SYNCHRONIZATION OF CARDIOVASCULAR OSCILLATORS IN THE PRESENCE OF NOISE

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1 Introduction

It has long been known that the heart of a healthy human subject in repose does not beat regularly. The rhythmic variation in the heart rate occurring at the frequency of respiration, known as respiratory sinus arrhythmia, has been the most studied cardio-respiratory interaction since Hales described changes in blood pressure related to the respiratory pattern in a horse [1]. Since then there has been much significant work on the cardio-respiratory interaction (e.g. [2, 3, 4]). However, studies of the interactions between the other processes involved in the dynamics of the cardiovascular system (CVS) are still in their infancy. It has recently come to be appreciated that, on the time scale of one average circulation period, the cardiovascular system behaves in many ways as a set of 5 coupled, autonomous, nonlinear oscillators of widely differing frequencies [5]. Synchronization and modulation of this cardiovascular oscillatory activity are important under both physiological and pathophysiological conditions. For example, there seems to be a relationship between the cardiorespiratory synchronization index (defined in [6]) and the standard deviation of the variability of heart rate [7], and an inverse relationship between the average cardiac frequency and the extent of its variation [8]. Control of the CVS appears to be maintained by a fine balance between variations of the oscillator eigenfrequencies. This further results in mutual amplitude and frequency modulation and, sometimes, mutual synchronization between the phases of the oscillators.

In this paper, we present and discuss the results of numerical simulations of the proposed model, focusing on the type of couplings and the effect of noise on the dynamics of the oscillators' interactions. In Section 2 we summarise very briefly the experimental observations that have been made to date, and which a satisfactory model may be expected to encompass; a fuller account is given in [9, 10, 11]. Section 3 discusses how the model is constructed, and Section 4 reports the results obtained from it under different assumptions about the coupling constants and the presence or absence of random fluctuations (noise) representing external influences and parts of the CVS that are not included explicitly in the model. Section 5 summarises the results and draws conclusions.

2 Background

Complex, multiple control mechanisms regulate both the frequency and the volume of blood expelled by the heart in each cycle, allowing the organism to respond to the metabolic demands of different parts of the body, to adjust the pressure and the capacity of the CVS, and react to external excitations sensed by the autonomous nervous system. The experimental observations that, taken together as a whole, point unequivocally to the dynamical nature of the rhythmic activity of the CVS, can be summarized very briefly as follows. (i) Five timescales are involved, whose physiological origin are obvious in the case of 1 Hz (heart beat), and 0.3 Hz (respiration), reasonably well established in the case of 0.1 Hz (intrinsic myogenic activity of smooth muscles), but not yet known with certainty in

the cases of 0.03 Hz (connected to autonomous nervous control) or 0.01 Hz (metabolically related endothelial activity [12]). (ii) All 5 basic frequencies are observed in *all* measured cardiovascular signals, including: heart-rate, blood flow, blood pressure, respiration and ECG. (iii) Continuous wavelet analysis reveals that the characteristic frequencies and amplitudes of the oscillatory processes are themselves of a slowly-varying periodic nature. (iv) In the amplitude-frequency plane each of the characteristic peaks averaged over time is relatively broad, and they seems to be superimposed on a broad (noisy?) spectral background. (v) In cases where the characteristic or basic frequencies were almost constant (e.g. in the case of a patient in coma), their linear combinations were clearly demonstrated. (vi) Recent analysis of cardiorespiratory synchrograms [7, 13, 14, 15] show that cardiac and respiratory oscillators can become synchronized in different *n:m* synchronization regimes; synchronisation phenomena also arise between some of the other oscillators [16]. (vii) One of the Lypunov exponents in blood flow is always found to be equal to zero within experimental and numerical error, indicating [17] that the source is governed by differential equations, or by a finite time map, and implying in turn the dominantly deterministic nature of the CVS signals.

3 The model

Guided by these experimental observations, we are using a system of five coupled oscillators as a model of CVS dynamics. The basic unit in the model [9, 10], corresponding to the autonomous part of an oscillator, is the Poincaré oscillator

$$\begin{aligned} \dot{x}_i &= -x_i q_i - \omega_i y_i + g_{x_i}(\mathbf{x}), \\ \dot{y}_i &= -y_i q_i + \omega_i x_i + g_{y_i}(\mathbf{y}), \quad q_i = \alpha_i(\sqrt{x_i^2 + y_i^2} - a_i), \end{aligned} \tag{1}$$

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. Although this choice is to some extent arbitrary, it is an oscillator that possesses the properties of structural stability, robustness and symmetry that are consistent with physiological understanding, and with the analyses of measured time series.

