake up or the gravitational stimulation, mimicked by the lower body negative pressure, will be considered. Neurally mediated syncope, baroreceptor failure and Parkinson's disease will be the examples showing that an alteration of the oscillatory pattern of the cardiovascular variables may precede the changes of the mean values of such variables. This peculiar pattern may result in valuable clinical information. Univariate and bivariate power spectrum analyses of RR interval, arterial pressure, MSNA and respiratory activity will provide a useful tool to explore such a complexity.
2. The study of the laterality of the post-ganglionic sympathetic nerve discharge activity at rest will emphasize the crucial role played by respiratory activity in modulating the efferent sympathetic vasomotor control. Concomitant right and left MSNA recordings, obtained from the peroneal nerves of healthy volunteers by microneurography technique, enabled to highlight a right prevalence of the normalized amplitude of sympathetic burst. Interestingly enough, this was observed in spite of

similarities in the bursts rate of right and left MSNA recordings. In order to avoid the confounding effects of different breathing frequencies on MSNA, we paced respiratory frequency at 0.25 *Hz* and referred all experimental conditions to controlled breathing. Finally, given the crucial role played by arterial carotid baroreceptors in modulating neural sympathetic discharge activity and its variability, we also evaluated whether a unilateral stimulation of these structures might result in any sided prevalence of MSNA. To this aim, single-sided and bilateral 0.1 *Hz* sinusoidal neck suction procedures were used to rhythmically unload carotid baroreceptors.

Patrick Hannaert

**SAPHIR - a multiscale, multiresolution modeling environment
targeting blood pressure regulation and fluid homeostasis :
current progress**

The project SAPHIR -a Systems Approach for PHysiological Integration of Renal, cardiac, and respiratory functions- aims at developing an open-source, and interactive modeling environment of human and animal cardiovascular and respiratory physiology. Using state-of-the-art multiscale simulation methods, it is based on modularity and hierarchical paradigms. As a first step, our model targets blood pressure and body fluid homeostasis, together with respiratory regulations and influences. To this end, the basic "core model" includes lumped-parameter inputoutput descriptions of relevant organs as modules, i.e., heart, vasculature, intra- and extracellular spaces, lungs, kidneys, and muscles.

Such an approach will allow for (i) selected extensions of the model (e.g., addition of a pancreas module and regulation of blood glucose) and (ii) assessment of system-level consequences of local perturbations (e.g., polymorphism, by substituting a block by a more detailed, mechanistic model). One important goal is to keep the model compact enough to insure fast execution time (in view of eventual use in clinical settings), yet to allow fairly detailed submodules (to maintain system-integrated feedback loops).

Progress is presented of our current re-implementations of two legacy models that treated overall regulation of blood pressure (Guyton et al., 1972), and fluid regulation (Ikeda et al., 1979). As modeling/simulation environments, Berkeley-Madonna^ä was used for Ikeda's model (JF, PB); Fortran (SRT, RW), Matlab/Simulink[©](PH, FG) and the M2SL C++ software library (developped by two of us, AH & VL), were used for Guyton's model.

Micol Pennacchio

Multiscale Modeling and Numerical Methods for the Bioelectric Activity of the Heart

An overview of the mathematical models and numerical methods generally used to simulate the heart bioelectrical activity is presented. Dealing with a periodic cellular assembling of the tissue we start considering the mathematical model at the microscopic level. Then, a rigorous derivation of a macroscopic model called bidomain is obtained from the microscopic properties of the tissue by using classical mathematical tools. The bidomain model consists in a degenerate reaction-diffusion system modeling the intra- and extracellular potentials of the anisotropic cardiac tissue. This system is coupled through the nonlinear reaction term with a stiff system of ordinary differential equations describing the ionic currents through the cellular membrane. The bidomain is the most complete model for the cardiac bioelectrical activity but its numerical resolution in a 3-dimensional geometry that takes into account the main features of the myocardium is characterized by numerical difficulties and complexity. This is due to the interaction of different scales in space and time hence large scale simulations are computationally intensive tasks.

