Invited guests

- Maja Bračič Lotrič (Univ. of Ljubljana, Slovenia)
- Silvio Cavalcanti (Univ. of Bologna, Italy)
- Gilbert Chauvet (Univ. of Paris V, France)
- Andrew Fowler (Oxford Univ., Great Britain)
- Michael Guevara (McGill Univ., Canada)
- Dirk Hoyer (Friedrich Schiller Univ., Jena, Germany)
- Eunok Jung (Oak Ridge National Laboratories, U.S.A.)
- Armin Leuprecht (Technical Univ. Graz, Austria)
- Abraham Noordergraaf (Univ. of Penn., U.S.A.)
- Johnny Ottesen (Roskilde Univ., Denmark)
- Alexander Panfilov (Utrecht Univ., Netherlands)
- Michael Rosenblum (Univ. of Potsdam, Germany)
- Loring Rowell (Univ. of Washington, U.S.A.)
- Wolfgang Schreiner (Univ. of Vienna, Austria)
- Virend Somers (Mayo Clinic, Rochester, U.S.A.)
- Aneta Stefanovska (Univ. of Ljubljana, Slovenia)
- Hien Tran (North Carolina State Univ., U.S.A.)
- Janos Turi (Univ. Texas, Dallas, U.S.A.)
- Mario Ursino (Univ. of Bologna, Italy)
- Peter Wabel (Technical Univ. Darmstadt, Germany)
- Nico Westerhof (Free Univ. Amsterdam, Netherlands)
- Robert Zietse (Univ. Hospital Rotterdam-Dijkzigt, Netherlands)
- Ulrich Zwiener (Friedrich Schiller Univ., Jena, Germany)

Titles of talks

1. M. Bračič Lotrič
   Cardiovascular dynamics - analysis of its oscillations and their synchronization

2. S. Cavalcanti
   Model-based analysis of pressure response to hemodialysis-induced hypovolemia.

3. G. Chauvet
   On the integration of physiological systems: the example of respiratory regulation

4. A. Fowler
   Mathematical modelling of respiratory control and the prediction of periodic breathing

5. M. Guevara
   Scale invariance in the cardiovascular system

6. D. Hoyer
   Evaluation of different types of cardiovascular-respiratory interdependencies - approaches by mutual information and phase synchronisation statistics.

7. E. Jung
   Simulations of valveless pumping using the Immersed Boundary Method: Parameter studies.

8. A. Leuprecht
   Computer simulations of blood flow in large arteries

9. A. Noordergraaf and J. Ottesen
   Implications of the integer ratio between cardiac and respiratory rates

10. A.V. Panfilov
    Electrophysiological model of the heart and its application to studying of cardiac arrhythmias

11. M. Rosenblum
    Quantitative analysis of cardiorespiratory interaction in healthy infants

12. L. Rowell
    Some crucial problems in cardiovascular control during exercise

13. W. Schreiner
    Modes of optimization of arterial tree models

14. V. Somers
    Cardio-respiratory interactions in neural circulatory control - insights from studies in health and disease.

15. A. Stefanovska
    The cardiovascular system as a system of coupled oscillators

16. H.T. Tran
    The human respiratory control system: models, applications, and analyses

17. J. Turi
    Feedback stabilization in differential equations with state-dependent delays

18. M. Ursino
    A Mathematical analysis of short-term cardiovascular regulation during changes in blood gas content and exercise

19. P. Wabel
    Model based control of hemodialysis

20. N. Westerhof
    Cardiac and arterial contribution to blood pressure in hypertension

21. R. Zietse
    Differences between our simulation study of intercompartmental fluid shifts during dialysis and the in vivo situation improve our understanding of dialysis

22. U. Zwiener
    Nonlinear dynamics in cardiovascular pathophysiology

Workshop Schedule Thursday

Time	Talk
7:30-8:45	**Breakfast**
9:00	**N. Westerhof** Cardiac and arterial contribution to blood pressure in hypertension
9:45	**E. Jung** Simulations of valveless pumping using the Immersed Boundary Method: parameter studies.
10:30	**BREAK**
11:00	**G. Chauvet** On the integration of physiological systems: the example of respiratory regulation
11:45	**A. Leuprecht** Computer simulations of blood flow in large arteries
12:05-13:30	**Lunch Break**
13:30	**D. Hoyer** Evaluation of different types of cardiovascular-respiratory inter-dependencies - approaches by mutual information and phase synchronisation statistics
14:15	**A. Noordergraaf and J. Ottesen** Implications of the integer ratio between cardiac and respiratory rates
15:45	**Outing**
19:00	**Dinner**

