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Coupled oscillators: Complex but not complicated cardiovascular and brain interactions

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Abstract— **Contemporary measurement techniques enable noninvasive observations of cardiovascular functions, both from the central and peripheral points of view. Cardiovascular dynamics is found to be characterised by several distinct frequency components, and these are present at each site of the system. The corresponding oscillatory processes are mutually dependent via couplings that lead to amplitude/frequency fluctuations of the characteristic peaks. New studies have been initiated to determine the interactions between the cardiovascular oscillations and some of the brain waves. The work will be reviewed and causal relations will be discussed with a special emphasis on detection of the depth of anæsthesia.**

I. INTRODUCTION

The cardiovascular system is complex and spatially distributed. The many connections between the system's components enable efficient regulation of blood flow through a closed system of vessels.

How do we approach the understanding of this complex system? Basically, there are two ways: a microscopic and a macroscopic approach. In the microscopic approach, one tries to analyse the function of each part of the system in great detail. The macroscopic approach, on the other hand, is interested in the collective behaviour of all parts. Both approaches are necessary to gain a complete understanding and the problem is where to start. Microscopic analysis of large complex systems inevitably results in a large system of differential equations. However, there are cases when a system that looks very complicated on the microscopic level exhibits rather simple macroscopic behaviour [1], [2].

We will show that the cardiovascular system is an example of such system. In the next section, we introduce the coupled nonlinear oscillators approach, the framework that we use for our studies of cardiovascular and brain oscillations. As background we describe the human cardiovascular system and present results of time-frequency analysis using wavelet transforms of several non-invasive measurements of cardiovascular signals. Studies of neuronal oscillations have been undertaken since the first human electroencephalographic (EEG) recording and the recent resurgence of interest in neuronal oscillations has led to an enhanced appreciation of their likely importance and to "the tantalizing conjecture that perception, memory and even consciousness could result from the synchronization of neuronal networks" [3]. The frequency scales for the neuronal oscillations, as presently revised, are presented in the fourth section. Recently, new studies have been initiated to determine the interactions between the cardiovascular oscillations and some of the brain waves [4]. This work will be reviewed in the final section, and causal relations between the cardio, respiratory and brain waves will be discussed with a special emphasis on detection of the depth of anæsthesia.

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II. COUPLED OSCILLATORS

The coupled nonlinear oscillators approach is marked by two major milestones: the introduction of the entrainment of collective oscillators by Winfree [5] and its analysis using the phase dynamics approach of Kuramoto [6]. Phase dynamics is obtained by reducing the number of degrees of freedom of the original dynamical system. The original dynamics should be perturbed weakly by noise, an external force or coupling to dynamics with a limit-cycle orbit. The latter applies to dissipative system, and the form of the phase dynamics is not dependent on the form of the original models. Their work of Winfree [5] and Kuramoto [6] further motivated the introduction of the theory of phase synchronization, facilitating studies of the interactions between coupled nonlinear and chaotic oscillators [7]. Coupled oscillators were proposed as a possible description of the dynamics of the cardiovascular system [8], [9] and synchronization and modulation between cardiac and respiratory oscillations were examined with particular care [10], [11], [12]. The emerging picture motivated additional studies, and methods for analysis of the direction of coupling among interacting oscillatory processes have recently been proposed (see [13] and the references therein).

III. CARDIOVASCULAR OSCILLATIONS

A. The system

The cardiovascular system, which consists of the heart and blood vessels, has one major function – transport. The total volume of blood circulates along the cardiovascular system in one minute on average. The circulatory system can be divided into two parts: the pulmonary circulation which moves blood through the lungs for exchange of oxygen and carbon dioxide; and the systemic circulation which supplies all other tissues (Fig. 1). The systolic and diastolic blood pressures have long been known to differ between the arterial and venous parts, and between the systemic and pulmonary circulation [14].