Numerical methods generally used to solve efficiently the bidomain model will be presented and discussed.

Vera Novak

Flow-pressure regulation in cerebrovascular disease

Stroke ranks third among the leading causes of death and is the leading cause of long-term disability in older adults. Adequate perfusion of regions surrounding the ischemic areas is essential for brain tissue recovery and the clinical outcomes after ischemic stroke. Dynamic cerebral autoregulation (dCA) reflects the ability to restore cerebral blood flow (CBF) in the face of sudden changes of perfusion pressure and increased metabolic demands. The efficacy of dCA is critically important during acute ischemia for maintenance of blood flow to ischemic areas and for avoidance of excessive hyperperfusion. In the absence of dCA, elevations of blood pressure (BP) may increase blood volume and lead to brain swelling, while low BP may promote infarct growth and long-term tissue damage.

Autoregulatory mechanisms rapidly adapt perfusion to accommodate variations in intracranial pressure and BP. As a result, beat-to-beat BP and BFV signals are nonstationary and their relationship is nonlinear under clinical conditions. Transcranial Doppler enables assessment of dCA from spontaneous BP and blood flow velocity (BFV) fluctuations and during interventions inducing sudden BP changes induced by the Valsalva maneuver, head-up tilt and sit-to-stand test. Conventional approaches typically model autoregulation using mathematical models that govern the dynamics of BP (as an input to the system) and CBF (as output) that can be approximated by a linear, time-invariant system. Fourier transform-based transfer function and coherence are used analytically to represent the relationship between the input BP and the output BFV. These techniques assume a linear relationship between two stationary signals that can only be met under very limited conditions, where these analyses have shown a significant phase lead of cerebral BFV with respect to systemic BP. These unrealistic requirements of signal properties may significantly limit their utility, even if direct measurements of CBF and intracranial pressure are made. Recently developed nonlinear approach called multimodal pressure-flow analysis (MMPF), to detect instantaneous changes in BP-BFV regulation. Because the MMPF technique does not assume stationarity and linearity of the signals and provides instantaneous BP-BFV phase shift, this technology is suitable for evaluation of autoregulation using the Valsalva maneuver and for continuous monitoring of dCA from spontaneous BP-BFV fluctuations. Therefore, novel modeling approaches that would allow prediction of unknown variables (i.e. intracranial pressure) are needed to improve assessment of autoregulation in medical diagnostics.

Shigehiko Ogoh**Static and dynamic modeling of the operating point of the arterial baroreflex.**

Arterial baroreflex operates by reflexively altering autonomic neural outflow to adjust heart rate, stroke volume, and total vascular conductance. Their function has been studied in a wide range of animal models using several invasive and direct techniques such as: i) surgical isolation of arterial vessels housing baroreceptor populations; ii) direct electrical stimulation of baroreceptor afferent fibers; or iii) surgical denervation of baroreceptor afferent fibers. This animal research has facilitated a more complete understanding of the mechanisms by which both the carotid and aortic baroreceptors modulate cardiovascular hemodynamics at rest and during exercise. However, for obvious ethical and technical reasons, implementation of these experimental strategies employed in animal research is not feasible in humans. As a result, less invasive techniques have been utilized to perturb the baroreceptors in an attempt to evaluate baroreflex function. The methodologies used in human studies will be presented in this lecture and include the infusion of vasoactive drugs (i.e., the Oxford technique), the variable pressure neck collar, and several dynamic or spontaneous measures of arterial baroreflex sensitivity. Most of these methodologies use simple linear regression or linear dynamic analyses models of input and output responses. However, the variable pressure neck collar technique utilizes logistic function modeling and is especially significant in identifying baroreflex resetting. The primary focus of this lecture will be on the methodological interpretation of each analysis technique and the advantage or disadvantage of each technique for evaluating the physiological response to the arterial baroreflex.