The activity of each subsystem is described by two state variables, the blood flow x_i, and the velocity of flow y_i, where $i = 1$ is generated by the heart, $i = 2$ by respiration, $i = 3$ by the myogenic oscillator, $i = 4$ by the neurogenic oscillator, and $i = 5$ by the metabolic oscillator. The mutual impact of the subsystems on each other is taken into account as coupling terms. Additional effects resulting from the spatial distribution of some of the systems, such as the myogenic, neurogenic and endothelial related metabolic activity, and the effect of additional subsystems acting on longer time scales than those considered, are taken into account as random noise.

The types of coupling between oscillators is currently unknown in most cases. For simplicity, therefore, we use linear couplings – further justified by the observation of the same basic frequency components in all the physiological signals, and by the fact that only very small amplitude combinatorial components are observed. It is well-known that time delays are very important in the description of physiological systems and are often used in modelling individual components of the cardiovascular system [18, 19, 20, 21, 22, 23, 24, 25, 26].

In our approach, however, we perceive the blood distribution system as one in which continuous information about every subsystem, acting with essentially different frequencies, is provided and fed back via coupling terms, automatically yielding a hierarchy of delays corresponding to the time scale on which each particular subsystem acts.

In some cases, the sign of the coupling term can be determined from existing physiological knowledge and experimental observations. Direct modulation of the heart frequency by respiration, and clear evidence of the corresponding combinational frequencies in the Fourier spectra for the subject in coma, suggest that unidirectional parametric coupling, i.e. cardiac frequency modified by respira-

tion, but not vice versa, must be included in the model. Moreover, the experimental evidence also suggests that most of the other couplings are also asymmetrical. Additional difficulties in the model synthesis are related to the fact that the myogenic, neurogenic and metabolic activities cannot be measured directly in physiological experiments using noninvasive techniques.

In what follows we will first introduce the model with linear coupling terms and discuss briefly their physiological relevance. We then consider the case of unidirectional parametric coupling and allow the cardiac frequency to be modulated by the rest of the system.

The function of the heart can be presented as

$$\begin{aligned} \dot{x}_1 &= -x_1 q_1 - y_1 \omega_1 + \eta_2 x_2 - \eta_3 x_3 - \eta_4 x_4 + \eta_5 x_5 - \eta_6 (\Phi_1 - \Phi_2) \\ \dot{y}_1 &= -y_1 q_1 + x_1 \omega_1 + \eta_2 y_2 - \eta_3 y_3 - \eta_4 y_4 + \eta_5 y_5 \,, \end{aligned} \tag{2}$$

where η_i are coupling terms. Respiratory sinus arrhythmia (see Section 1) refers to frequency modulation of the heart rate: the heart beats faster during inspiration and slower during expiration. Comparable modulation phenomena can also be observed in each part of the circulatory system: the amplitude of the flow component resulting from the heart beat in the peripheral blood flow is modulated by the frequency of respiration. It was shown that the coupling between the heart and respiration enables both modulation and synchronisation to occur. At the moment just a single term (η_2) is used in the model for the cardio-respiratory coupling, although it is evident that in reality several mechanisms are involved.

Negative influences of the myogenic ($-\eta_3$) and neurogenic systems on the heart ($-\eta_4$) are considered. The autonomous nervous system processes the information sensed by receptors and continuously adjusts the heart rate. The heart is innervated by both divisions of the autonomous nervous system – the sympathetic increases, and the parasympathetic decreases, the frequency and amplitude of myocardial contractions. Parasympathetic tone predominates in healthy resting humans. Increased metabolic activity results in an increased heart rate: a positive control loop is therefore assigned to the metabolic system (η_5).

The difference between the inflow (Φ_1) on the arterial side and the outflow (Φ_2) to the venous side also contributes to the flow of blood generated by the heart. The dynamics of each of the other oscillators and their couplings at *any point of the cardiovascular system* can be described in a similar way [10]. However, the cardiac contribution to the flow at each point results not only from the influences of local regulatory mechanisms, but also from the integration of the pressure (P) and flow (Φ) values along the entire system. A global effect of the pressure on the myogenic and the neurogenic activity, and of the flow on metabolic activity, is also to be expected. Therefore, in [9, 10] the model was extended to describe the activity of the oscillators that regulate the flow of blood *along the cardiovascular system*

