Workshop

on

Cardiovascular, Respiratory and Metabolic Control Modeling

organized by

Special Research Center for Optimization and Control

and

Departments of Mathematics and Physiology

University of Graz

Graz (Austria), June 11 - 14, 2003

MACSI-net event "Cardio Point" embedded

Special Research Center "Optimization and Control"

The special research center (SRC F-003) "Optimization and Control" 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 and thus contributing significantly to the solution of problems which are of concern to our society. The interdisciplinary efforts within the SRC lead to innovative solutions to solve such problems. The SRC also provides the necessary scientific environment and training for young researchers to cooperate in similar research projects. The SRC F-003 is supported by the Austrian Science Fund. The following subprojects are organizing this workshop.

- F307: Infinite dimensional systems and approximation.
- F310: Optimization of a mathematical model for fundamental control mechanisms in the cardiovascular system.
- F312: Identification of models of the adaptation of the heart function to the demands of the cardiovascular and cardiorespiratory system.
- F323: Optimization of Fluid Balance: Blood pressure control and clinic applications such as hemodialysis.

Workshop Organizers

Thomas Kenner – Daniel Schneditz (Dept. Physiology)
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SFB Workshop Support

Inge Puntigam – David Auerbach – Mostafa Bachar – Jürgen Wimmer

Presenters

- Ovide Arino (Centre de Recherche IRD, France)
- Alona Ben-Tal (University of Auckland, New Zealand)
- Maja Bračič Lotrič (University of Ljubljana, Slovenia)
- Silvio Cavalcanti (University of Bologna, Italy)
- Martin Fink (University of Graz, Austria)
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- Richard Hughson (University of Waterloo, Canada)
- Michael Levine (Clinical Physics Group, St Bartholomews Hosp. London, United Kingdom)
- John K. Li (Rutgers University, U.S.A.)
- Frantisek Marsik (Institute of Thermomechanics ASCR, Czech Republic)
- Peter V.E. McClintock (University of Lancaster, United Kingdom)
- Malte Meesmann (Juliusspital, Wuerzburg, Germany)
- Ronney Panerai (University of Leicester, United Kingdom)
- Gernot Plank (University of Graz, Austria)
- Marco di Rienzo (Fondazione Don C. Gnocchi, Milano, Italy)
- Peter Robbins (Oxford University, United Kingdom)
- Maria Pia Saccomani (University of Padua, Italy)
- Gerhard Stark (University of Graz, Austria)
- Vito Starc (University of Ljubljana, Slovenia)
- Aneta Stefanovska (University of Ljubljana, Slovenia)
- Merryn Tawhai (University of Auckland, New Zealand)
- Karl Thomaseth (Institute of Biomedical Engineering, National Research Council, Italy)
- Hien Tran (North Carolina State University, U.S.A.)

- Jacek Waniewski (Intitute of Biocybernetics and Biomedical Engineering, Polish Academy of Sciences, Poland)
- Ewald Weibel (University of Berne, Switzerland)
- Nico Westerhof (Free University Amsterdam, Netherlands)

MACSI-net event "Cardio Point" presenters

- Frédèric Wilquem Numeca (Brussels, Belgium)
- Kai U. Markus (Technical University, Aachen, Germany)
- Michael Mlynski (CWA GmbH, Aachen, Germany)
- Marc Thiriet (Universite Pierre et Marie Curie, Paris, France)
- Paolo Zunino (Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland)

MACSI-net (MAthematics, Computing and Simulation for Industry) is set up as a network to promote the use of mathematical models, computing, and simulation in industry and where both enterprises and university institutions make connections and co-operate to solve problems, to their mutual benefit. In particular the network focuses on strategies to increase the interaction between industry and academia in order to: help industry with advanced mathematical and computational tools and to increase awareness in academia of industrial needs. The network promotes activites such as **Cardio Point** which is embedded in this workshop.

The Cardio Point Event consists of a series of presentations on Thursday and a **round table discussion** which will be held on Friday. The aim of the discussion is to collect ideas for collaborative research as well as to initiate collaborations in the field of cardiac and cardiovascular modelling preferably between academic and industrial partners.

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Auditors

Markus Baumann (co-presenter)
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Wednesday Workshop Schedule

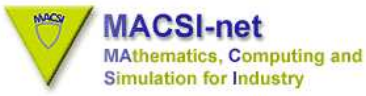
Time	Talk
7:15-8:15	**Breakfast**
8:30	**N. Westerhof** Ventriculo-arterial coupling determines pressure and flow
9:15	**A. Stefanovska** Causal relations between cardio, respiratory and neural oscillations
10:00	**Break**
10:30	**M. Meesmann** Modeling the blood-pressure response to ventricular premature beats
11:15	**G. Stark** Modeling in cardiovascular medicine: The clinicians point of view
12:00-12:45	**Lunch**
13:30	**E. Weibel** Modeling design and functional integration in the oxygen and fuel pathways to working muscle
14:15	**J.K. Li** Modeling Myocardial Stunning
15:00	**Break**
15:30	**F. Marsik** Numerical model of human cardiovascular system-Korotkoff's sound simulation
17:00-17:45	**Dinner**
18:15-22:00	**Outing for Graz tour**

Thursday Workshop Schedule: Morning Session

Time	Talk
7:00-8:00	**Breakfast**
8:00	**M. Saccomani** Some results on parameter identification of nonlinear systems
8:45	**O. Arino** Delay differential model of intra-venous glucose dynamics
9:30	**Break**
10:00	**K. Thomaseth** Modeling and analysis of glucose and free fatty acids kinetics during glucose tolerance tests
10:45	**A. de Gaetano** A model of the euglycemic hyperinsulinemic clamp
12:00-12:45	**Lunch**

Thursday Workshop Schedule: Afternoon Session

Cardio Point



Time	Talk
13:15	**MACSI-net event: CARDIO POINT** Welcome
13:30	**F. Wilquem** Modeling local hemodynamics through By-Pass Grafts out of the heart area: a sample of a collaborative framework
14:05	**K.U. Markus** Identification of problems in automatic heart signal analysis
14:40	**M. Mlynski** Malfunction diagnosis for implantable devices: Discussion of different aggregation technique
15:10	**Break**
15:40	**P. Zunino** Mathematical modelling of mass transfer in the vascular system and related clinical applications
16:15	**M. Thiriet** Image-based flow computations in saccular aneurisms, using various image processing techniques
16:50	**Cardio point** Discussion
17:15 -18:00	**Dinner**
18:15	**Bus leaves for Schloss Eggenberg**

Friday Workshop Schedule

Time	Talk
7:15-8:15	**Breakfast**
8:30	**M. Tawhai** From cell to integrated whole organ: computational modeling for the Lung Physiome
9:15	**P. Robbins** Simple models for physiological description and hypothesis testing in respiratory physiology
10:00	**Break**
10:30	**M. Levine** Mathematical models in the study of respiration
11:15	**A. Ben.Tal** Gas exchangers and their interactions with the heart
12:00-12:45	**Lunch**
13:30	**M. di Rienzo** Baroreflex linear and nonlinear contribution to blood pressure-heart rate coupling during spontaneous behavior
14:15	**P.V.E. McClintock** Noisy oscillatory dynamics of the cardiovascular system
15:00	**Break**
15:30	**A. Stefanovska** Inferring parameters for the coupled oscillators of the cardiovascular system
16:10	**Cardio Point** Round Table Discussion
17:30	**bus leaves for Reception at LH Styria**

Saturday Workshop Schedule

Time	Talk
7:15-8:15	**Breakfast**
8:30	**H.T. Tran** Modeling cerebral blood flow control during posture change from sitting to standing
9:15	**R. Panerai** Cerebral blood flow autoregulation:are we barking at the wrong tree?
10:00	**Break**
10:30	**R.L. Hughson** Searching for the vascular component of the arterial baroreflex
11:15	**V. Starc** Long term regulation of the mean arterial pressure based on the metabolic activity of the brain: a mathematical model simulation
12:00-12:45	**Lunch**
14:00	**J. Waniewski** A mathematical model of local vasodilatation during peritoneal dialysis
14:45	**G. Plank** The shock energy necessary for successful defibrillation depends on the degree of disorganization of the reentrant activation pattern
15:30	**Break**
16:00	**S. Cavalcanti** Model-based analysis of pressure response to hemodialysis-induced hypovolemia
16:45	**M. Fink** Modeling the human cardiovascular-respiratory control system: an optimal control application to orthostatic stress
18:00	**Dinner**
19:00	**Outing**

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Delay Differential model of Intra-Venous Glucose Dynamics

A model of the variations of the glucose after intra-venous injection of a bolus of glucose is proposed. The model is a nonlinear system of delay differential equations, of the first order, with infinite delay both in the glucose and the insulin. A mathematical analysis of the model was performed and is briefly commented upon here, together with some other models in the literature.