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Johnney T. Ottesen**Modelling feedback mechanisms regulating the cardiovascular system - on the track of syncope induced by orthostatic stress.****Abstract**

During postural change in sit-to-stand and head-up-tilt experiments blood is first drawn by gravity from the upper body regions toward the lower body regions causing an immediately decrease in central pressure. The drop in arterial pressure is rapidly counteracted by various feedback mechanisms regulating the blood pressure resulting in the reestablishment of the normal blood pressure. The main feedback mechanism in this regulation is believed to be the short term *baroreceptor feedback mechanism* controlling heart rate and vein compliances among others things.

The overall function of the baroreceptor feedback mechanism is roughly known. However, the underlying bio-chemical mechanistic processes are not fully understood and they are not easily investigated in vivo for ethical reasons. By a methodology called the mathematical microscope a mathematical model is developed making the invisible visible and the inaccessible accessible, making an *in silico* investigation of the feedback mechanism possible. In our case the methodology or rather strategy of *the mathematical microscope* will illustrate how access to the otherwise inaccessible separate links of the baroreceptor feedback chain regulating the heart rate can be obtained. Hereby insight into an individuals control system like a "fingerprint" may be obtained which may be of relevance for the treatment of several diseases such as hypertension.

Syncope is the medical term for temporary loss of consciousness, described as "fainting" or "passing out". It is usually related to temporary insufficient blood flow to the brain and in our case caused by a sudden drop in blood pressure due to sit-to-stand and head-up-tilt. Injure as a result of syncope is a common problem, accounting for 3 percent of emergency room visits and 6 percent of hospital admissions. Syncope is a sudden incident believed by some to be the result of a crash in or breakdown of the control system. In contrast to the heart rate regulation a unifying description of pressure changes during sit-to-stand and head-up-tilt shows that multiple simultaneous control mechanisms may be important to understand both sit-to-stand and head-up-tilt experiments. This complex multi-input multi-output control system will be discussed in the talk.

Chi-Sang Poon**Homeostasis of exercise hyperpnea and optimal sensorimotor integration: The internal model paradigm.**

Traditional control theories are built upon a rich mathematical foundation which provides rigorous solutions for specific control problems. However, many complex control problems in real life do not lend themselves to exact mathematical or computational solutions. The human brain is faced with many challenging control problems where modern robotics pales by comparison. This talk will cover research work done at MIT on adaptive optimal control strategies employed by the brain. Mathematical modeling of various biological processes leads to new insights for the intelligent estimation, identification and control of nonlinear stochastic or chaotic dynamical systems.

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Wen Wang

Cutaneous Microcirculation and Tissue Oxygenation

The cutaneous microcirculation has a unique anatomical arrangement that accommodates different and sometimes conflicting functions - the supply of nutrients, clearance of waste products and control of heat exchange. This paper concerns with the transport of oxygen to tissues of the papillary layer of the dermis and the epidermis. This is the region between the sub-papillary plexus and the surface of the skin.

The first part of the talk is on in vivo measurements of oxygen partial pressure (pO_2) in dermal papillae of healthy human subjects using oxygen-sensitive micro-electrodes (tip diameter $\sim 5m$) that were developed in house. When the skin is covered with paraffin oil, pO_2 increases with depth from values close to zero at the surface to about $40 - 50 mmHg$ close to the sub-papillary plexus. The gradient appears to be steepest through the outer $30mm$ that corresponds to the epidermis. When microvascular blood flow in the immediate vicinity of the tissue is occluded, pO_2 falls exponentially to a value $10 - 20 mmHg$ below its pre-existing value. From this, it would appear that the oxygen supply to the epidermis is vulnerable to very local reductions in perfusion. Our observation that pO_2 increases with depth would be predicted if all oxygen is delivered to the papillary dermis and epidermis from the sub-papillary plexus. Under physiological conditions, however, oxygen can enter the outermost layers of the skin from the atmosphere to meet the needs of the epidermis.