Workshop Schedule Friday

Time	Talk
7:30-8:45	**Breakfast**
9:00	**M. Rosenblum** Quantitative analysis of cardiorespiratory interaction in healthy infants
9:45	**A. Stefanovska** The cardiovascular system as a system of coupled oscillators
10:30	**BREAK**
11:00	**U. Zwiener** Nonlinear dynamics in cardiovascular pathophysiology
11:45	**J. Turi** Feedback stabilization in differential equations with state-dependent delays
12:30-14:30	**Lunch Break**
14:30	**A.V. Panfilov** Electrophysiological model of the heart and its application to studying of cardiac arrhythmias
15:15	**A. Fowler** Mathematical modelling of respiratory control and the prediction of periodic breathing
16:00	**BREAK**
16:30	**M. Guevara** Scale invariance in the cardiovascular system
17:15	**M. Ursino** A mathematical analysis of short-term cardiovascular regulation during changes in blood gas content and exercise
18:30	**Dinner**

Workshop Schedule Saturday

Time	Talk
7:15-8:15	**Breakfast**
8:30	**H.T. Tran** The human respiratory control system: models, applications, and analyses
9:15	**W. Schreiner** Modes of optimization of arterial tree models
10:00	**BREAK**
10:30	**L. Rowell** Some crucial problems in cardiovascular control during exercise
11:15	**R. Zietse** Differences between our simulation study of intercompartmental fluid shifts during dialysis and the in vivo situation improve our understanding of dialysis
12:00-13:15	**Lunch Break**
13:15	**P. Wabel** Model based control of hemodialysis
14:00	**S. Cavalcanti** Model-based analysis of pressure response to hemodialysis-induced hypovolemia.
15:00	**Outing**
18:30	**Dinner**

Abstracts

Maja Bračič Lotrič

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Cardiovascular dynamics - analysis of its oscillations and their synchronization

Time series resulting from recordings of blood circulation, i.e. heart rate variability, respiration, blood flow and blood pressure, are nonstationary because the system is far from equilibrium. They are composed of oscillations on different time scales. The characteristic times of oscillation span from around one second for the heart rate of a resting, healthy human to minutes, days and even years. To distinguish them, logarithmic frequency resolution is necessary.

Each of the characteristic frequencies varies in an oscillatory fashion. Under these conditions, estimation of the frequency content requires a method that allows for an adjustable window length. Wavelet analysis, a scale-independent method, was therefore chosen. The window is not only translated along the signal, but is also scaled. High frequency components are analyzed with a short window, while longer windows are used for the lower frequency components. In this way, good frequency resolution for low frequencies, and good time resolution for high frequencies, are obtained.

The frequency content corresponding to repetition times from around one second to few minutes, i.e. from 0.0095 to 2 Hz, was estimated from signals recorded simultaneously in humans. Within this frequency interval, five characteristic peaks were detected in all signals and all measured subjects, around 0.01, 0.04, 0.1, 0.2 and 1 Hz, the latter two corresponding to the respiratory and cardiac systems.

We have observed short episodes of synchronization or entrainment of the cardiac and respiratory rhythms in healthy relaxed subjects, and so we may infer that the coupling between heart and respiratory systems is of the kind that enables synchronization to exist. Synchronization is not, however, a state of the system but, rather, a process of adjustment of its rhythms. The two interacting systems are not isolated, and they face the influence of other physiological systems whose impact may be to change the stability or even the existence of phase-locked solutions. Episodes of synchronization were also observed among some of the other oscillatory processes.

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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]. Moreover, there is evidence supporting the hypothesis that an impaired autonomic regulation, unable to provide efficient compensatory response to hypovolemia, could play a pivotal role in the onset of acute hypotension [2]. To prevent overly large circulatory stresses, on-line monitoring of blood volume is rapidly gaining acceptance in clinical practice [3]. 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 few parameters representative of patient vascular reactivity [4]. Currently, we are using this approach to investigate the hypothesis that parameters representative of patient efficacy in venous capacity and vascular resistance regulation could change in hemodialysis with collapse compared with hemodialysis without collapse. To test this hypothesis, mean arterial pressure (MAP), heart rate (HR) and changes in relative blood volume (BV) were recorded in 7 hypotension-prone subjects during 2 consecutive sessions: the first one terminated with collapse and second one without collapse. The same set of hemodynamic data was recorded in 7 control subjects during 2 consecutive sessions without collapse. BV and HR data collected in each session were used as inputs to the simulator, and the simulated MAP was fitted to the measured data by identifying model parameters relative to the control of venous capacitance and peripheral resistance. Model-based computer analysis revealed a significant reduction ($-67.00 \pm 27.2\%$ $p < 0.05$) of the parameter representative of efficacy in venous capacitance regulation in the sessions with collapse with respect to the ones without collapse. No significant difference was observed when comparing the values of this parameter in

the two sessions of control subjects. No difference in the parameter relative to the control of peripheral resistance was found in both hypotension-prone and control subjects.