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Gas exchangers and their interactions with the heart

Complex interactions exist between the respiratory system and the cardiac output in humans. Some examples of such interactions are Cheyne-Stokes respiration (a sleep-disordered breathing associated with heart failure), Respiratory Sinus Arrhythmia (changes in heart rate pattern as a result of paced respiration) and synchronization between ventilation rate and heart rate. These interactions provide the motivation for the study presented in this talk.

There are different sources for the interactions between the heart and the lung. The heart and the lung are coupled mechanically and are both affected by the expansion and contraction of the thoracic cage. The control centers of the heart and the lung are located in close proximity in the brain and are both sensitive to changes in the levels of oxygen and carbon dioxide in the blood. Respiration and cardiac output are also coupled in the gas exchange process itself.

This talk is concerned with the gas exchange process. A series of simplified models for lung function and gas exchange will be presented. These models

take two main features in mammalian lungs into account: the facts that the lungs are flexible and can hold air. The models can be regarded as the controlled system (plant) and can be used to study the relationship between certain inputs (e.g., heart rate and ventilation rate) and certain outputs (e.g., partial pressures of oxygen and carbon dioxide in the blood).

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Model-based analysis of pressure response to hemodialysis-induced hypovolemia

In spite of the recent technological advances in the artificial kidney, symptomatic arterial hypotension and related cardiovascular instability are still the most frequent intratreatment complications of hemodialysis. Impaired preservation of plasma volume and inadequate regulation of cardiovascular functions are important factors in the loss of blood pressure control during hemodialysis [1]. To prevent excessive circulatory stress, on-line monitoring of blood volume is rapidly gaining acceptance in clinical practice [2]. Simultaneous monitoring of changes in circulating blood volume and arterial pressure allows the pressure response to hypovolemia to be characterized. Recently, we proposed a new approach, based on computer simulation, to extract from the pressure response to hemodialysis-induced hypovolemia, a small set of parameters representative of patient cardiovascular reactivity [3-5].

Currently, we are using this approach to investigate the hypothesis that parameters representative of a patient's capacity for cardiovascular regulation can be affected by exposure to acetate during hemodialysis. Acetate is a powerful stimulus of nitric oxide synthesis (NOS) and nitric oxide regulates the adrenergic and cholinergic responses to hypovolemia. To test the hypothesis that acetate inhibits β-adrenergic response, mean arterial pressure (MAP), heart rate (HR) and changes in relative blood volume (BV) were recorded in 12 subjects during 2 sessions of conventional bicarbonate dialysis (BD, dialysate containing 3 mEq/L acetate) and 2 sessions of acetate-free

biofiltration (AFB). A hemodialysis machine employing blood volume control (*Hemocontrol*™, Hospal, Italy) was used to produce the same BV changes in all four sessions. Data collected in each session were analyzed with the simulation model and model parameters related to the adrenergic response were identified. Model-based computer analysis revealed a lower increase in peripheral resistance (9 % BD vs 16 % AFB $p < 0.05$) and greater decrease in stroke volume (20 % BD vs 10 % AFB, $p < 0.01$) in sessions with acetate-containing dialysate.

References

[1] Daugirdas J.T. (1991): "Dialysis hypotension: a hemodynamic analysis", Kidney Int., Vol. 39, pp. 233-246

[2] Steuer RR, Leypoldt JK, Cheung AK, Harris DH, Conis JM. (1994): "Hematocrit as an indicator of blood volume and a predictor of intradialytic morbid events", *ASAIO J.*, Vol. 40, pp. M691-M696

[3] Cavalcanti S., Di Marco L.Y. (1999): "Numerical simulation of the hemodynamic response to hemodialysis-induced hypovolemia", *Artif. Organs*, Vol .23, pp. 1063-1073

[4] Cavani S., Cavalcanti S., Avanzolini G. (2001): "Arterial pressure response to hemodialysis-induced hypovolemia: a sensitivity analysis", *ASAIO J.*, Vol. 47, N. 4, pp. 377-388

[5] Cavalcanti S., Cavani S., Santoro A. (2002): "Role of short-therm regulatory mechanisms on pressure response to hemodialysis-induced hypovolemia", *Kidney Int.*, Vol. 61, pp. 228-238

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Modeling the human cardiovascular-respiratory control system: an optimal control application to orthostatic stress

In this talk we describe a model of the human cardiovascular-respiratory control system. The cardiovascular control system involves a complex set of interrelationships between heart rate, blood pressure, cardiac output, and

blood vessel resistance, and, at the current time, a complete description of the control structure and interdependencies of control elements is lacking. While ventilatory control is better understood, the interaction between control of cardiac function and ventilation is not completely elucidated.

We will approach the modeling of the control system by viewing it as an optimal control problem. Many physiologists assume that optimization is a basic concept in the evolution of biological systems (see, e.g., Swan 1984 [3]). We present a model developed in Timischl 1998 [4] which has been used to study congestive heart failure [1] and will adapt this model to study the transition from lying down to standing up and the phenomenon of orthostatic stress.

The model can provide a basis for developing information on steady state relations and also to study the assumption of optimally acting physiological control systems as well as provide a basis for developing and studying the complex physiological control mechanisms of the cardiovascular-respiratory system.

Sudden change in position (from lying down to standing) results in change in physical stress (orthostatic stress) on the cardiovascular system. As a result, steady state and dynamic variation in the system occurs. System response to orthostatic stress has been extensively studied (see e.g., Heldt et.al, 2002 [2]) but a number of issues are not well understood.

The model is adapted using extra compartments and control loops to study the control of blood pressure and the avoidance of severe hypotension which could result from sudden change in position. The purpose is to elucidate and study those factors that influence cardiovascular adaptation to orthostatic stress and provide insight into such conditions as orthostatic intolerance, cerebral blood flow changes and fainting, as well as problems arising from sustained weightlessness (which induces a unique stress environment on the system). Diagnostic identification of physiological conditions by parameter grouping is sought as an ultimate goal. Data is presented and compared to simulated results.

Supported by the FWF: SFB *Optimization and Control*.

References

[1] J. J. Batzel, S. Timischl, and F. Kappel *Combined Human Cardiovascular-Respiratory Control Model with State Space Delay: application to congestive heart failure*, Technical Report 191 Spezialforschungsbereich F-003 Bericht, Karl-Franzens-Universität, 2000,

[2] T. Heldt, E.B. Shim, R.D. Kamm, and R.G. Mark, *Computational modeling of cardiovascular response to orthostatic stress*, J. Appl. Physiol. 92(3), pp. 1239-1254, 2002.

[3] G. W. Swan, *Applications of optimal control theory in biomedicine*, Marcel Dekker, Inc., New York, 1984.

[4] S. Timischl, *A Global Model of the Cardiovascular and Respiratory System*, PhD thesis, Karl-Franzens-Universität Graz, 1998.

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A model of the euglycemic hyperinsulinemic clamp

No abstract available

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Searching for the vascular component of the arterial baroreflex

Short-term regulation of arterial blood pressure is accomplished by complex interactions of feedback and feed forward information from the arterial (ABR) and cardiopulmonary baroreceptors (CPBR) that modulate cardiac output (heart rate, HR and stroke volume) and total peripheral vascular resistance (TPR). The efficiency of the HR-component of the ABR to a change in systolic blood pressure has been extensively studied. Likewise, the CPBR regulation of TPR has been characterized as a function of central venous pressure (CVP). There is relatively less information on the response of TPR

to a change in stimulus at the ABR because many manipulations of BP used to simulate the ABR directly influence TPR.

Recently the system identification technique, autoregressive moving average analysis (ARMA) has been used to study the HR-component of the ABR. Its computational advantage is that it can separately solve the input:output relationship for multiple inputs (e.g. SBP and respiration) and a single output (e.g. HR). We applied a similar approach to study the regulation of two different vascular beds, the cerebral circulation and the total peripheral circulation. In the former, we examined the simultaneous effects of arterial PCO_2 and mean perfusion pressure on cerebral blood flow velocity or cerebral vascular resistance. In the peripheral circulation, we examined the effects of inputs to the CPBR and ABR (as stimulated by CVP and ABP respectively) on the vascular output response (TPR).

The results for the HR-component of the ABR and the cerebrovascular responses were both consistent with expected physiology.

That is, the gain of the HR-component was -0.58 $\pm$ 0.17 beats/min/mmHg in the supine position and -0.30 $\pm$ 0.07 beats/min/mmHg in the upright position ($P < 0.05$). The cerebrovascular resistance increased (0.013 $\pm$ 0.003 CVRindex units/mmHg) as expected for an increase in cerebral perfusion pressure.

Unexpectedly for the peripheral circulation, TPR was observed to increase in response to an increase in MAP (0.20 $\pm$ 0.03 TPRunits/mmHg) with no difference between upright and supine postures, while the CPBR relationship confirmed a reduction in TPR for an increase in CVP.