The second part of the talk is on theoretical modelling. A 3-dimensional multilayered model based on the anatomical arrangement of upper layers of the skin has been developed, which includes the stratum corneum, the germinal layer, dermal papilla, papillary loop, and subpapillary plexus. Parameters, such as oxygen diffusivity, solubility, and consumption rate, took different values in different layers, reflecting heterogeneity in tissue properties. Transport of oxygen in the blood and in tissues was considered under different flow rates and skin surface boundary conditions. pO_2 distribution was calculated using values for parameters based on measurements. The model revealed a number of results:

1. Diffusion of oxygen from the air into the skin accounted for approximately 10% of the oxygen consumption in superficial layers of the skin under normal skin conditions. This supply of O_2 , however, was restricted to superficial regions of the epidermis, due to the low O_2 diffusivity and solubility in the stratum corneum, and high oxygen consumption in the germinal layer.
2. Papillary loops served for rapid delivery of the oxygen to the germinal

layer, where intensive oxygen consumption existed. Changes in the blood flow rate there affected the pO_2 distribution in the dermal papilla.

3. Subpapillary plexus was the main source of the oxygen supply to the superficial layers of the skin, and accounted for approximately two-thirds of the total oxygen supply there under normal skin surface and blood flow conditions.
4. There were regions in the epidermis, where tissue pO_2 was below or very close to the critical oxygen partial pressure. Cells in these regions were either inactive or under constant threat of oxygen starvation when fluctuations in blood circulation occurred.

The study demonstrates the need of close interaction between experimental and theoretical studies in biomedical engineering.

Contributing Talks

Contributing talks will be 25 minutes.

Contributing Presenters

- Radu Cascaval (University of Colorado Springs)
- Nandu Goswami (Medical University of Graz)
- Borat Kirn (University of Maastricht)
- Giannessi Massimo (University of Bologna)
- Janos Turi (University of Texas at Dallas)

Abstracts of contributor talks

Radu C. Cascaval

**Modeling the peripheral circulation in the human arterial system
and nonlinear waves in fractal networks.**

Abstract

We describe a new time domain analysis of the pressure waves in the peripheral circulation, using a nonlinear model for wave propagation along trees. The key ingredient is the evidence that dispersion (amplitude-dependent velocity) of the pressure waves plays an important role, in particular in the formation and propagation of the reflected waves, a phenomenon not captured by linear models. The timing of the reflections as well as the different speeds of the reflected waves are particularly relevant in view of the complex geometry of the peripheral circulation. The advantage of the time domain analysis, compared with linear impedance models, is that it applies for non-periodic flows and also allows the direct implementation of accurate time-dependent controls, such as those exhibited in the control of the peripheral resistance. We will also illustrate the impact of these nonlinear dispersive models on the dynamics of pressure and flow rates in the entire human arterial system.

Nandu Goswami

Neuroendocrine responses to extreme Cardiovascular stress.

Abstract

Extreme stress reveals regulatory features of physiological systems that otherwise might not be observable. One such example is upright standing (orthostasis) in an accelerational environment (gravity) that can lead to critical levels of cerebral blood flow and loss of consciousness (syncope). The physical changes exerted upon the blood- pressure and volume drop in the upper body parts are amongst them- entail nervous and hormonal (i.e., neuroendocrine) effects. Orthostatic stress can be experimentally simulated by the application of Lower Body Negative Pressure (LBNP) and passive Head up Tilt (HUT). During these stresses, there is blood pooling in the lower extremities and depending on the level and duration of the suction several neuroendocrine responses are elicited. Notably there is an increase in heart rate or an increase in total peripheral resistance or both. These compensatory responses aim to ensure that the mean arterial blood pressure and cerebral blood flow is maintained. Failure to do this leads to sudden sympathetic withdrawal characterized by vasodilatation in the peripheries and bradycardia as well as reduced cerebral blood flow and eventual fainting (vasovagal syncope). This presentation summarises types of cardiovascular stressors, particularly orthostatic, defines the exact protocols used to induce experimental hypovolemia, and outlines neuroendocrine responses. It then elaborates in detail how this procedure is done in the laboratory and finally, concludes with some results which clearly summarise the above mentioned responses (from baseline, tilting, LBNP application, syncope and return to baseline). This has wide range of clinical applications ranging from aviation and spaceflight medicine to clinical care of patients.