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On the integration of physiological systems; the example of respiratory regulation

A crucial problem in physiology is the determination of couplings between organisms sub-systems. Because a complex system is composed of interacting parts, a unique formalism is needed which can involve the whole system as well as its components. Another difficulty results from the hierarchical nature of the biological system, which requires traversing levels of organization. Why considering hierarchical systems? In biology, structural hierarchy appears clearly in the usual schema: nucleus, cell, tissue, organ, organism. However, constraints appear because functional processes evolve in a hierarchical structural system. We may note that traversing levels of organization correspond to a structural discontinuity, i.e. a structural border between distinct functional processes. So, the hierarchy describes a specific physiological process at each level, of course coupled with processes evolving in

adjacent levels. We have proposed to describe these systems in terms of functional interactions from a source to sinks, with transformations in the sink which correspond to distinct functional process (Chauvet, 1993a). This is the case of the transport of a molecule through the membrane of the target cell.

Structural discontinuities result in the non-locality of the global functional processes (Chauvet, 1993b). In a space without structural discontinuity, processes are local, however giving rise to non homogeneous structures (e.g. chemical reactions far from equilibrium (Prigogine, 1971)). The non-local process allows for the passage from a structure in which phenomena are local to another in which phenomena are also local. Then, the difficulty of the formalized description results from this discontinuity in which functional processes are different and necessary to the transport of the interaction.

A new formalism, called S-Propagator formalism (Chauvet, 1996, 1998), has been proposed to study the dynamics of hierarchical physiological systems, i.e. to traverse levels of organization. We have shown that the dynamics depend on operators that correspond to the usual models that describe elementary physiological mechanisms. A general n-level field equation which corresponds to an identical diagram for any physiological function is:

$$\begin{aligned} \frac{\partial \Psi^s}{\partial t}(s,t) &= \nabla_s \left(D^s \nabla_s \, \Psi^s(s,t) \right) \\ &+ \sum_{s' \in D_s(s)} P_{s',s} \left[\Psi^c \right] \Psi^s \left(s', t - \frac{d(s',s)}{v^s} \right) + \Gamma_s \end{aligned} \quad (1)$$

In this equation, Ψ^s s is the field variable, e.g. the dioxide concentration in lung capillaries, and P is the propagator at the lower level, i.e. in this example the transport of O2 molecules from alveolar bags at s' where the concentration is c(s',t) into the current bag where the concentration is c(s,t), then across the membrane and on the vascular side. A new interpretation of the observed phenomenology is suggested and applied to the respiratory system, the nervous system, and their couplings. We show how they are involved in the general equations.

The approach proposed here for the integration of coupled physiological systems is based on the representation of the biological system in terms of non-local functional interactions between the structural units. The non-local operator H is then associated with the interaction, which represents the transport of matter from one point to another, such that the corresponding equation is a field equation: $H_\Psi = \Gamma$ where Ψ is the field variable and Γ is the local source. The same type of equation (1) is valid at each level, and is associated with a set of differential equations. The non-local operator H_l is expressed in terms of the S-Propagator that is the product of specific operators describing the passage of the interaction through the levels of organization. Each operator may be analytically described by a specific model

with appropriate assumptions for the specific experiment to interpret. An important advantage of this formalism is the ability to describe physiological systems in the same framework.

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Andrew Fowler

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Mathematical modelling of respiratory control and the prediction of periodic breathing

The Mackey-Glass (1977) model of respiratory control serves as a useful if misleading toy model for pedagogical purposes. The more complicated Grodins-Buell-Bart (1967) model suffers from its very complexity. In this talk we show how it can be reduced to surprisingly simple forms, and we use the resulting simplified model in two ways to illustrate the role of central and peripheral chemoreceptors in causing Cheyne-Stokes respiration and periodic breathing. We discuss difficulties involved in interpreting the model results clinically, and we offer some possible directions for future model development.

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Scale invariance in the cardiovascular system

The His-Purkinje system is the specialized, rapidly conducting system responsible for bringing excitation more-or-less simultaneously to the many working muscle cells in the ventricles. It has been suggested that the branching nature of this system results in a fractal anatomic network. Moreover, this anatomic fractal is then supposed to somehow confer fractal or scale-invariant properties onto the QRS complex of the electrocardiogram, which reflects activation of ventricular muscle.

In particular, the $1/f^{\alpha}$ ($\alpha \cong 4$) falloff with frequency f in the power spectrum of the QRS complex has been attributed to such scale-invariant dynamics. We show that there is a much less esoteric explanation for this $1/f^{\alpha}$ spectrum: the pulse-like nature of the QRS complex itself.