Observed on the macroscopic level, the heart acts as a pump that drives the blood through a closed circuit of elastic vessels. The respiratory activity is a generator of pressure

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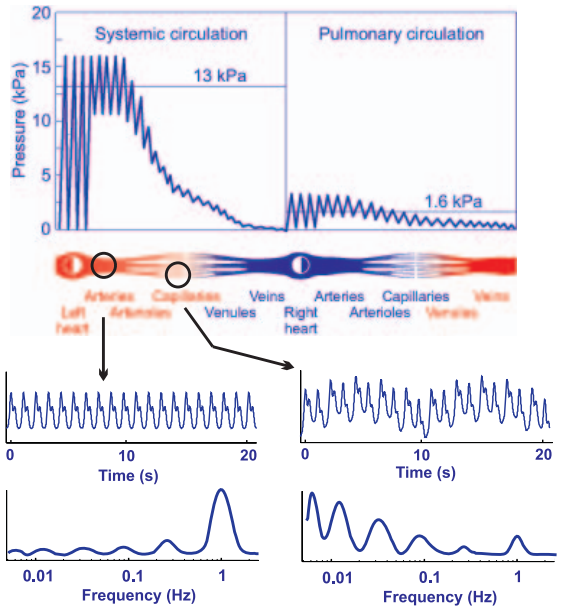

Fig. 1. The pulmonary and systemic circulation and the pressure distribution (modified from Folkow and Neil, 1971). The maximum is known as the systolic and the minimum as the diastolic pressure. In addition, based on recent measurements and analysis, the blood flow through the aorta and the capillaries and the amplitudes of their time-averaged wavelet transforms are indicated. While the amplitude of the oscillations generated by the heart as the main pump into the system dominates the aortic flow (bottom left), the amplitude and the corresponding power of oscillations in the capillary flow result from the central and peripheral regulatory mechanisms acting on a wide frequency scale (bottom right). The six spectral peaks are usually estimated from 30-min recordings, while, for the sake of clarity, only 20-sec segments are presented here (for details see eg [9], [15] and [16]).

that assists in the return of blood to the heart. The flow of blood also depends on the resistance of the vessels which is controlled by adjustment of their diameters. Consequently, the power of cardiac oscillations dominates the aortic flow and is significantly decreased in blood flow through the capillaries.

B. Oscillations

Time-frequency analysis of signals derived from respiration, cardiac function and blood flow revealed the existence of five almost periodic frequency components in the frequency interval from 0.0095-2.0 Hz [9], [15]. Recently, a sixth oscillatory component was identified in the interval 0.005-0.0095 Hz [16]. The frequency intervals are summarized in Fig. 2.

The cardiac and respiratory oscillations have frequencies of around 1.0 and 0.3 Hz, respectively. They originate centrally and are propagated through the system. In contrast, the low-frequency oscillations involved in the regulation of the vessels' resistance are generated locally. However, it is the continuous circulation of blood through the system of closed tubes that coordinates the local oscillatory activity of each individual mechanism and evidently synchronizes it for much of the time. Hence each physiological mechanism manifests as a single almost periodic process that we can observe at the macroscopic level. Consequently, the peaks in the low-frequency interval are broadened and can be best distinguished using logarithmic frequency resolution.

The physiological origin of the low-frequency oscillations has been investigated using laser Doppler flowmetry (LDF). The oscillations at around 0.1, 0.04, 0.01, 0.007 Hz have thus been associated respectively with the intrinsic myogenic activity of vascular smooth muscle, the neurogenic activity of the vessel wall, and two different mechanisms of vascular endothelial function [17], [18]. Nitric oxide and endothelium-derived hyperpolarizing factors are hypothesized to be involved in the oscillations near 0.01 and 0.007 Hz [16]; however the precise mechanisms giving rise to them need to be further elucidated.

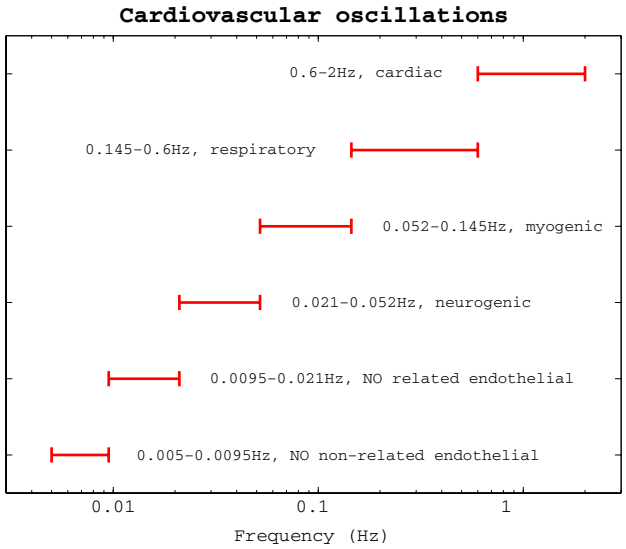

Fig. 2. The characteristic frequencies of cardiovascular oscillations in humans in the frequency interval from 0.005 to 2 Hz as defined or used in [9], [15]-[21].