$$\begin{aligned} \dot{x}_1 &= -x_1 q_1 - y_1 \omega_1 + \eta_2 x_2 - \eta_3 x_3 - \eta_4 x_4 + \eta_5 x_5 + \\ &+ \eta_6 \int_0^l P(z,t) dz + \eta_7 \int_0^l \Phi(z,t) dz \\ \dot{y}_1 &= -y_1 q_1 + x_1 \omega_1 + \eta_2 y_2 - \eta_3 y_3 - \eta_4 y_4 + \eta_5 y_5 \,, \end{aligned} \tag{3}$$

$$\begin{aligned} \dot{x}_2 &= -x_2 q_2 - y_2 \omega_2 + \theta_4 x_4 + \theta_5 x_5 + \\ &+ \theta_6 \int_0^l P(z,t) dz + \theta_7 \int_0^l \Phi(z,t) dz \\ \dot{y}_2 &= -y_2 q_2 + x_2 \omega_2 + \theta_4 y_4 + \theta_5 y_5 \,, \end{aligned} \tag{4}$$

$$\begin{aligned} \dot{x}_3 &= -x_3 q_3 - y_3 \omega_3 + \gamma_4 x_4 - \gamma_5 x_5 - \gamma_6 P \\ \dot{y}_3 &= -y_3 q_3 + x_3 \omega_3 + \gamma_4 y_4 - \gamma_5 y_5 \,, \end{aligned} \tag{5}$$

$$\begin{aligned}\dot{x}_4 &= -x_4 q_4 - y_4 \omega_4 - \rho_2 x_2 + \rho_3 x_3 - \rho_5 x_5 - \rho_6 P \\ \dot{y}_4 &= -y_4 q_4 + x_4 \omega_4 - \rho_2 y_2 + \rho_3 y_3 - \rho_5 y_5 \,, \end{aligned} \tag{6}$$

$$\begin{aligned}\dot{x}_5 &= -x_5 q_5 - y_5 \omega_5 + \sigma_2 x_2 - \sigma_3 x_3 - \sigma_4 x_4 + \sigma_6 \Phi \\ \dot{y}_5 &= -y_5 q_5 + x_5 \omega_5 + \sigma_2 y_2 - \sigma_3 y_3 - \sigma_4 y_4 \,. \end{aligned} \tag{7}$$

where $\eta_i, \theta_i, \gamma_i, \rho_i$ and σ_i are coupling terms and Φ and P are the flow and pressure at any point of the circulatory system. The flow Φ is generated by the heart, so that $\Phi(0,t) = x_1(t)$. The pressure P is generated by the lungs and $P(0,t) = x_2(t)$. We have assumed the flow to be in the z direction. The blood returns to the right atrium of the heart at pressure of 0 Pa and at almost 0 Pa from the pulmonary vein to the left atrium. There, the value of $P(l,t)$ becomes 0. By analogy, we may assume the value for Φ at this boundary condition $\Phi(l,t) = 0$. The blood flow along the circulatory system can be described as

$$\begin{aligned}\frac{\partial \Phi}{\partial t} &= -\kappa_1 \frac{\partial P}{\partial z} - \kappa_2 x_5 \qquad ;\ \kappa_i > 0 \\ \frac{\partial P}{\partial t} &= -\mu_1 \frac{\partial \Phi}{\partial z} + \mu_2 x_3 + \mu_3 x_4 \,;\ \mu_i > 0, \end{aligned} \tag{8}$$

where κ_i, μ_i are control parameters.

4 Preliminary results of numerical simulations

We have carried out a digital simulation of the above model, using a high-speed pseudo-random generator [27] for the increment Δx_1. Time series for each of the oscillators were generated by a sampling frequency of 100 Hz. For each set of parameters 82 min records were generated. To simplify manipulations with the multi-dimensional coupling vector we have built a MatLab based graphical user interface providing for real time control of all the parameters of the system.

The flow component of each of the oscillators can be presented graphically after each run for a selected set of parameters. Here, we focus on the cardiac and respiratory components. Since the time series of the cardiac flow is, to a great extent, comparable to heart rate variability, we also focus on its spectral content. At this stage, however, as we shall see below, the simplified model is only capable of reproducing time variability of the heart rate to a limited extent. A windowed Fourier transform is used for calculation of the spectra. A time window of 246 s was used for estimation of the power spectrum, and the calculation was repeated for 20 windows, with no overlaps between them. The power spectrum presented here is thus a time average over the spectra obtained within 20 windows. In reality, all measured signals contain time variable frequency content and for estimation of their spectral components we need time-frequency methods, i.e. the wavelet transform.