The qualitative similarity between peripheral and cerebral circulations suggested that the peripheral vascular response to spontaneous variations in arterial pressure might reflect a myogenic response that in the cerebral circulation is called autoregulatory.

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Mathematical models in the study of respiration

The respiratory system acts in conjunction with the circulation to control the oxygen and carbon dioxide in the extra cellular fluid. Time series analysis of respiratory recordings and mathematical models have been used for a long time to study this system. The time series exhibit oscillations of longer period than the breathing cycle superimposed upon the respiratory pattern and these can be interpreted as representing the feedback delays in the system. It has been proposed that the pattern of breathing is determined by a requirement to regulate arterial blood gases while minimising the work due to breathing. Mathematical models have incorporated the chemical feedback loops and the mechanics.

Typically in NREM sleep the breathing pattern is very regular apart from occasional deep sighs. The deep sighs are followed by decaying oscillations which change their period and damping with increasing age. Another pattern which occurs occasionaly is a regular cyclic oscillation in which bursts of a few breaths are separated by pauses in breathing. This latter pattern is called Periodic Breathing (P.B).

Models of the variations in blood gases and the chemical feedback loop suggest that the changes in period and damping of the sigh responses and also the PB pattern may be a reflection of changes in the gains and thresholds of the chemoreceptor responses.and also the relation between cardiac output, thoracic gas volume and the transport delays due to circulation. Our current studies are concerned with the hypothesis that the patterns are also determined by the requirement to minimise the work of breathing. We have examined time series derived from continuous recordings of respiratory volume and oesophageal pressure. These were made from infants during non-rapid eye movement sleep (NREM), when the system is thought to be uninfluenced by higher centres and entirely under the influence of automatic control.

We first examined the periodic breathing pattern. The question is whether the pattern of volumes is such as to minimise the work of breathing? We derive the mechanical parameters and the timing of each breath from the actual records. It is then possible to compare a theoretically derived ideal pattern of volumes giving minimum overall work with the actual pattern. The

actual pattern hunts around the theoretically ideal pattern. These results support the possible existence of a feedback loop minimising the work.

Further work on the regular breathing is in progress.

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Modeling Myocardial Stunning

Myocardial stunning is a post-ischemic dysfunction that persists after coronary reperfusion despite the absence of irreversible damage. The exact mechanisms underlying myocardial stunning remain unclear. We investigated this aspect with computer models in conjunction with data obtained from canine experiments.

We first developed a model that can explain some of the mechanisms involved in myocardial stunning. This was a lumped model incorporating time varying elastic elements, dual myocardial regions, visco-elastic properties, geometry of the ventricular bulge, regional wall stress, and segment lengths. This model was successful in producing results that were consistent with the canine myocardial stunning data and was effective in modeling the dominant observable features of stunned myocardium, such as systolic bulging, delay in shortening, decreased percent shortening, and increased end diastolic length. It was not effective in analyzing stunning at the muscle fiber level.

For this reason, we subsequently developed a single myocardial muscle fiber model. This model consisted of three elements: a contractile element, a series elastic element, and a parallel elastic element. The model generated length information based on time dependent force and contractile stiffness functions. This model was initially evaluated by entering the same regional parameter values used in the global dual region ventricular model. First a reduction of the contractile stiffness function was applied by reducing the peak stiffness by 30 %, and then the rates of activation and deactivation were reduced by 20 % while maintaining the peak values constant. The three-element model produced results very similar to the canine ventricular model and provides a reasonably accurate model of the myocardial tissue and its deficiencies during stunning.

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Identification of Problems in automatic Heart Signal Analysis

Heart signal analysis revealed over the past 100 years a lot of powerful diagnostic methods for assessing chronic and acute cardiac events such as myocardial infarctions, arrhythmia or cardiac circulatory disorders. Two major techniques of signal assessment have been established:

- surface electrocardiograms (ECG)
- internal electrocardiograms (EGM)

The ECG delivers information about signal morphology for diagnostic of cardiac circulatory disorders or of conduction disorders. Long term recordings for at least some hours (Holter) are mainly used for obtaining information about events such as arrhythmia detection and for risk stratification (e.g. after myocardial infarctions).

EGM analysis which has to be obtained with electrodes, that are introduced into the human body, can deliver electrophysiological "maps" of the human heart with the possibility to find electrical foci of arrhythmia, but it is also integrated into current pacemaker devices and implantable cardioverters/defibrillators (ICD), which compute heart signals for arrhythmia diagnosis and therapy delivery.

ICDs have to differentiate potentially "dangerous" tachycardia requiring urgent therapy delivery from fast heart rhythms, that do not need a therapy. Suppressing a required therapy is potentially dangerous, in contrast, a false positive diagnosis which causes inadequate therapy delivery is mostly not dangerous but is not well tolerated by the patient.

A future task is to improve this diagnostic functions and to help the users with the diagnosis of an arrhythmia. Additionally, prediction of arrhythmia based on morphologic changes or changes in heart rate variations that preceding the arrhythmia could provide new therapeutic options and predictive information.

It will surely be a challenging task to separate the huge intraindividual differences in signal morphology and -variability from those indicating "dangerous" or at least important diagnostic findings.

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Numerical model of human cardiovascular system-Korotkoff's sound simulation

The numerical simulation of the Korotkoff's sound is realized by the 14th segments hemodynamic model of the cardiovascular system developed in the Institute of Thermomechanics, Czech Academy of Sciences. The cardiovascular system is being modelled by four segments of the pulsating heart and by ten vascular segments of pulmonary and systemic circuits connected with the heart in series. The behaviour of the cardiovascular system is described by its hemodynamic variables, i.e. the blood pressure, volume and by the cardiovascular paramaters such as the blood vessels compliance and resistance. The blood inertia and the physico-chemical variables such as the cardiac action potential, the calcium, potassium and sodium concentrations are included to the model. By this model is the Korotkoff's sound simulated in the systemic arteries for the different resistance and compliance values. By the numerical simulation is possible to find the relation between the onset of the Korotkoff's sound and elastic properties of blood vessels.

The results of the simulation by 14th segments model show that the frequency of these sounds depends on the blood inertia constants (inductance) and on resistances and elastic properties of the blood vessels. The frequency of the sound increases with decrease of the arterial compliance.

To understand better the Korotkoff's sound generation, the systemic arterial flow is studied in detail by distributed parameter model. The analysis of the self-excited oscillation in a collapsible tube (systemic artery) is based on the one-dimensional model where the effect of the expected flow separation is replaced by the viscous friction change along the tube.

The analysis of the unsteady arterial blood flow and finding of the relationships between oscillations, i.e. the Korotkoff's sounds, and elastic properties of blood artery, shows that the frequency of that sound depends not only on the blood flow type (laminary or turbulent flow) and on the artery properties (viscosity, elasticity) but on a transmural pressure, as well. Its frequency increases with the decrease of the compliance (or alternatively on the Young modulus increase). The conclusion is similar as in the 14th segment model discussed above.

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Noisy oscillatory dynamics of the cardiovascular system

Signals derived from the cardiovascular system (CVS) are notoriously difficult to analyse because they are time-varying, noisy, and of necessarily limited duration. Although the CVS is evidently a highly complex mechanism, the application of techniques drawn from nonlinear science has yielded many insights into its nature, and has provided strong evidence for a large degree of determinism in the way it functions; yet there is compelling evidence that random fluctuations (noise) also play an important role. It is clear that several distinct oscillatory processes occur on widely differing timescales, and that they are coupled: the occurrence of modulation [1,2] and synchronization [3] phenomena between some of them suggests that an understanding of the signals requires the CVS to be considered as an entity. The extent to which the CVS can be modelled as a stochastic nonlinear dynamical system [4], viz. as a set of coupled oscillators subject to noise, is reviewed. Ongoing exploratory investigations of possible applications based on this perception are summarized, including studies of the changes that occur in diabetes, congestive cardiac failure, and after acute myocardial infarction. In each case it is hoped to improve understanding of the underlying pathophysiology, and to develop new noninvasive techniques for early diagnosis and for assessment of the efficacy of treatment.

References

[1] A. Stefanovska and M. Bračič, Physics of the human cardiovascular system, *Contemporary Physics* **40**, 31–35 (1999).

[2] M. Bračič, P.V.E. McClintock and A. Stefanovska, Characteristic frequencies of the human blood distribution system, in D.S. Broomhead, E.A. Luchinskaya, P.V.E. McClintock and T. Mullin, ed., *Stochastic and Chaotic Dynamics in the Lakes*, American Institute of Physics, Melville, NY, 2000, pp 146–153.

[3] A. Stefanovska, H. Haken, P.V.E. McClintock, M. Hožič, F. Bajrović and S. Ribarič, Reversible transitions between synchronization states of the cardiorespiratory system. *Phys. Rev. Lett.* **85**, 4831–4834 (2000).