These results suggest that the cardiovascular system as a whole, including the microcirculation, can usefully be treated as a single entity. In terms of frequencies, it is irrelevant at which point we observe the system, or which function we choose to measure: each regulatory mechanism is reflected on every site, and can be detected in each cardiovascular function; however its amplitude may differ with respect to the function and the site of observation (see Fig. 1). Moreover, the characteristic frequencies of the oscillatory components are shown to be confined to the same intervals in resting healthy subjects as in resting subjects with cardiovascular diseases [15]. The power within each interval can be used as a quantitative measure for charactersising the state of the system [9], [15].

Clinical and experimental studies have included patients with diabetes mellitus, myocardial infarction and cardiac failure. The perturbations of the cardiovascular oscillations brought about by exercise, anaæsthesia, and ageing have also been examined. For example, based on the logarithmic frequency resolution of the wavelet transform of the heart rate variability (HRV) signal, cardiac autonomic dysregulation was detected [19] in diabetic patients prior to clinical signs

of cardiac autonomic neuropathy. Anæsthesia is another state where clinical application of the cardiovascular oscillations approach may be significant. In the recent study [20] a substantial decrease of the low frequency components was demonstrated in the blood flow recorded by LDF during local anæsthesia.

The existence of characteristic peaks leads to the inference that each subsystem can be described mathematically as an oscillator [21], [22]. The systems are mutually dependent via couplings that lead to amplitude/frequency fluctuations and hence further broadening of the characteristic peaks.

C. Interactions

Simultaneous measurements of the cardiac and respiratory functions enable analysis of the cardiorespiratory interactions. The resultant modulation of the cardiac frequency, known as respiratory arrhythmia, has long been known to play an essential role in the overall performance of the system. Synchronization analysis [7], [10], [11] has confirmed that, in a conscious healthy subject at rest, the two systems can synchronize. We have shown that synchronization and modulation can coexist [11] and that the respiratory system is the driving system at all respiration frequencies, whether paced or spontaneous [13]. Two different methods, time-phase bispectral analysis [23] and a new inference technique [24], were used to demonstrate the existence of a *nonlinear* cardio-respiratory interaction.

Phase synchronization between the cardiac and respiratory oscillations has been investigated during anaesthesia in rats [9]. Synchrograms and the time-evolution of synchronization indices were used to show that the system passes reversibly through a sequence of different phase-synchronized states as the anaesthesia level changes, indicating that it can undergo phase transition-like phenomena. It was found that the synchronization state may be used to characterize the depth of anaesthesia.

IV. NEURONAL OSCILLATIONS

Studies of the interactions between the cardiovascular oscillations and brain waves were then initiated [4]. The frequency scales for the neuronal oscillations in the rat cortex, as recently revised by Buzsáki and Draguhn [3] are summarized in Fig. 3. Neuronal oscillations span an even wider frequency interval than cardiovascular oscillations, covering frequencies from 0.025 Hz to 600 Hz.

V. INTERACTIONS BETWEEN NEURONAL AND CARDIOVASCULAR OSCILLATIONS

Experiments were performed on 10 adult, male Wistar rats each weighing approximately 250 g. The animals were anæsthetized with a single intraperitoneal injection of ketaminhydrochloride (45 mg/kg b.w.) and xylazinhydrochloride (7 mg/kg b.w.) and placed in a darkened Faraday cage. The depth of anæsthesia was assessed at 5 min intervals by a nociceptive stimulus, the skin pinch-test, applied to the sole of the animal's front paw. Simultaneous recordings were made of EEG over the left and right parietal cortex, of