Time variability was taken into account in synchronization analysis between the cardiac and respiratory oscillators. The synchronization or mutual adjustment of the cardiac and respiratory rhythms was analysed using a recently proposed method for the detection of synchronization between irregular and non-stationary oscillators [28]. The relative phase of the heartbeats within individual respiratory cycles Ψ_1, was calculated for each set of parameters using the marker events method. The occurrence of synchronization was examined in a synchrogram, constructed by plotting the normalised relative phase of the cardiac component within 1 respiratory cycle, $\Psi_1 = \frac{1}{2\pi}(\Phi_r(t_k) \mathrm{mod} 2\pi)$, where t_k is the time of kth heartbeat and Φ_r is the instantaneous phase of respiration. Horizontal plateaus in the synchrogram are then interpreted as representing a constant phase difference, and thus the occurrence of phase synchronization. We have considered linear couplings, with and without noise in the system, and parametric couplings.

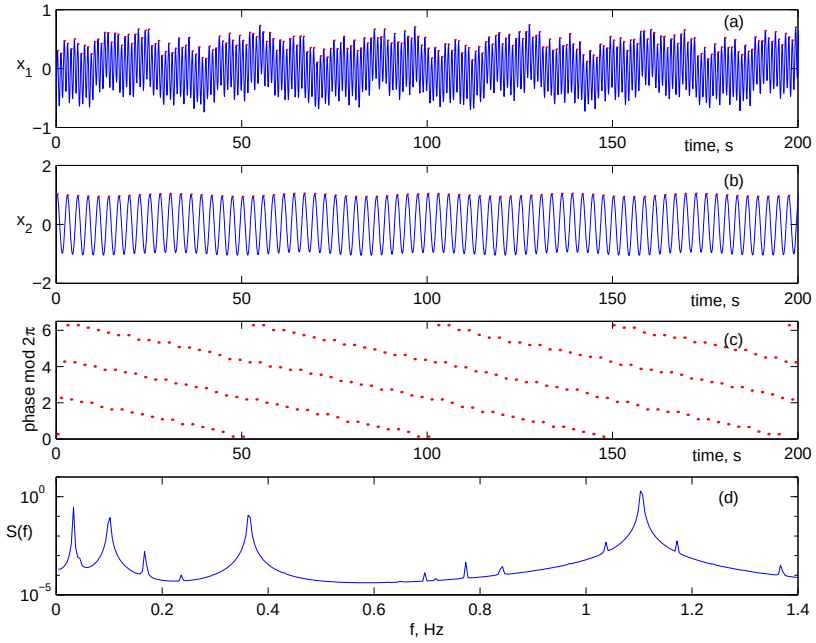

Figure 1: The results of modelling with deterministic linear couplings, in the absence of fluctuations. (a) and (b) The time series showing the rhythmic activities of the cardiac and respiratory oscillators, x_1 and x_2. (c) The corresponding cardio-respiratory synchrogram. (d) Power spectrum of the time series for the flow generated by cardiac oscillator, x_1. The component x_1 is comparable to the heart rate variability signal, which is obtained from the instantaneous cardiac frequency, determined by two successive R-peaks in the ECG signal.

(a) Linear couplings without noise

The set of equations (3)-(7) described in the previous section includes coupling with the multiple degrees of freedom of the CVS accumulated in the blood pressure and blood flow. However, here we start with a simplified version of the model, taking into account the description of the flow at a point in the cardiovascular system, of the form (2) introduced above for the cardiac oscillator. Hence, in the first stage, no effect of multiple degrees of freedom was taken into account. Our preliminary analysis of the model shows that it is possible to identify at least one set of parameters that enables the characteristic features of the time series and power spectra to be reproduced. The choice of frequencies was based on the values extracted from experiments, and their ratio was kept such that the system was set in a non synchronized regime. We emphasize that whether or not this parameter set is unique remains for the present an open question. However, our initial results have already suggested some further experiments to try to clarify the matter. For the present studies, the model parameters were set as follows –

$\alpha_1 = 1.0,\ a_1 = 0.5,\ f_1 = 1.1$ Hz, $\eta_2 = -\eta_3 = -\eta_4 = \eta_5 = 0.5$,
$\alpha_2 = 1.0,\ a_2 = 1.0,\ f_2 = 0.36$ Hz, $\theta_4 = \theta_5 = 0.1$,
$\alpha_3 = 1.0,\ a_3 = 1.0,\ f_3 = 0.1$ Hz, $\gamma_4 = \gamma_5 = 0.1$,
$\alpha_4 = 1.0,\ a_4 = 1.0,\ f_4 = 0.04$ Hz, $\rho_2 = \rho_3 = \rho_5 = 0.1$, and
$\alpha_5 = 1.0,\ a_5 = 0.5,\ f_5 = 0.01$ Hz, $\sigma_2 = \sigma_3 = \sigma_4 = 0.1$.