[4] P.V.E. McClintock and A. Stefanovska, Stochastic nonlinear dynamics of the cardiovascular system, in Z.M. Arnez, C.A. Brebbia, F. Solina and V. Stankovski, ed., *Simulations in Biomedicine V*, WIT Press, Southampton, 2003, pp 57–68.

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Modeling the blood-pressure response to ventricular premature beats

Ventricular premature beats have been used to characterize the risk for patients after myocardial infarction. This risk stratification has recently been improved by estimating the so called heart rate turbulence (HRT), i.e. the deceleration of the sinus beats following a ventricular premature beat. This response is mediated at least in part by the oscillations in the aortic blood pressure following a premature beat. In the following we report on a model adaptation to data which were derived from a multicenter study on noninvasive measurements of ECG and blood pressure in patients with heart disease. These recordings include a 30 minute period of noninvasive blood pressure and a high resolution ECG-recording. For the blood pressure from the first sinus beat after a ventricular premature beat either an overshoot over previous systolic values or a gradual return to default values was observed. Interestingly, with good left ventricular function there was usually no overshoot. On the contrary, patients with decreased left ventricular function showed a marked overshoot.

In a first step, we fed our data, i.e. a given series of coupling intervals, into well known cardiac models, such as that of Ten-Voorde (1992), and watched the blood pressure behavior. It turned out, that the models did not satisfyingly reflect the observed blood pressure oscillations. For this reason, we expanded parts of the models, such that the desired pattern approximately appeared. This was achieved by introducing a more subtle left ventricular function curve, keeping track of the endsystolic volume in the chamber and a modified windkessel function. After parameter fitting a detailed picture of the hemodynamics appeared for each patient. It was found that left ventricular function and, in particular, postextrasystolic potentiation was crucial for

the prediction of the blood pressure response. It seems promising to test these model parameters against the HRT parameters for risk stratification in patients with cardiac disease.

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Knowledge based diagnosis for implantable devices: discussion of aggregation techniques

Implantable devices, above all implantable cardioverter defibrillators (ICD), have become complex electronic systems, which have to deal with changing operating conditions during their service time. Changes include lead dislodgment, increased pacing thresholds, inadequate therapy due to changed medical conditions with the patient, etc. Identifying such changes, determining the root cause and performing countermeasures is a difficult and demanding task, especially for beginners. To assist the physicians in this task CWA develops in cooperation with the University Clinics of Aachen a knowledge based system, which suspects possible changes, suggest additional tests to identify actual changes and proposes appropriate countermeasures.

These kind of diagnosis belongs to the domain of aggregation problems. After an introducing to the diagnosis for ICDs, this presentation gives a short survey on aggregation problems, common techniques and known aggregation operators. In the third section we discuss the usage of the Scalar Fuzzy Control (SFC) to represent and apply unprecise knowledge in aggregation problems. The SFC is a newly suggested extension to the Fuzzy Set Theory, providing the possibility of easy representation and implementation of unprecise human knowledge. We will give a short summary on the SFC and introduce its usage in aggregation problems.

Yet a still remaining difficulty is to determine the aggregation weights as real numbers. This is especially true for huge aggregation problems with cross-indications of the causes, i.e. a cause does not only indicate one hypothesis, but several different hypothesis, possibly each with a different aggregation weight. Another problem is that for the malfunction diagnosis on ICDs the aggregation has to be performed in several steps, with each step using the results of the former step. Thus an aggregation weight does not only influence a specific aggregation, but indirectly the following aggregation steps too.

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Cerebral blood flow autoregulation: are we barking at the wrong tree?

Cerebral blood flow (CBF) is controlled by metabolic, myogenic and neurogenic mechanisms that tend to maintain an appropriate supply of oxygen to the brain, despite large fluctuations in arterial blood pressure (ABP). The term dynamic autoregulation has been used to define the CBF, or CBF velocity (CBFV), transient response to sudden changes in ABP. Classical modelling techniques have also been used to describe the ABP-CBFV dynamic relationship during spontaneous fluctuations in ABP. These approaches provided a basic understanding of system properties, but have not been able to explain most of the CBFV variability.

The main problem lies with an univariate definition of cerebral autoregulation whereby the contribution of other variables, such as arterial pCO_2, respiration, intracranial pressure, and cognitive state is often ignored. In addition, very little work has been done on non-linear methods, despite the fact that adjustments in vessel diameter, or cerebrovascular resistance, make the ABP-CBF relationship intrinsically non-linear. Another important limitation has been the assumption of constant parameter models making no allowances for time-varying characteristics of CBF regulation. This assumption has important conceptual consequences for assessment of clinical tests of cerebral autoregulation regarding measurement reproducibility.

Finally, the contribution of spatial heterogeneity has been largely ignored, mainly due to technical limitations of Doppler ultrasound that restricts measurement to large arteries. Together, these limitations present a formidable

challenge requiring the formulation of a new paradigm for studies of CBF regulation in humans involving the extension of the measurement space and new analytical/modelling tools capable of handling non-linear, time-varying multivariate models.

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The shock energy necessary for successful defibrillation depends on the degree of disorganization of the reentrant activation pattern

Cardiac arrhythmias are pathologic condition which might lead to the breakdown of the organized electrical activity of the heart and in consequence to the loss of the heart's capability to pump blood. Arrhythmias are driven by reentrant circuits which are maintained by phase singularities. Flutter-like arrhythmias are mainly driven by a single rotor, whereas in the case of fibrillation-like activation pattern many phase singularities are present at the same time. Common experimental and clinical practice to restore a normal activation sequence is to deliver a strong electrical shock to the tissue. Whether the shock energy needed for a successful termination of a reentrant circuit depends on the degree of disorganization of the activation pattern was examined in this study.

A three-dimensional bidomain model of cardiac tissue was used to investigate the influence the degree of disorganization of reentrant activation patterns on the success rate of defibrillation shocks. A model of the human atrial action potential incorporating an ACh dependent K+ channel and electroporation was used. A S1-S2 cross shock protocol was applied to initiate reentry. The spatial distribution of the ACh concentration was varied to obtain either a single rotor, or spiral wave breakup with multiple wavelets. Defibrillation shocks were delivered to both activation patterns to determine the shock strength for successful termination of the reentry.

The results of this study showed that the shock energy needed for successful defibrillation is significantly higher in presence of multiple wavelets compared to the single rotor case.

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Baroreflex linear and nonlinear contribution to blood pressure – heart rate coupling during spontaneous behavior

In this study we investigated 1) the coupling existing between arterial blood pressure and heart rate variability in daily life and 2) the baroreflex contribution to such a coupling. For this purpose we developed a procedure based on the estimation of the Cross-Mutual Information (CMI) between systolic blood pressure (SBP) and RR-Interval (RRI) beat-to-beat values. CMI has been selected because of its capability to quantify both linear and nonlinear components of the coupling between variables over time scales in the order of minutes. This procedure has been used to analyze data recorded in spontaneously behaving cats before and after the surgical opening of the baroreflex loop as obtained by a sinoaortic denervation. In intact animals we observed that the cumulative physiological level of the coupling between SBP and PI corresponds to about 40 % of the theoretical maximal coupling. After sinoaortic denervation CMI values drastically dropped with respect to baseline levels (-70 % on average). Thus use of CMI indicates that over a time scale in the order of minutes the arterial baroreflex is the major determinants of the SBI-PI link, accounting for about 2/3 of the total measured coupling existing between these variables.

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Simple models for physiological description and hypothesis testing in respiratory physiology

This presentation will outline some simple models that we have used to address a range of physiological questions. These will include:

1. Models of the ventilatory response to hypoxia. These models have been used to summarize physiological function and to distinguish between competing hypotheses by comparing the fit of the associated models to the data.

2. Models of breath-to-breath variability. These models have been used to describe the correlation that exists between successive breaths. They have been used to provide a parallel noise model that can be fit simultaneously with deterministic models of the ventilatory response to various stimuli.

3. Models of the ventilatory response to carbon dioxide. These models have again been used to test hypotheses in respiratory control, and will illustrate the importance of a noise model in hypothesis testing. These studies will also illustrate the use of the models in experimental design and an experimental approach to model validation.

4. Models of respiratory gas exchange. Simple, single compartment models of the lung have been used to devise various algorithms to estimate gas exchange at the pulmonary capillaries from indirect measurements of gas exchange at the mouth. Here we use a simple multi-compartment model to generate test data to compare algorithm performance in a setting where gas exchange at the pulmonary capillaries can be known.

Overall, this presentation aims to illustrate the usefulness of simple models for description and hypothesis testing within respiratory physiology.