Giannessi Massimo

A comprehensive Cerebrovascular Simulation Model for Teaching and Research

The mathematical relationships between cerebral perfusion pressure (CPP), intracranial pressure (ICP) and cerebral blood flow (CBF) as well as the autoregulatory control of these quantities by the normal brain, have been well described [1]. However, the alterations occurring in these quantities in pathological conditions and their complex non-linear relations are difficult to be understood in simple qualitative terms; for this reason, their analysis can benefit from the use of mathematical models.

In past years, we developed a comprehensive mathematical model of the cerebral circulation, which included many different aspects of patho-physiological relevance: cerebral autoregulation, cerebrospinal fluid (CSF) circulation, CO₂ reactivity, intracranial compliance, ICP dynamics and venous collapsibility. With that model, we were able to simulate several physiological phenomena and clinical results on head injured patients [2].

Results show that the model is able to simulate autoregulation to arterial pressure changes and CO₂ reactivity very well, and to predict intracranial instability (plateau waves) in patients with reduced intracranial elasticity and reduced CSF outflow. Moreover, the model is able to reproduce the measured time pattern of middle cerebral artery velocity and ICP in different head injured patients through a best fitting procedure, and using values of parameters which lie within the range reported in the patho-physiological literature.

The previous model, however, included just a single blood pathway inside the brain, i.e., it assumed no difference in cerebral hemodynamic among the different brain regions. For this reason, that model was not able to simulate conditions characterized by regional differences in brain circulation, such as those occurring during occlusion or stenosis of an intracranial vessel, during ischemia in a brain territory, or as a consequence of regional differences in metabolism. In these conditions, the situation is made particularly complex by two phenomena: CBF regulation mechanisms work in a different way on the individual districts, depending on the local value of blood flow; the different districts communicate upstream via the Circle of Willis, and, although to a lesser extent, via downstream anatomical collaterals.

So we developed a mathematical model of cerebral hemodynamics, with separate regulation of multiple brain regions. The main sectors included in the model are: the Circle of Willis, the hemodynamic circulation in the six districts perfused by the cerebral arteries, venous return with collapsible veins, CSF circulation, and intracranial elasticity. Furthermore, each cerebral district is independently regulated following changes in CPP and CO₂ tension. This model can be used to analyze cerebral hemodynamics during unilateral stenosis or occlusion of an internal carotid artery (ICA), as well as to assess the compensatory role of the Circle of Willis and of cerebrovascular regulatory mechanisms. Results show that, in normal subjects, the action of local blood flow regulation mechanisms and compensation by the Circle of Willis ensure adequate ipsilateral blood flow even in the presence of total unilateral ICA occlusion. However, a steal phenomenon is observed (i.e., a decrease of blood flow in the ipsilateral region) following hypercapnia. Sensitivity analysis on the calibre of the communicating arteries reveals that the anterior communicating artery plays a pivotal role in ensuring blood flow in the ipsilateral side during ICA stenosis. The model may have important clinical and educational applications, allowing assessment of blood perfusion to different

brain regions in various patho-physiological cases.

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Borut Kirn

**Model-Based linear decomposition of myocardial strains:
activation time and contractility mapping**

Abstract

Patients with severe conduction disorders and heart failure are treated with cardiac resynchronization therapy (CRT), in order to improve systolic left ventricular (LV) function. However, a considerable part of these patients does not respond to the therapy. Standard selection criteria are based upon indices of mechanical asynchrony, e.g., septum-to-posterior wall motion delay, and interventricular and intraventricular mechanical asynchrony. They are all aiming to quantify asynchrony of activation within the LV wall. However, systolic function of the left ventricle deteriorates not only due to asynchronous activation but due to a combination of asynchronous activation and regionally decreased contractility. Therefore, accounting for regionally decreased contractility in the criteria as well may improve the selection of responders.

As an initial step towards assessing the influence of incorporating contractility in the patient selection, we developed a model based technique to reveal simultaneously the maps of both asynchrony and regional decreased contractility from measured strain signals.