In Figure 1 results corresponding to the presence of linear coupling terms only are shown. It can be seen that the power spectrum of the oscillations in the blood flow, generated by the heart, reproduce the main characteristic features observed experimentally in the peripheral blood flow signal measured by a laser Doppler technique, including the position and relative intensities of the peaks. However, the widths of the peaks, and correspondingly the variability of the heart and respiration rates, are

much smaller then those observed experimentally. In particular, no epochs of synchronization are observed in the cardio-respiratory synchrograms.

Here we note that variation of the coupling parameters and/or natural frequencies will also give rise to synchronization in the system. However, motivated by the experimental observation of short episodes of synchronization [7, 13, 14], we concentrate on the mainly non-synchronized state: we are interested in establishing whether or not it is possible to reproduce in numerical simulations the regime where short epochs of synchronization occur.

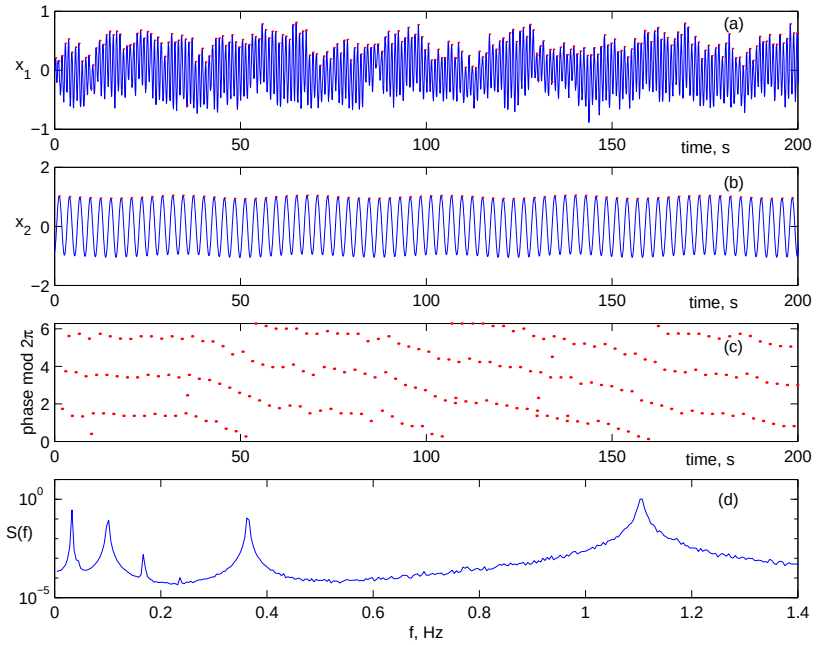

Figure 2: Results of modelling with linear couplings, in the presence of fluctuations. (a) and (b) The time series showing the rhythmic activities of the cardiac and respiratory flow components. (c) The corresponding cardio-respiratory synchrogram. (d) Power spectrum of oscillation in the blood flow generated by the cardiac activity.

(b) Linear couplings in the presence of noise

In the next step, couplings with multiple degrees of freedom accumulated in the blood pressure and blood flow were added in an attempt to introduce the globally distributed effects of the CVS. However, at this stage equations (3)-(7) were not modelled numerically to their full extent and $\eta_6 = \eta_7 = \theta_6 = \theta_7 = \gamma_6 = \rho_6 = \sigma_6 = 0$. Rather, a fluctuational term was added to the cardiac oscillations (2)

$$\begin{aligned} \dot{x}_1 &= -x_1 q_1 - 2\pi f_1 y_1 + g_{x_1}(\mathbf{x}) + \xi(t), \\ \langle \xi(t) \rangle &= 0, \quad \langle \xi(t)\xi(0) \rangle = D\delta(t), \end{aligned} \tag{9}$$

Thus, all influences of the rest of the system are lumped in the fluctuational term $\xi(t)$. The addition of the random term, very interestingly, resulted in epochs of synchronization in the cardio-respiratory synchrograms. Without noise, only the standard regimes of phase-locking, phase modulation, and their interplay, could be observed. However, the heart rate variability remains very small suggesting, that parametric coupling probably plays an important role in the cardiac activity.