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Some results on parameter identification of nonlinear systems

Recently, differential algebra tools have been applied to the study of a priori identifiability of dynamic systems described by polynomial or rational equations [2, 3]. We recall that the concept of parameter identifiability deals with the (theoretical) uniqueness of solutions to the problem of recovering the model parameters from noise free input-output data [1]. These methods are based on elimination theory for algebraic differential systems, the main tool being the computation of the so-called characteristic set of a certain differential ideal associated to the polynomials defining the dynamic system. This characteristic set can in principle be found by symbolic computation and provides the so-called exhaustive summary of the model.

Here we will show that the reparametrization of the input-output relation of the system by the exhaustive summary plays a major role not only in a priori identifiability but also in parameter estimation of nonlinear models. The reparametrization is in fact a linear reparametrization of the input-output relation of the model and can be used to derive explicit one-shot least squares estimates of the parameters. This allows to avoid the usual bottleneck of nonlinear parameter optimization which has to be performed by iterative optimization routines which are often unreliable, in the sense that they give no guarantee of converging to a true minimum, and hence require expensive and time consuming random search in the parameter space.

Recovering the true parameters from the exhaustive summary (which is possible if and only if the model is a priori globally identifiable) is a problem of solving a system of (static) algebraic equations which is much easier and can be approached by standard algorithms.

Difficulties can arise in evaluating various derivatives of the input-output functions required in setting up the regression equation. These difficulties may be addressed in various ways, e.g. by spline or exponential smoothing in biomedical applications, depending on the problem at hand.

Our algorithm has been tested in one and two dimensional Michaelis-Menten model where the choice of initial values of the parameters is critical since nonlinear least squares minimization problem shows many local minima. Our method structurally has only one minimum and does not require initial values for the unknown parameters.

References

[1] S. Audoly, G. Bellu, L. D'Angiò, M.P. Saccomani and C. Cobelli, Global identifiability of nonlinear models of biological systems, *IEEE Trans. Biomed. Eng.*, vol. 48, no. 1, pp. 55-65, 2001.

[2] L. Ljung and S.T. Glad, On global identifiability for arbitrary model parameterizations, *Automatica*, vol. 30, no. 2, pp. 265-276, 1994.

[3] M.P. Saccomani, S. Audoly, L. D'Angiò, Parameter identifiability of nonlinear systems: the role of initial conditions, *Automatica*, vol. 39, pp. 619-632, 2003.

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Long term regulation of the mean arterial pressure based on the metabolic activity of the brain: a mathematical model simulation

Regulation of the mean arterial pressure (MAP) is in short term mediated mainly by the arterial baroreflex action, which is, however, reset in a variety of circumstances, such as during physical exertion, hypoxia, changes in body temperature, and cognitive activation of the brain. The resetting of the reflex was at least in part attributed to the "Central command" action of the regulatory centers.

Here we propose a common mechanism to govern the Central command action to the baroreflex to achieve the long term regulation of the MAP. We hypothesize that the primary task of the cardiovascular system (CVS) control is to assure the oxygen supply to the brain, adequate to its metabolic activity. The control is governed by a hypotetic substance X, excessively generated in slightly anaerobic conditions: its production increases with the metabolic activity of the brain, and its elimination increases with the oxygen blood supply. This substance has two actions. It stimulates the sympathetic system to reset the baroreflex function curves to a higher level, resulting thus the central command action. In addition, when applying to act on the local blood vessels, the described metabolic mechanism also reproduces the characteristics of the local autoregulatory blood flow, depending on the metabolic activity of the tissue, including the lower and upper autoregulatory limit.

To test the hypothesis, we used our mathematical model of the CVS to investigate whether all states or maneuvers that interfere with the brain metabolism (increased metabolic activity or disturbances in the vascular supply) reproduce changes in the mean arterial pressure, consistent with those published in the literature. The CVS model consisted of the heart, the arterial, venous and the central venous compartment, all with non-linear compliance properties. The heart was described as a variable elastance pump. The resistance vessels exhibited autoregulatory properties. The regulatory part of the system included the baroreflex response, its heart rate, cardiac contractility and the reduction of the unstressed venous volume component, all mediated by changes in MAP. We considered that all reflex components are reset to a higher value in parallel to the increased concentration of the substance X, produced under slightly anaerobic conditions.

The model behavior was found to be consistent with the proposed hypothesis: states with increased metabolic activity or disturbed vascular supply were all connected with the shift of the baroreflex response to a higher level, as reported in the literature by the central command action, and as explained by metabolic balance of the brain in our model. Specifically, it occurred during simulation of the cognitive or motor activation of the brain or heating of the body or due to circadian temperature changes, as well as during increased intracranial pressure or during hypoxia or in proximal stenosis of the cerebral arteries. In some of those states, the MAP was set to a higher level, whereas in others the cardiac output was increased at a steady MAP.

The proposed mechanism provides an explanation of the set-point of the MAP control. It gives a certain degree of economy to the body in the real life. Finally, it may also explain the so called ischemic reflex of the central nervous system.

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Modeling in cardiovascular medicine: the clinician's point of view

No Abstract Available

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Inferring parameters for the coupled oscillators of the cardiovascular system

The work is based on the idea that the cardiovascular system can be modelled as a set of coupled oscillatory systems. The starting point is that signals derived from the human cardiovascular system (CVS) are exceptionally complex, being time-varying, noisy, and of necessarily limited duration. Yet an appropriate analysis of them may be expected to yield detailed information about the dynamics of the underlying physiological processes.

In our new approach, the conditional probability is obtained by expressing it in terms of a white noise path integral. Taking advantage of this idea, we have derived a concise and fast iterative Bayesian inference scheme. The proposed inference technique does not just filter out the dynamical information from noisy time series. Rather, it *uses the internal noise in the system to infer dynamical information*. That is why the internal noise in the system is actually an advantage for inference. This same technique can be applied to the N-dimensional case to provide us with parameters for the oscillatory components of CVS variability in different frequency ranges. The preliminary application to the measured CVS oscillations will be presented which confirms the appropriateness of developing a stochastic nonlinear model.

References

[1] A. Stefanovska and M. Bračič, Physics of the human cardiovascular system, *Contemporary Physics* 40 (1999) 31–35.

[2] A. Stefanovska, M. Bračič Lotrič, S. Strle and H. Haken, The cardiovascular system as coupled oscillators?, *Physiological Measurement* 22 (2001) 535–550.

[3] A. Stefanovska, D.G. Luchinsky and P. V. E. McClintock, Modelling couplings among the oscillators of the cardiovascular system, *Physiological Measurement* 22 (2001) 551–564.

[4] P. V. E. McClintock and A. Stefanovska, Noise and determinism in cardiovascular dynamics, *Physica A* 314 (2002) 69–76.

[5] V. N. Smelyanskiy, D. A. Timucin, D. G. Luchinsky, A. Stefanovska, A. Bandrivskyy and P. V. E. McClintock, Time-Varying Cardiovascular Oscillations, in N. S. Namachchivaya and Y. K. Lin eds. *Nonlinear Stochastic Dynamics*, (proceedings of the IUTAM Symposium in Allerton Park, University of Illinois, Urbana, August 2002), Kluwer, Amsterdam, in press.

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Causal relations between cardio, respiratory and neural oscillations

A directionality index based on conditional mutual information is introduced and applied to the instantaneous phases of weakly coupled oscillators. Its abilities to distinguish unidirectional from bidirectional coupling, as well as to reveal and quantify asymmetry in bidirectional coupling, are demonstrated using numerical examples of quasiperiodic, chaotic and noisy oscillators, as well as cardiorespiratory data.

Simultaneous measurements of the neural and cardiorespiratory phenomena associated with anæsthesia in rats are then presented. Techniques drawn

both from nonlinear science [1] and from information theory [2,3] are applied to reveal and quantify *causal* relationships between the cardiac, respiratory and neural oscillations, and to explore how these change during anæsthesia.

A pronounced spectral peak is detected in the electroencephalogram (EEG) during anæsthesia. It suddenly diminishes when the anæsthetic starts to wear off; simultaneously, the sign of the strong [4] cardio-respiratory interaction abruptly reverses. The respiratory and neural oscillations synchronise strongly during deep anæsthesia, whereas the cardiac and neural oscillations synchronise only transiently, just before the spectral peak in the EEG decreases. The neural oscillation is shown to be driven by respiration during deep anæsthesia, but this driving disappeared during emergence from anæsthesia.

The new nonlinear and information theoretic techniques used in this study allow us to reveal, and to quantify, the causal relationships that exist between the respiratory, cardiac and neural oscillations. We note in conclusion that some of the results may carry implications, not only for anæsthesia, but also for waking states in health and disease.

References

[1] Rosenblum, M. G., Cimponeriu, L., Bezerianos, A., Patzak, A. & Mrowka, R. Identification of coupling direction: Application to cardiorespiratory interaction. *Phys. Rev. E.* **65**, 041909 (2002).