Another time-series to which scale-invariant dynamics has been attributed is heart rate. The power spectrum of a 24-hour recording of the interbeat interval typically falls off with frequency as $1/f^{\alpha}$ at low frequencies, with $\alpha \cong 1$. This $1/f$ characteristic has again been taken as evidence for the existence of a fractal time-series, self-similarity, scale invariance, and even chaotic dynamics. However, the circadian sleep-wake cycle, which involves a large excursion in average heart rate, makes a large contribution to the power spectrum, being the predominant contributor to the spectrum at very low frequencies. Indeed, since this waveform is essentially square-wave in shape, this circadian rhythm produces a $1/f^2$ contribution to the power spectrum, starting at the lowest possible frequencies. The 24-hour sleep-wake cycle thus provides a $1/f^2$ "skeleton" upon which are added the contributions from processes with higher fundamental frequencies (e.g. ultradian rhythms, movement, 10-sec rhythm, respiration). There are many blood-pressure control systems, operating with characteristic times ranging from seconds, through minutes and hours, to days (see e.g. Fig. 22-1 in Guyton A.C., *Textbook of Medical Physiology*, 5th Edition, 1976). It should thus not be a surprise that the action of these various control systems produces appreciable frequency content over several decades of frequency in the power spectra of the blood pressure and the interbeat interval (*via* e.g. the baroreceptors). The addition of these other spectral components raises the high-frequency end of the log-log plot of the spectrum, so that the (averaged) overall spectrum is often quite well fit by a straight line with a slope of approximately -1 (i.e. $1/f$ spectral falloff). However, restriction of the fit to the lowest decade of frequency often reveals the presence of the underlying $1/f^2$ component attributable to the 24-hour circadian component. Synthesized interbeat interval signals, such as a linear trend or a sine wave that

has a period slightly different from 24 hours, also result in $1/f^{\alpha}$power spectra. These findings indicate that caution should be exercised in imputing scale-invariance, etc... to physiologic signals.

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Evaluation of different types of cardiovascular-respiratory interdependencies - approaches by mutual information and phase synchronisation statistics

The fluctuations of the heart rate are related to several mechanisms of the complex autonomic functioning such as respiratory heart rate modulation and phase dependencies between heart beat cycles and breathing cycles. The underlying processes are basically non-linear.

We introduce mutual information measures which provide access to non-linear interdependencies as counterpart to the classical linear respiratory heart rate modulation analysis. The phase interdependencies between the heart beat cycles and the respiratory cycles are evaluated by means of histogram statistics and dynamic properties of the instantaneous phase differences and corresponding surrogate data using randomised phase relations.

By means of the introduced measures a quantitative characterisation of those cardiorespiratory behavioural aspects is enabled which can be interpreted in terms of "relative coordination" based on coupled non-linear oscillators and in terms of complex dynamics based on multi-matched control loops.

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Joint work with: Ulrich Zwiener, Reinhard Bauer, Michael Eiselt

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Simulations of valveless pumping using the Immersed Boundary Method: parameter studies

Flows driven by pumping without valves are observed, motivated by biomedical applications: cardiopulmonary resuscitation (CPR) for the thoracic pump model and the human fetus before the development of the heart valves. The direction and magnitude of the fluid inside a loop of tubing which consists of (almost) rigid and flexible parts are investigated when the boundary of one end of the flexible segment is forced periodically in time. Despite the absence of valves, a net flow around the loop is generated by a valveless mechanism in a circulatory system. A startling result, "the direction and magnitude of the flow depend upon the parameters, such as frequency, amplitude, compression duration, and the fraction of the flexible boundary being compressed", is observed.

The Immersed Boundary Method that is applicable to problems involving an elastic structure interacting with a viscous incompressible fluid is used in these simulations.

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Computer simulations of blood flow in large arteries

It is widely accepted that there exists a correlation between local blood flow behavior and the genesis and development of arterial disease. Consequently, the study of hemodynamic phenomena at specific regions in the vascular system has become a field of research world-wide. A deeper understanding of pathological processes can be gained by the mathematical modeling and numerical simulation of the occurring flow effects which is enabled by the significant advances in numerical mathematics and the essentially increased power of computers. Over the past years several contributions have been made and increasingly more elaborate models of the vascular system have been developed in order to gain a better insight into the physiological processes. The advantages of the numerical approach are numerous where numerical techniques and the computer simulations yield detailed and accurate quantitative results. The presentation deals with the computer simulation of arterial blood flow effects where the essential features are the anatomically

correct modeling of the complex vessel geometries and the consideration of time-dependent flow domains. The development of suitable techniques for the reconstruction of geometrical individual morphologies is an important step. The description of blood flow uses the incompressible Navier-Stokes equations applying the Arbitrary Lagrangian-Eulerian modification in order to face the time-varying geometry. Elastic behavior of blood is modeled by a constitutive relation of Jeffrey's type. The numerical solution of the flow problem applies a velocity-pressure correction method, where the theoretical framework for the projection scheme is provided by the Helmholtz decomposition principle. The numerical approach uses streamline upwind stabilized finite elements.

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Implications of the integer ratio between cardiac and respiratory rates

Several investigators have reported observations in which the ratio heart frequency/respiratory frequency proved to be integer numbers. These were found in humans, both in space and on earth, as well as in warm blooded animals. They occurred primarily in healthy normals during deep sleep. The ration was reported to vary widely, from as low as 2 to as high as 7, with a preference for 3 and 4 in the human [1].

Donders, one of Harveys critics, proposed in 1856 that the "respiratory pump" assists the circulation of blood through a valveless mechanism [2], an idea that was debated for decades [3] without arriving at a firm conclusion. In this report, implications of the integer ratio will be analysed to arrive at a fuller understanding of the respiratory pump issue. To this end, a model of the central systemic venous system in conjunction with the right heart was developed. It retains their basic properties in spite of simplifications. This nonlinear model was described in the form of equations, which were solved in closed form.