We found that the measured strain signals in asynchronous contracting left ventricle can be described with the extended one fibre model. In this model, the representative contractile fibre has been replaced by a series of fibre segments, each having its own activation time and contractility. Applying the model in reverse, the measured maps of regional circumferential strain as a function of time were converted to maps of activation time and contractility using linear decomposition with two representative components. Obtained maps of activation time and contractility were in agreement with clinical diagnosis of left bundle branch block and ischemia in model animals and patients. Presented technique is more robust and generates less noise than conventional also non-invasive techniques for mapping activation time.

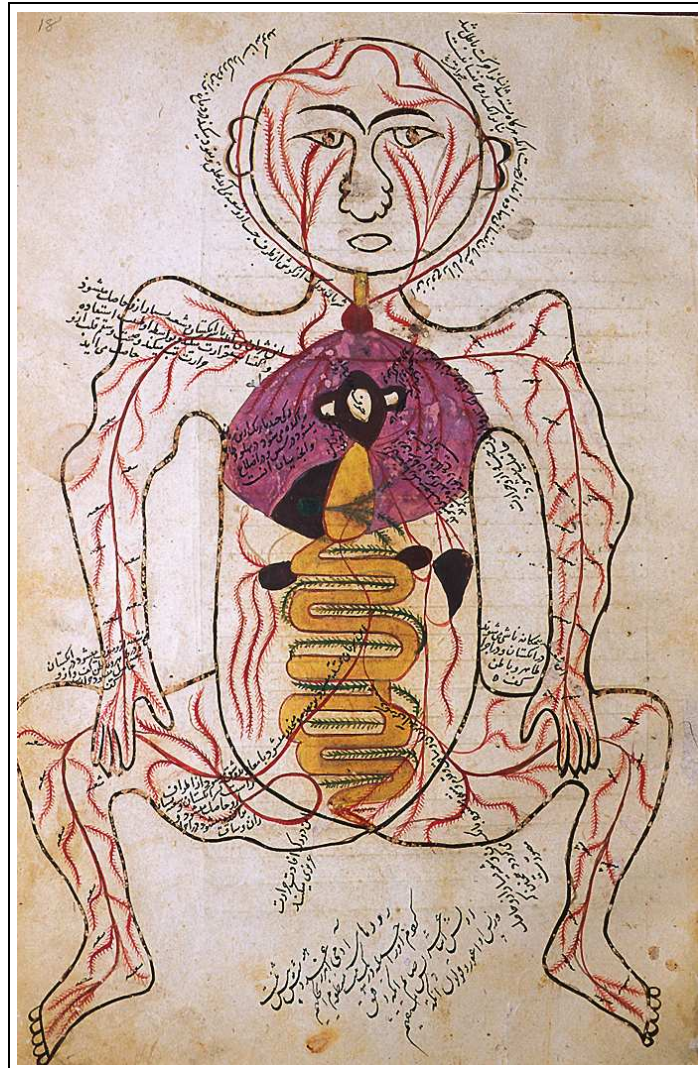
Janos Turi

Parameter Identification in a Respiratory Control System Model

Abstract

In this talk we study parameter identification issues by computational means for a set of nonlinear delay equations which have been proposed to model

the dynamics of a simplified version of the respiratory control system. We design specific inputs for our system to produce "information rich" output data, needed to determine values of unknown parameters. We also consider the effects of noisy measurements in the identification process. Several case studies are included .



Ibn Sina (980-1037), is known in the West as Avicenna. He wrote the famous medical work "The Canon of Medicine", which is surely one of a handful of books that shaped the history of medicine. The Canon is seen to be the definitive codification of all Greco-Arabic Medicine, and became the basis for half of the medical curriculum of European Universities in the latter part of the 15th century. Not only did Avicenna succeed in organizing existing knowledge of the time with the Canon, but Avicenna's accomplishments also included the identification and description of meningitis, the study of the manner of spread of epidemics and the contagious aspect of the spread of tuberculosis.

NOTES