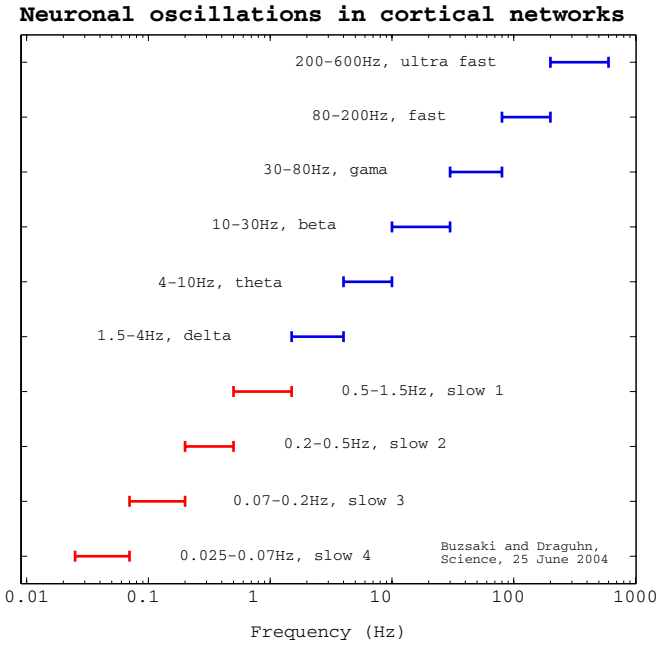

Fig. 3. The frequency scales of neuronal oscillations in rats as recently revised by Buzsáki and Draguhn [3]. The conventional frequency intervals consisting of δ, θ, β and γ bands are extended to incorporate fast and ultra fast γ waves and several slow δ waves.

the electrical activity of the heart (ECG), and of respiration measured with a piezo probe attached over the animal's chest. The three signals were sampled at 1 KHz with 16 bit resolution. The study will be presented in detail elsewhere [4], while here we summarize briefly the main results.

The instantaneous phases of the cardiac (i.e. heart rate variability or HRV) and respiratory oscillations were obtained by the marked events method, $f(t) = \frac{1}{t_{k+1}-t_k}$ where t_k and t_{k+1} are the times of two consecutive peaks. The instantaneous phases were then obtained as $\phi(t) = 2\pi\frac{t-t_k}{t_{k+1}-t_k} + 2\pi k$, $t_k \leq t < t_{k+1}$, linearly interpolated, and resampled with Δt = 0.05 s. The analytic signal concept was used to obtain the instantaneous frequency corresponding to the slow-1 δ-oscillations in the EEG. An analytic signal $\zeta(t)$ was constructed from the original time series. This is a complex function of time defined as $\zeta(t) = s(t) + \imath s_H = A(t)e^{\imath\phi(t)}$, where $A(t)$ is the amplitude and $\phi(t)$ is the phase of the signal $s(t)$, and $s_H(t)$ is its Hilbert transform. The instantaneous phase is given by $\phi(t) = \arctan\frac{s_H(t)}{s(t)}$.

For inferring information about the coupling we use a method based on information theory [10] that enabled us to evaluate both the strength and asymmetry (directionality) of the coupling. The reliability of these measures was checked through the use of surrogate data.

In all 10 rats, injection of the single bolus of anæsthetic resulted in two distinctly different stages of anæsthesia. The first period is characterized by the presence of strong slow-1 δ-oscillations, but no significant presence of any other oscillations, in the EEG. During the second period, slow-1 δ-oscillations are markedly decreased. The causal relationships between slow-1 δ, cardiac, and respiratory oscillations during

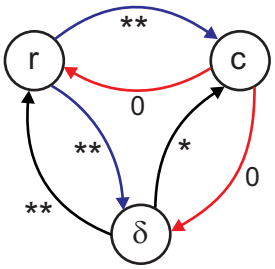

Fig. 4. Interactions between cardiac (c), respiratory (r) and slow-1 δ EEG (δ) oscillations in rats anæsthetised by ketamine-xylazine during deep anaæsthesia The strengths of coupling are indicated by the number of stars.

deep anaæsthesia are presented in Fig. 4. It is evident that respiration drives the cardiac oscillations strongly, whereas there is no significant influence in the opposite direction. On the other hand, the respiratory and slow-1 δ-oscillations are bidirectionally coupled. Finally, the slow-1 δ-oscillations drive the cardiac activity, but without any evidence of significant influence in the opposite direction. We conclude that interactions occur between the oscillatory processes, both within and between the cardiovascular and the neuronal systems. The strengths and directions of these interactions may in principle be used for characterization of the state of the organism as demonstrated here for the case of deep anæsthesia.

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