Analysis of the results shows that in the steady state under the condition of an integer ratio, venous return flow, though modulated by the respiration,

is on average not influenced by the presence or absence of respiration. This suggests that the Donders claim is not valid in the general formulation in which it was originally presented. However, if the condition of an integer ratio is eliminated, venous return is influenced by respiratory activity, both through modulation and in average value. This means that Donders proposal would apply to the periods of wakefulness and activity.

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Alexander Panfilov

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Electrophysiological model of the heart and its application to studying of cardiac arrhythmias

Cardiac arrhythmias are the leading cause of the death in the industrialized countries accounting for about 1 death in 10. In most of the cases cardiac arrhythmias occur due to abnormalities of propagation of electrical waves of excitation in the heart.

My talk will review basic regimes of abnormal wave propagation in cardiac tissue such as reentrant sources or spiral waves and discuss the relation between their dynamics and types of cardiac arrhythmias.

Then I will focus on a new approach in mathematical cardiology: developing of a realistic computer model of the heart. This model is based on detailed anatomical data on heart structure and fiber orientation field. It will be discussed the strategies of modeling of atria and ventricles of the heart, the choice of equations for cardiac tissue and some numerical issues.

Finally, I will show the results of study of cardiac arrhythmias using the electrophysiological model of the heart. The main focus will be on the most

dangerous arrhythmia: ventricular fibrillation. In particular, I will discuss the possible mechanisms of ventricular fibrillation such as the restitution hypothesis, Moe's multiple wavelet hypothesis, idea of induced fibrillation and some others. It will be shown the results of study of ventricular fibrillation in our electrophysiological model of the heart. The fibrillation will be induced via the phenomenon of spiral breakup (restitution hypothesis). I will show the patterns of excitation which occur on the surface of the heart and in three dimensions, discuss the problem of quantification of ventricular fibrillation and possible implications of the resolution hypothesis for pharmacological management of ventricular fibrillation.

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Quantitative analysis of cardiorespiratory interaction in healthy infants

We use the recent developments in the theory of synchronization of irregular (noisy or chaotic) oscillators to address the cardiorespiratory interaction. We discuss the notion of phase for complex systems as well as the methods of instantaneous phase estimation from data. Next, we discuss how the strength of the interaction can be quantified by means of the analysis of interrelation between the phases. We introduce and compare several synchronization indices. Using model and real data sets as examples, we demonstrate that the index based on the stroboscopic approach is mostly suitable for the analysis of cardiorespiratory interaction. As the next step, we consider the problem of detecting the direction of interaction of two systems. The main idea here is that in case of unidirectional coupling ($1 \to 2$) the perturbations in the system 1 can be traced in the system 2, but not vice versa. We use this idea to introduce the directionality index that quantifies the asymmetry in coupling.

Finally, we report the results of experimental study in a group of healthy infants. We conclude that one of the quantitative measures - the conditional probability index - allows reliable detection of synchronous epochs of diferent

order $n : m$ and, thus, makes possible an automatic processing of large data sets. It turned out that the average degree of synchronization varies with the age of the newborns.

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Some crucial problems in cardiovascular control during exercise

Two classes of problems are addressed. Problem I concerns factors that enhance or impede optimal mechanical coupling of the heart and vasculature. At rest resistive and capacitive properties of the peripheral vasculature restrict the ability to raise cardiac output (CO); this means that CO is a determinant of end diastolic volume (EDV), but conversely, EDV is a determinant of stroke volume (SV) and CO. So, what passive physical properties and mechanical factors determine the distribution of blood volume so as to maintain or raise EDV and SV during exercise? We must consider, for example: a) complex mechanical interactions between the heart and pericardium and their interactions with the lungs, chest wall and diaphragm; b) interactions between veins (and venous volume) and surrounding structures; c) effects of blood flow on venous pressure and volume in compliant vs. non-compliant organs; and effects of muscle contractions on arterial and venous volumes and flows - including additional effects of posture and gravity. The key functional links in mechanical coupling between the heart and peripheral circulation are the cardiac muscle length-tension relationship and the peripheral vascular pressure-volume-flow relationship.

Problem II concerns those reflexes that may control the circulation during exercise. We ask: what error signals are sensed and regulated by the autonomic nervous system (ANS)? Does the ANS primarily correct mismatches between blood flow and metabolism - or flow errors - or does it correct mismatches between CO and vascular conductance - or pressure errors - or both? Open-loop gains for muscle chemoreflexes (MCR) which correct flow errors, and the arterial baroreflex, which corrects pressure errors are similar. A large margin for flow error militates against a tonically active role for MCR during exercise. Conversely, stimulus response curves for the carotid sinus baroreflex plus consequences of interference with either the pressure signal or the reflex suggest a major role for the baroreflex.