[2] Paluš, M., Komárek, V., Hrnčíř, Z. & Štěrbová, K. Synchronization as adjustment of information rates: Detection from bivariate time series. *Phys. Rev. E* **63**, 046211 (2001).

[3] Paluš, M. & Stefanovska, A., Direction of coupling from phases of interacting oscillators: An information-theoretic approach. *Phys. Rev. E*, in press (2003).

[4] Stefanovska, A., Haken, H., McClintock, P. V. E., Hožič, M., Bajrović, F. & Ribarič, S. Reversible transitions between synchronization states of the cardio-respiratory system. *Phys. Rev. Lett.* **85**, 4831–4834 (2000).

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From cell to integrated whole organ: computational modeling for the Lung Physiome

Almost all respiratory disorders result in an impairment of gas exchange, but because of the complexity of the integrated pulmonary system, the means by which gas exchange is impaired can differ markedly between different diseases. Therefore a predictive model that is capable of investigating the complex interactions within the healthy or diseased lung must include detailed structural information and the ability to couple many different processes over a wide range of scales of interest.

The Human Physiome Project [1,2] is a multi-centre programme to develop, archive and disseminate quantitative information and integrated models of the function of organelles, cells, tissues, organs, and organ systems. The long-range goal of the project is to understand and describe human physiology and pathophysiology, and to use this understanding to improve human health. A major aim is to develop computational models that integrate quantitative and comprehensive observations from many laboratories. The project aims to reach down through sub-cellular modelling to the molecular level and the database generated by the Genome Project, and to build up through whole organ and whole body modelling to clinical knowledge and medical applications. Major advances have been made in developing the Cardiome (Heart Physiome), Endotheliome, and Microcirculation Physiome.

The Lung Physiome project aims to couple the wealth of pulmonary genomic and cellular data now becoming available with computational methods capable of dealing with the anatomical and biophysical complexity of the physical processes within the lungs. The Lung Physiome aims to incorporate and unify existing pulmonary imaging, structural, functional, and genetic data and mathematical models at each level of structural or functional detail into a database for the lung. This publicly available database is currently being developed at the Bioengineering Institute [3], and will ultimately provide a means to construct anatomically- and biophysically-based, quantitative and predictive mathematical models of aspects of the pulmonary system. Such models will combine emerging genetic knowledge with systems physiology to enable respiratory disease processes and the effects of therapeutic interventions, whether through drugs or mechanical means, to be modeled and examined in silico.

References

[1] Hunter P. J., Robbins P., and Noble D. The IUPS human physiome project. Pflugers Arch - Eur J Physiol 445(1): 1-9, 2002.

[2] Hunter P.J., and Borg T. K. Integration from proteins to organs: the Physiome Project. Nat Rev Mol Cell Biol 4(3):237-43, 2003.

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Image-based flow computations in aneurisms, using various image processing techniques

Large-artery diseases as aneurisms (blood vessel bulging) or stenoses (vessel lumen narrowing) are a major cause of death in western societies.

Because haemodynamic factors are involved in genesis and development of such artery wall diseases, numerical simulations of blood flow during a whole cardiac cycle are useful for complete medical check-up, for treatment planning and for prognosis after treatment.

Computational domains must be based upon angiographies because of huge between-subject variability in vessel anatomy and in lesion shape, which affect the flow. Various techniques of (i) medical image acquisition, (ii) 3D reconstruction and (iii) numerical procedures can be used. Every technique has its own advantages and drawbacks. However, they share a common feature: they are associated, whatever the selected method, with modeling and assumptions. The stage of geometrical modeling is crucial.

Several available techniques of 3D reconstruction from parallel-contour point set have been compared while investigating the flow field in a vessel segment with a saccular side aneurism in the context of poor-quality images and partially saved slices of the scan set. Different slice connection procedures, based on Delaunay triangulation, are used.

After three-dimensional reconstruction of the same vascular region, whatever the technique, the associated facetisation is then improved to get a

computation-adapted surface triangulation, after a treatment of vessel ends for suitable boundary conditionning.

A simplification procedure, possibly preceeded by a surface smoothing stage, based on the Hausdorff distance, yields a geometric surface mesh which is a good approximation of the surface geometry and contains far less nodes than the initial facetisation. The computational surface mesh must take into account shape and size requirements for the mesh elements. An anisotropic geometric metric map based on the local principal directions and radii of curvatures is constructed in the tangent planes related to the mesh vertices. This metric map prescribes element sizes proportional to the local curvature of the surface. Once the volumic mesh is obtained, flow of incompressible Newtonian blood (red blood cells are assumed neither to have time enough to aggregate nor to deform in the large blood vessels) is computed using in vivo non-invasive flowmetry.

The finite element method uses a P1-P1 bubble element. The convective term is approximated by the method of characteristics. The solution is obtained via a generalized Uzawa-preconditioned-conjugate gradient method. The initial condition is given by a stationary Stokes problem with the same boundary condition as the unsteady one. The stem peak Reynolds number based on the peak cross-sectional average velocity and on the trunk radius at the entrance cross section is equal to 1110; the Stokes number (the frequency parameter) and the Strouhal number are equal to 11.2 and 0.11 respectively. The numerical results not only depends on the mesh size but also on the domain configuration which can slightly vary according to the quality of the input data and the technique of the 3D reconstruction.

The observed differences, although reasonable in the context of multimodeling, may be significant. The flow data must thus be used qualitatively, in order to improve the medical checkup, to help the physician to plane the treatment and to control the posttherapeutic vessel state. The helpful numerical results can never lead to definite conclusions, because variables of interest are estimated rather than properly quantified.

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Modeling and analysis of glucose and free fatty acids kinetics during glucose tolerance tests

Physiological regulation of glucose and lipid homeostasis involves many metabolic pathways that have been discovered with complicated in vitro and in vivo experimentation. Detailed knowledge of these complex metabolic control mechanisms is however not sufficient to fully understand the pathogenesis of type 2 (or non insulin dependent) diabetes, which is considered an epidemic disease in modern countries. A current opinion in metabolic research is that glucose intolerance in type 2 diabetic patients is associated with a derangement of biological control mechanisms of free fatty acids (FFA) production, as well as lipid storage in tissues other than adipose tissue. For this reason new approaches are necessary to quantify in individual patients macroscopic physiological processes that may be associated with the development of the diabetic disease.

A new model-based approach is presented here for analyzing glucose and FFA kinetics during clinical tests such as the intravenous (IVGTT) and oral (OGTT) glucose tolerance tests. A major role in the model is played by insulin that not only activates uptake and storage of carbohydrates in tissue cells but also inhibits breakdown of energy depots represented by triglycerides stored in adipose tissue. For analyzing FFA kinetics a new model has been formulated on the basis of physiological knowledge and tested using IVGTT data. For describing glucose kinetics during OGTT, the minimal model of glucose disappearance (MINMOD), originally proposed for IVGTT, has been adapted to the experimental situation with oral route of glucose intake. Results obtained in a large group of patients indicates that pathophysiological information obtainable with MINMOD from OGTT is similar to that from IVGTT. Moreover, a significant relationships was found between the degrees of insulin-mediated inhibition of FFA production and glucose disposal. This indicates that the proposed OGTT model is a promising approach for investigating the relationship between glucose and FFA kinetics in large cohorts of subjects.

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Modeling cerebral blood flow control during posture change from sitting to standing

Hypertension, decreased cerebral blood flow, and diminished cerebral blood flow control, are among the first signs indicating the presence of cerebral vascular disease. In this talk, we will present our work on developing mathematical models for systemic blood pressure and cerebral blood flow control (auto- and baroreceptor regulation) during posture change from sitting to standing. The mathematical model is based on compartmental modeling describing the pulsatile blood flow and pressure in a number of compartment of the systemic arteries. These compartments include the upper body, the legs, and the brain. Physiologically based control mechanisms will be added to explore how arterial and cerebral blood pressure drop as a consequence of posture change from sitting to standing. The effect of time delays involving a delay for the onset of control as well as the duration of the control will also be presented. Finally, to justify the fidelity of our mathematical model and control mechanisms development, we will show validation results of our model against experimental data.

This is a joint work with Mette Olufsen (North Carolina State University) and Johnny Ottesen (Roskilde University).

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A mathematical model of local vasodilatation during peritoneal dialysis

Standard dialysis fluid infused into the peritoneal cavity induces local vasodilatation in submesothelial tissue, as demonstrated by direct exposure of blood capillaries to dialysis fluid (Miller, 1979) and by kinetic clinical studies

of peritoneal transport (Imholz et al, 1994, Grzegorzewska, 1995, Waniewski et al, 1996). The reason for vasodilatation may be the presence of highly concentrated glucose and lactate in dialysis fluid combined with its acidity. The control of local perfusion by vasoactive factors infused to blood or added to dialysis fluid was also attempted in many clinical and experimental studies (Douma et al, 1997). The kinetic studies demonstrated that diffusive mass transport coefficients are inflated by about 60 % at the beginning of the study, but decrease later exponentially and reach the steady state after about 2 hours (Waniewski et al, 1996).