Wolfgang Schreiner

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Modes of optimization of arterial tree models

Assuming that arterial trees fulfill their task in an optimized fashion, one can expect that a procedure involving "optimization" has the potential of inducing model structures closely related to what is found in reality. This is the basic idea of constrained constructive optimization (CCO), a computational technique developed to generate optimized models of arterial trees from first principles. Without the input of anatomical data, CCO generates the structure of a tree of tubes by adding segment by segment in a geometrically optimized fashion. In analogy to the development of living systems each step of CCO growth is determined by the structure developed in the preceeding steps. Accordingly, the procedure may be interpreted as a generator whose rules develop along the structure generated. Minute changes at early stages evolve to major differences later on.

Several different optimization modes and boundary conditions can be employed: Different random number sequences, shapes of perfusion domain, bifurcation laws and optimization targets. Optimization may either be performed under preset terminal flows or under uniform shear stress between blood and the vessel walls. The dispersion of shear stress itself as an optimization target proved unstable.

A further mode of guiding CCO model structure is "staged growth". It draws on the fact that segments generated during the initial phase turn into the major branches later on and all other segments arrange appropriately. Staged growth has been successfully used to model large coronary arteries along the epicardium.

Current projects include the evaluation of structure and perfusion along the concepts of fractal analysis as well as interfaces for entering gross coronary models derived from individual patients.

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Joint work with: R. Karch, F. Neumann, M. Neumann

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The cardiovascular system as a system of coupled oscillators

We present a modelling approach to the cardiovascular system, treating it as a system of coupled oscillators. It concentrates on the oscillatory nature of the dynamics on the time-scale of one average circulation period. The aim is to develop the simplest possible model that is able to reflect the oscillatory character of cardiovascular dynamics and is capable of reproducing the main statistical and dynamical features characteristic of the measured time series. These include the form of spectra and the frequency/amplitude variations of the heart rate, respiration, blood flow and blood pressure, and the main features of the synchronization phenomena that are observed experimentally.

The model synthesis was based upon the experimental observation that *five* main frequency components can be found in various physiological time series, e.g. blood pressure, blood flow, ECG and respiration. Accordingly, a system of five coupled oscillators was chosen to model the dynamics. The basic unit in the model, corresponding to the autonomous part of the oscillator, possesses the properties of structural stability, robustness and symmetry that are consistent with physiological understanding, and with the analyses of measured time series:

$$\begin{aligned} \dot{x}_i &= -x_i q_i - \omega_i y_i + g_{x_i}(\mathbf{x}) \\ \dot{y}_i &= -y_i q_i + \omega_i x_i + g_{y_i}(\mathbf{y}) \\ q_i &= \alpha_i(\sqrt{x_i^2 + y_i^2} - a_i) \end{aligned}$$

where $\mathbf{x}$, $\mathbf{y}$ are vectors of oscillator state variables, α_i, a_i, and ω_i are constants and $g_{yi}(\mathbf{y})$ and $g_{xi}(\mathbf{x})$ are linear coupling vectors. The activity of each subsystem is described by two state variables, the blood flow x_i, and the velocity of flow y_i, where i denotes the i-th oscillator corresponding to one of the physiological systems, viz. the cardiac, respiratory, myogenic, neurogenic or endothelial activities. The impact of other subsystems, acting on slower time scales, is taken into account as coupling terms and/or as random noise.

A key feature of the model synthesis is the treatment of the couplings between oscillators. The nature of the couplings is currently unknown for most of the relationships between the subsystems. In the model linear couplings are therefore introduced. Oscillators with linear couplings are found to reproduce the main characteristic features of the experimentally obtained spectra. To explain the variability of cardiac and respiratory frequencies, however, it is essential to take into account the rest of the system, i.e. to

consider the effect of noise. It is found that the addition of noise also results in epochs of synchronization, as observed experimentally. Preliminary analysis suggests that there is a mixture of linear and parametric couplings, but that the linear coupling dominates.

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The human respiratory control system: models, applications, and analyses

Mathematical models of the human respiratory system have been developed since 1940 to study a wide range of features of this complex system. The phenomena collectively referred to as periodic breathing (including Cheyne-Stokes respiration and apneustic breathing) have important medical applications. The hypothesis that periodic breathing is the result of delay in the feedback signals to the respiratory control system has been studied by several investigators since the early 1950s. In this talk, we will describe a mathematical model, which is a nonlinear system of five differential equations with state-dependent delays in the feedback control loop, for the respiratory control system. This model has been used to study the phenomena of periodic breathing and apnea as they occur during quiet sleep in infant sleep respiration at around 4 months of age, which is a time frame of high incidence of sudden infant death syndrome (SIDS).

Furthermore, analyses that were done on a simplified mathematical model of two nonlinear delay equations to illuminate the effect of delay on the stability will be shown. Recent study to validate the mathematical model using experimental data will also be discussed.

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Feedback stabilization in differential equations with state-dependent delays

In this presentation we consider the problem of feedback stabilization in a class of functional differential equations with state-dependent delays. In particular, we show that a constant steady state of the controlled state-dependent delay equation is exponentially stable if a zero solution of a corresponding linear equation is exponentially stable. As an application, we consider the stability of steady states in a system of delay equations, proposed to model the dynamics of respiration in humans.

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A mathematical analysis of short-term cardiovascular regulation during changes in blood gas content And exercise

In the first part of this work we present a mathematical model of the short-term cardiovascular control to acute changes in blood gas content. The model includes a pulsating heart, the systemic and pulmonary circulation, a separate description of the vascular bed in organs with the higher metabolic need (coronary, cerebral and skeletal muscle circulation), and the local effect of oxygen and CO2 on these organs. Moreover, the model also includes the action of several reflex regulatory mechanisms: the peripheral chemoreflex, the lung-stretch receptor reflex, the arterial baroreflex, and the response of the central neural system to medullary changes in O2 and CO2. These reflex mechanisms work by modifying the vagal activity to the heart and the sympathetic activity to the resistance vessels, systemic veins and to the heart. The main aspects of the model are validated by comparing simulation results with data from the literature. By using a single set of parameters the model is able to correctly reproduce the acute response to various perturbations, including normocapnic hypoxia, normoxic hypercapnia, hypocapnic hypoxia and hypercapnic hypoxia (asphyxia).

The second part of this work briefly summarizes the very last improvements performed on the model, in order to mimic the cardiovascular response to dynamic exercise. This response depends on the interaction among several additional mechanisms, both local (decrease in venous O2, saturation,

accumulation of metabolites in the perivascular space of the organ under exercise, muscle pump), reflex (baroreflex activation, lung stretch receptors) and central. A good reproduction of the result in the literature can be achieved assuming that a central command causes a decrease in vagal tone, and an increase in sympathetic activity, especially towards the systemic venous vascular bed. Finally, these model results are critically discussed and lines for future works pointed out.

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Joint work with: Elisa Magosso

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Model based control of hemodialysis

Hemodialysis is the treatment of choice for patients with chronic or acute renal failure. Hemodialysis replaces the two main functions of the kidney: detoxification and fluid removal (Ultrafiltration, 2-4 l). The plasma water depletion induces a transient reduction of circulatory blood volume (20 - 30%), thereby causing hypovolemia that perturbs cardiovascular functions. An impaired autonomic-mediated regulation of cardiovascular function may cause the onset of sudden dramatic decrease in arterial pressure, which has been recognised to be one of the most serious complications of hemodialysis occurring in 30% of all treatments. Therefor it is important to introduce novel approaches to integrate hemodynamic data collected during the hemodialysis procedure to manage the therapy and reduce the risk of hypotensive episodes. An identification phase of three hemodialysis treatments on the same patient is used to adapt a model to the patient specific impairments. The model represents a closed circulatory system, including three compartments and a non pulsatile heart model. The model controls the systemic resistance and venous volume shift through an integrated control loop. The initial conditions are calculated through an inverted heart model, using cardiac output as an input. The adaption of the model to the patient is not only based on mean arterial pressure but additionally on cardiac output. After the identification this model allows to calculate non measurable parameters like total peripheral resistance, venous pressure or unstressed venous volume. These parameters are known to represent the state of the cardiovascular system much better then the mean arterial pressure. A controller is designed and presented that calculates online during the treatment the Ultrafiltration Rate, which is set on the Dialysis Machine.

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Cardiac and arterial contribution to blood pressure in hypertension

Blood pressure results from the interaction of the heart, the pump, and the arterial system, the load. When the arterial load is increased, by a larger peripheral resistance and decreased arterial compliance, and hypertension follows, the heart will remodel or hypertrophy. We therefore wondered if and how much the remodeled or hypertrophied heart contributes to blood pressure.

We constructed a simplified model of the heart and arterial load. The cardiac part of the model is based on the varying elastance concept (Suga et al., 1973) and is described with 3 parameters: diastolic (Emin) and end-systolic (Emax) pressure-volume relations, and the intercept of these relations with the volume axis (Vd). Venous return is represented by venous filling pressure (Pv). The normalized time-varying elastance curve is taken constant on basis of the report by Senzaki et al. (1996), where it was found, in the human, that the normalized curve is similar for many normal and pathological conditions. The arterial load is modeled with a four-element windkessel model (Stergiopulos et al., 1999). This model, with a total of 8 parameters, was tested on human and animal data and shown to produce accurate aortic pressures and flows.

We used the data of Ganau et al. (1992) to derive the eight parameters for normotensive subjects and 4 groups of hypertensive subjects. The four groups of hypertensive patients were: normal left ventricle, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy. Using the derived parameters the model accurately predicts the systolic and diastolic blood pressure for all these conditions.

Using the model, with the known parameters we can now derive the individual contribution of the arterial load and of the heart to the blood pressure. In the normotensive subjects blood pressure is 124/77 mmHg. In the hypertensive patients with still normal left ventricle the systolic pressure is 145 mmHg. The increase of 21 mmHg is for about 50% due to the arterial load increase and about 50% due to the changed left ventricle. In concentric remodeling almost the entire pressure increase results from the increased load alone. In concentric hypertrophy both the arterial load change and cardiac change contribute equally to the systolic blood pressure increase. In eccentric hypertrophy the pressure increase is mainly the result of the change in cardiac pump function.