A mathematical model based on partial differential equation for diffusive transport of small solutes, with capillaries uniformly distributed within the tissue as sink/source of the solute, was applied for the theoretical analysis of this phenomenon (Waniewski et al, 1999). It was shown that, assuming uniform change of perfusion in the whole tissue, blood flow rate must be increased six times, and the capillary surface area by two - three times, to account for the observed initial inflation of diffusive mass transport coefficients. This result was in concordance with experimental evidence that perfusion of the tissue may be increased up to 10 times by dialysis fluid, but only in a thin layer of the tissue (Granger et al, 1984).

A modified nonlinear distributed model is now proposed with vasodilatation induced by a vasoactive factor that diffuses into tissue from dialysis fluid, and induces the increased perfusion in the tissue layer, which it is able to penetrate (typically 200 - 300 microns). A threshold for the efficiency of the factor is assumed, with the full efficiency if its local concentration is above the threshold. The initiated vasodilatation decreases later exponentially with time. It is shown that this hypothesis yields a good agreement with the kinetic change of diffusive mass transport coefficients.

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Modeling design and functional integration in the oxygen and fuel pathways to working muscle

Muscle work is powered energetically by a continuous and integrated supply of oxygen and fuels to the mitochondria in support of oxidative phosphorylation.The simple pathway for oxygen leads from air through lung and

circulation to capillaries and mitochondria; no oxygen is stored. The fuel pathway is more complex as it offers alternatives: (1) two different fuels (glucose, fatty acids) are used; (2) their supply to mitochondria is either direct from capillaries or indirect through intracellular stores of glycogen and triglycerides. Thus different models establish quantitative structure-function relations for these two pathways even though both use the circulation of blood for transport.

The animal world shows great differences in energy needs, between large and small mammals, and between sedentary and athletic species. This allows a test of the validity of such models and to ask whether the design of the pathways is adjusted to cover the variable needs according to the principle of symmorphosis. By comparative physiology we estimated the capacity for oxidative phosphorylation, and measured the morphometric the parameters that determine the functional capacity of the pathways. We found the structures of the pathway for oxygen, the mitochondria, the capillaries, the heart, the blood, and the lung, to be all co-adjusted to aerobic capacity of muscle, but the co-adjustment is often not simple and may involve more than one structure. In the pathway for fuels we found those structures that are shared with the oxygen pathway, such as the capillaries, to be adjusted to the needs for oxygen rather than fuel supply. High substrate needs in exercising animals are covered mainly by drawing fuels from intracellular stores of glycogen and fat. The diverse but coadjusted design of the two pathways ensures efficient and well-matched fluxes along these powerlines for oxygen and fuel supply.

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Ventriculo-arterial coupling determines pressure and flow

The ventricle can be described by its time-varying pressure-volume relation. A good approximation of this description can be obtained using 4 parameters:

The slopes of the diastolic and systolic pressure volume relations (E_{min} and E_{max}), the intercept of the relations with the volume axis (V_d), and the ventricular filling pressure or filling volume (V_0). The time pattern of the slope of the pressure-volume relations ($E(t)$) was shown to be a load and disease independent variable and is used as input.

The arterial load can be described by the three element windkessel and thus consists of three parameters: peripheral resistance R, total arterial compliance C, and aortic characteristic impedance Z_c.

All the parameters can be determined from pressures, flow and volume measurements in the intact organism. We here concentrate on the left heart and systemic circulation.

Based on this knowledge we will do the following:

1. Show that with this limited number of parameters the cardiovascular system can be described accurately.
2. Apply dimensional analysis to arrive at a sensitivity analysis of the parameters.
3. Derive coupling parameters of ventricle and arterial load.
4. Compare the parameters in different mammals and study normalized arterial input impedance.
5. Discuss other coupling parameters proposed in the literature.
6. Show the contributions of heart and arterial load in exercise and disease.

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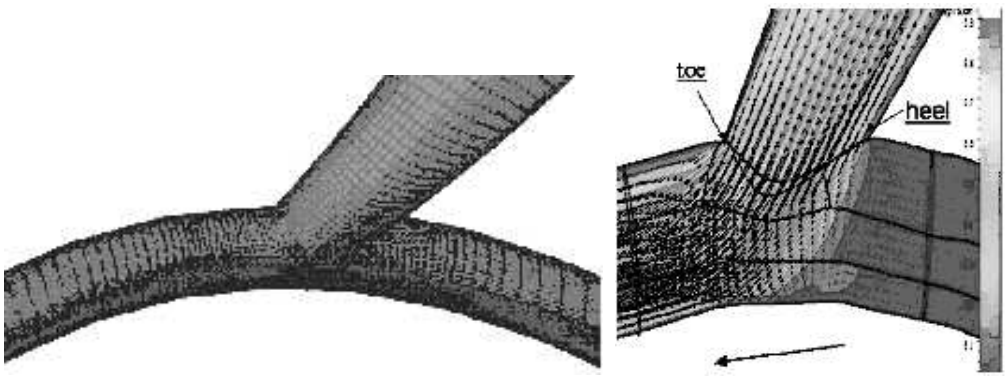
Modeling local hemodynamics through by-pass grafts out of the heart area - a sample of collaborative framework

Arterial blockage is nowadays one of the major sources of deaths in the western countries. In few dedicated circumstances, a surgical procedure that consists in including biological or synthetic grafts to bypass severely stenosed or occluded arteries is used in order to keep a proper irrigation of the heart. This solution is however not perfect and failures may occur, mainly due to clot formation or to the development of intimal hyperplasia.

It is today commonly admitted that potential problems are strongly related to the blood flow structure in the arteries In particular, reduced or negative wall shear stress, which can be related to vortices, are quite favourable for the development of atheromatous plaques. It is therefore fundamental to be able to track precisely such fluid phenomena. A biphasic and predominantly diastolic pattern characterizes physiological flows in this context. More complex issues are related to the competition between flows in the graft and the stenosed native artery, the size discrepancy or the angle between the graft and the artery.

This presentation discusses the major issues linked to the numerical modelling of blood flow through by-pass grafts out of the heart area. The talk will be based on a sample of Belgian collaborative framework set up between surgeons, research laboratories and software development industry. It will outline the major advantages, interests and difficulties met so far in such a mixed environment.

Issues linked to 3D geometry acquisition, reconstruction and variability, modelling of flow pulsatility and fluid-structure interaction challenges will in particular be addressed. The latter aspect is particularly critical to account for the effect of the wall motion on blood flow and determines the mechanical stresses within the arterial wall itself in the frame of an active remodelling; it also has major implications in the design and optimisation of end vascular prostheses.



A sample of mesh and solution in bifurcation area (saphenous vein graft)

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Mathematical modelling of mass transfer in the vascular system and related clinical applications

Motivations. Blood flow provides nourishment and removes wastes from tissues. A crucial point to understand this basic function is to study the mass transfer across capillaries and arterial walls. This is a particularly challenging task because of the heterogeneity of the physical properties of the arterial wall.

Mechanics of trans-capillary exchange. The arterial wall is a complex structure made of several layers, precisely the endothelium (the innermost layer with respect to the lumen) the intima, the internal elastic lamina, the media and finally the adventitia (the outermost one). In order to describe the transfer of chemicals through the walls, many phenomena must be taken into account. Precisely, molecules can diffuse into the wall, but are also transported by the filtration of plasma from the lumen to the outer wall. Moreover, the aforementioned tissues can be regarded as porous structures filled with plasma. Consequently, depending on the relative dimensions of the pores with respect to the considered molecules, selectivity effects and frictional phenomena should be suitably modelled.

Starting from the basic equations describing the physiological phenomena at hand, we set up a well posed system of partial differential equations to describe the transfer of molecules through the arterial walls.

For the delicate question of characterizing the physical properties of the tissues constituting the walls, we apply an electric analogy for mass transport processes, aiming to reconstruct the physical parameters from availableconcentration measurements.

Clinical applications. Digital medical imagery systems and increasing computational power resources make nowadays possible the application to these complex mathematical model to realistic situations. More precisely, we take into account the following applications.

- Transfer of low-density lipoproteins (LDL) from the blood to the arterial walls. The study of LDL concentration into the arterial wall has a key role in the understanding of atherosclerosis. Indeed, accumulation of LDL in tissues may trigger inflammatory reactions in the arterial wall, which seem to be one of the first phases of atherosclerosis.

- Dynamics of drug release in drug-eluting stents. Advanced atherosclerotic lesions are often surgically treated with vascular stents that prevent the occlusion of the vessel. In some cases, stents are coated with drugs that are slowly released to the surrounding tissue preventing proliferation of smooth muscle cells, the so called restenosis. The dynamics of these drugs into the wall of the vessel can be simulated by the aforementioned models in order to evaluate the drug penetration in the tissue and its residence time.

- Kinetic modelling of chemical exchange in peritoneal dialysis. A simplified version of the models describing mass transfer through the arterial walls (where only time dependence is taken into account) is applied to study the removal of blood toxins during peritoneal dialysis. This research puts into evidence the importance of fitting the physical parameters of the considered mathematical models on clinical measurements in order to enhance the reliability of the predictions. Numerical results will be compared with extensive clinical trials.

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Understanding the Liebau effect

The original Liebau (1954) pump was made by connecting two (elastic) tubes of different diameters and wall thicknesses via a reducer to form a single length. By placing the larger (diameter) end into a reservoir and squeezing periodically at a point on the larger tube Liebau obtained a pumping effect: despite the purely reciprocating action of the squeezing, a net flow out of the reservoir, through the smaller tube and into another container occurred. The reciprocating squeezing motion he employed was not peristaltic (directional), so that peristaltis as a mechanism could be ruled out. Later Liebau (1955a) found that pumping could be obtained using (inelastic) pipes with a T-joint into whose open end a reciprocating piston had been inserted. A further variation which Liebau (1955b) discussed was by connecting two tubes of different elasticities or diameters at both ends to form a closed circuit. He

found three elements in the configuration to be essential for the pumping effect: that there be two different diameters/elasticities; that the motion occur impulsively (with relatively rapid acc/deceleration phases) and that (for the case of the circuit) the percussion point not be midway along one of the tubes (assymetric).

Takagi and Saijo (1983) studied a configuration similar to the above. The difference is that the source was not provided by squeezing, but rather by a T-section in whose one arm a reciprocating piston system injected and withdrew fluid from the pipe. They did numerical work and their search for suitable dimensionless groups was unsuccessful.

An analytic solution which we find yields a small but finite pumping effect. A non-dimensional combination analogous to the classical λ and Re of pipe friction fame may be formed. On casting the pumping effect into these terms the experimental data collapse well.

Supported by the FWF: SFB *Optimization and Control*.

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Oscillations, synchronization and optimization

The heart beat - the easiest measurable and best known biological variable - is generated by the interaction between a surprising number of internal, and a variety of external rhythms. The same is also true for other variables like blood pressure, respiration, blood density, etc.. There are three important phenomena which are of particular interest. 1) All biological variables oscillate. This phenomenon appears to be essential for their optimal adjustment and therefore, for the efficiency of control. 2) Biological oscillators tend to synchronize. 3) There are indications that in biological systems parameters as well as variables are adjusted according to rules, which include adaptation as well as optimization.

The magnitude of biological variables in animals of different size (weight), can be described statistically as so-called "allometric" functions of the body mass. These functions describe what in physiology is called "biological similarity". Among other examples time periods of heart beat and the breath to

breath period are longer in larger animals, whereas pressure values are nearly the same in animals of different size. The optimal adjustment of variables, parameters and the optimal development of structures is summarized as symmorphosis by E. Weibel in his book (2000). We can show that oscillations and synchronization are a characteristic feature of all biological variables. It is proposed that such oscillations may be important for an optimization according to a search mechanism as it was first discussed by I. Priban (1965). In order to study oscillations and synchronization in human beings over longer periods we apply an EKG-based noninvasive technique for long-term recording for the analysis of the heart beat, the frequency spectrum of the heart rate, its synchronization with other rhythms, the circadian variations, including sleep and the effect of stress and rehabilitation. Since the human eye is especially sensitive to colors, we display the results in color-coded form.

Supported by the FWF: SFB "Optimization and Control".

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Bedside identification of hemodynamic variables by dilution of ultra-pure dialysate during hemodialysis

Aim: Indicator dilution provides information on hemodynamic parameters during hemodialysis (HD) such as blood volume (BV), central blood volume (CBV), and cardiac output (CO). However, manual operation of current techniques limits their widespread acceptability. It therefore was the aim to develop an automatic approach for simple bedside identification of these parameters during HD.

Methods: The 4008H-HDF machine (Fresenius Medical Care, Bad Homburg, Germany) has the potential to inject defined volumes of ultra-pure dialysate at correct temperatures in multiples of 30 mL into the extracorporeal blood line at the relatively slow rate of 150 mL/min. Thus, the classic bolus approach to calculate CO and CBV from the first transient of indicator injected as a short bolus cannot be used in this setting. Dilution curves were therfore analyzed by a two-compartment blood volume model where the exchange between central and peripheral compartments was determined

by systemic blood flow. A blood volume monitor (BVM, Fresenius Medical Care, Bad Homburg, Germany) specially adapted for sampling rates of approximately 10Ḣz was used to detect the changes in blood water concentration (BWC) by ultrasonic means. The accuracy and the reproducibility to measure BV tested in in-vitro experiments was $1.3 \pm 2.1\,\%$. CBV and CO were compared to data obtained by standard saline dilution technique (HD01, Transonic Systems, Ithaca, NY). Results: During the treatment the software continuously analyzed the BWC data for plausibility. Acoustic prompts called for specific actions such as activating or deactivating the fast sample mode of the BVM and the HDF-bolus injection, respectively. The BWC transients recorded during the dilution phase were analyzed for appearance times and detrended for BWC changes caused by continuing ultrafiltration and vascular refilling. Extracted dilution curves were then used to fit the two-compartment model. Model identification used the Marquardt-Levenberg algorithm while data acquisition was still active in the background. As soon as BV was available from the first dilution test, the software determined the time course of absolute BV(t) as well as instantaneous vascular refilling rates calculated from delivered ultrafiltration-rates.

Conclusion: On-line identification of BV, vascular refilling and other hemodynamic parameters could be useful to control ultrafiltration during HD and to prevent intradialytic morbid events. The system has the potential for complete automation with the implementation of appropriate control inputs to the BVM and HDF modules of the HD machine.

Supported by Fresenius Medical Care, Bad Homburg Germany and by the Austrian Science Fund, project #F323.

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Session Chairs

Workshop Session Co-Chair Schedule Wednesday

Morning Session	F. Kappel and M. Levine
Afternoon Session	T. Kenner and A. Stefanovska

Workshop Session Co-Chair Schedule Thursday

Morning Session	D. Schneditz and E. Weibel
Afternoon Session	MACSI-net event

Workshop Session Co-Chair Schedule Friday

Morning Session	J. Batzel and R. Li
Afternoon Session	M. Bachar and R. Panerai

Workshop Session Co-Chair Schedule Saturday

Morning Session	D. Auerbach and N. Westerhof
Afternoon Session	M. Fink and M. Tawhai

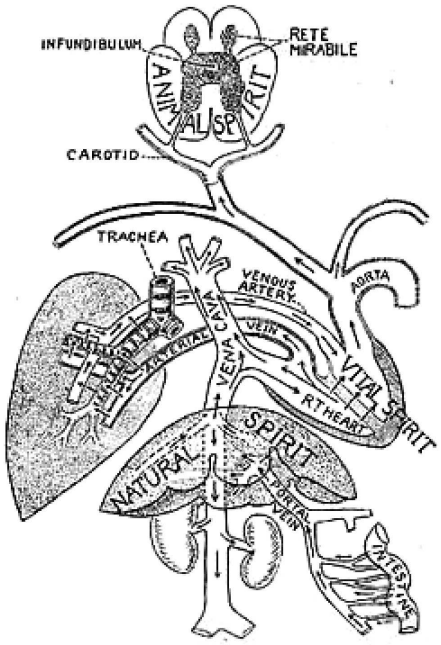
Outings

- Tuesday evening: 20:00: Welcome dinner at St. Martin
- Wednesday: Leave 18:15 Tour of Graz 18:30-20:30
- Thurdsay: Leave 18:15 Tour of Schloss Eggenberg and reception 18:15-21:00
- Friday: Leave 17:30 Reception with Styrian Landeshauptmann 18:30-20:00, Starke Haus 20:30
- Saturday: walk to Gasthaus Orthacker

Loss of control

General Information

- Meals are free for invited speakers and those staying at the workshop site with the full pension option. Other guests are welcome to have lunch or dinner at the conference site. Lunch price 8 Euro and dinner price 6 Euro.
- Drinks at meals are not free. Please pay for drinks in the "Oberwolfach-style", i.e., consult the price list and put the money in the box provided. Refreshments at workshop breaks are free.
- There are nice restaurants nearby: Gasthaus Kehlberghof, Gasthaus Orthaker, and Gasthaus Dokterbauer. Ask the staff for directions.
- There is a very convenient bus connection to the center of the city. Take bus 31 at the bottom of the hill. Bus stops at Jakominiplatz and Hauptplatz in the center of the old city.



Galen