Another approach to study blood pressure is to describe the heart as a pump by means of the pressure-flow relation, the pump function curve (Elzinga and Westerhof, 1973) and describe the arterial system on basis of traveling waves. In hypertension, when reflection is increased, the heart hypertrophies, which results in a pump function graph that approaches a flow source. With a flow source reflections have a stronger effect on aortic pressure, resulting in a higher systolic pressure (Westerhof and O'Rourke, 1995). We conclude that when the heart remodels or hypertrophies the changed pump characteristics contribute to the high blood pressure.

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Differences between our simulation study of intercompartmental fluid shifts during dialysis and the in vivo situation improve our understanding of dialysis

We recently introduced a mathematical model to study the intercompartmental fluid shifts during hemodialysis (HD) and ultrafiltration (UF) (ASAIO J 2000). We analyzed the relative importance of variables such as blood urea concentration, the sodium concentration gradient and ultrafiltration by performing a sensitivity analysis. Some parameters, such as the permeability coefficients, compliance, and initial ratio of different volume compartments were taken from literature, although they likely to change during dialysis therapy. Continuous blood volume monitoring (BVM) technique enables real time observation of the relative change in blood volume (RBV) during HD and UF. We compared the changes in fluid and solute fluxes that are predicted, to those observed during actual treatment. Our mathematical model showed that UF volume and the size of the sodium gradient are the most important factors influencing the fluid shifts. However, in clinical practice, when RBV was plotted against ultrafiltration volume, we found a huge inter and intra-individual variability in RBV (NDT 1999). Moreover, when we increased the sodium gradient by hypertonic sodium infusions (3%), RBV did not increase significantly as compared to istonic saline infusions (NDT submitted; Abstract ASN 1999). During diffusive dialysis (DD)), the rapid fall in the urea concentration of the extracellular compartment is predicted to induce a volume shift from the extracellular to the intracellular compartment, which will lead to a decrease in blood volume by 1.4%. However, in the vivo situation, we showed that RBV increased during DD (Blood Purif 2000). We must assume that all these findings are caused by changes in the parameters that were taken from literature. Indeed, diffusive dialysis dialysis induces a decrease in vascular resistance and thereby changes in regional blood distribution, compliance and total permeability coefficient. Moreover, we showed that the hypertonic sodium infusions during dialysis reduced vascular tone. We conclude that large differences exist between our simulation study of fluid shifts during dialysis and the in vivo situation. However, these discrepancies have improved our understanding in the dialysis treatment, as these differences can be explained by a change in vascular tone.

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Nonlinear dynamics in cardiovascular pathophysiology

The evaluation of nonlinear properties within cardiovascular dynamics can give (i) the chance of better causal understanding and (ii) the origin of new therapy principles. In abnormal or disturbed cardiovascular regulation, we determined (i) "classical", (ii) recently developed nonlinear or complexity parameters, and (iii) those of nonlinear coordination. We found characteristical changes in hypoxia and during autonomous blockades. Taking simultaneously into account other main systemic parameters relevant for the disorders it is possible to explain the biopathological importance of the changed dynamics.

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Joint work with: D. Hoyer, R. Bauer, B. Walter

Session Chairs

Workshop Session Co-Chair Schedule Thursday

Morning Session	F. Kappel and M. Guevara
Afternoon Session	J. Batzel and P. Wabel

Workshop Session Co-Chair Schedule Friday

Morning Session	T. Kenner and J. Ottesen
Afternoon Session	M. Bachar and A. Stefanovska

Workshop Session Co-Chair Schedule Saturday

Morning Session	D. Schneditz and A. Noordergraaf
Afternoon Session	D. Auerbach and W. Schreiner

Outings

- Wednesday 19:30: Welcome get-together at the Kirchenwirt Resturant next to the Maria Trost church
- Thurdsay: Walking tour of Graz beginning about 15:45
- Friday: Evening tour of the Schlossberg beginning around 19:30
- Saturday: Bus tour to Riegersburg and a Buschenschank beginning around 15:00

General Information

- Meals are free for invited guests and others 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 A.S. 100 and dinner price A.S.75.
- Drinks at meals and (as well as coffee and beverages at breaks) are not free. Please pay for drinks in the "Oberwolfach-style", i.e., consult the price list and put the money in the basket at the bar in the dining room or coffee room.
- There are three good restaurants nearby: the Kirchenwirt besides the Maria Trost church, Restaurant Ohnime across the street, and the Roseggerhof 2 km. along the wood path from Maria Trost to Graz.
- There is a very convenient tram connection to the center of the city. Take Tram 1 at the bottom of the hill. Tram stop Hauptplatz is the central stop.

Special thanks to the following people who helped with this workshop:
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