(c) Parametric couplings without noise

Just for comparison we show in Figure 3 results corresponding to purely parametric deterministic coupling of the heart rhythmic activity to the rest of the system in the form

$$\dot{x}_1 \quad = \quad -x_1 q_1 - y_1(\omega_1 + \eta_2 x_2 - \eta_3 x_3 - \eta_4 x_4 + \eta_5 x_5)$$

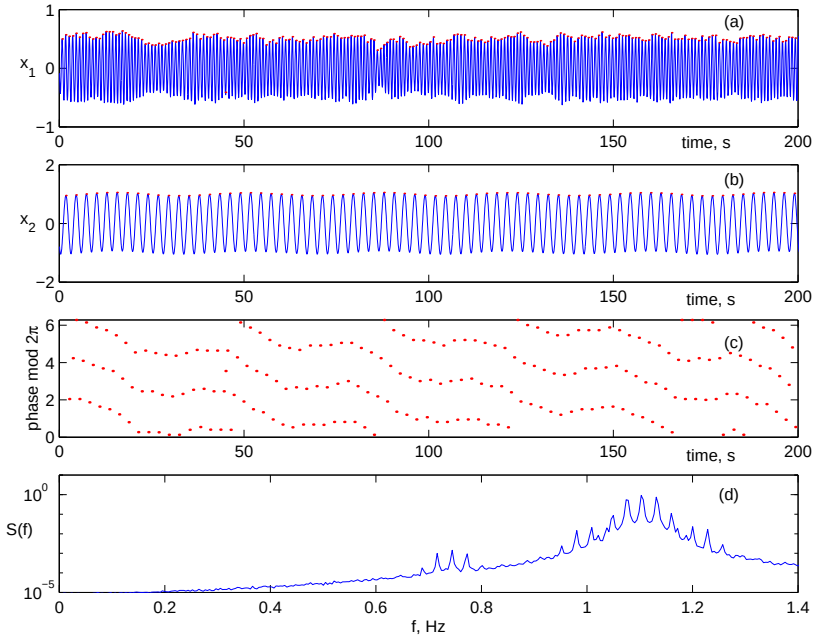

Figure 3: The results of the modelling with pure deterministic parametric couplings. (a), (b), (c), and (d) are the same as in figures 1 and 2.

$$\dot{y}_1 \quad = \quad -y_1 q_1 + x_1(\omega_1 + \eta_2 y_2 - \eta_3 y_3 - \eta_4 y_4 + \eta_5 y_5)\,, \tag{10}$$

It can clearly be seen that although the heart rate variability can be increased dramatically the power spectra and the cardio-respiratory synchrogram still differ substantially from those observed experimentally [5].

Synchronisation of a noisy van der Pol oscillator with modulated natural frequency has already been analysed in the context of the cardiorespiratory interaction [14]. Frequency locking was obtained only if the amplitude of modulation exceeded some threshold value. Moreover, the presence of noise smeared this locking effect, while quasiperiodic modulation, as also considered in our case, resulted in frequency locking without phase locking.

Modulation and synchronisation may or may not coexist in parametrically coupled systems in the presence of noise. This was also observed for the cardiorespiratory interaction, where generally the intensity of synchronisation appears to be inversely proportional to the modulation of cardiac frequency by the respiratory related rhythm [7]. However this relation is changed in subjects with cardiovascular disease suggesting that this two mechanisms are essential for the functioning of the cardiovascular system. Whether it is the parametric coupling enables that this interplay to occur is a point that remains to be clarified.

5 Summary and conclusions

The results obtained suggest that the type and strength of the linear coupling in our model can be determined quite accurately through comparison of the observed and simulated time series. We find that, in order to reproduce the main dynamical features of the cardiac rhythmic activity, both linear and parametric couplings must be taken into account, with the linear couplings being dominant. Fluctuations are found to play an important role in CVS dynamics: they are not only responsible (at least in part) for the experimentally observed and numerically reproduced broadening of the main spectral peaks, but also for a number of regimes of synchronization. In particular, we note that the

model is capable of reproducing the different synchrogramme patterns of observed experimentally including e.g. the standard phase-locked regime and the regime of continuously varying phase both in the presence and in the absence of noise. We were specially interested to establish whether it is possible to reproduce the regime where there are short epochs of synchronisation. It turns out that such behaviour can be reproduced numerically (Fig. 2) *only* in the presence of fluctuations.

A qualitative explanation of this phenomenon within the framework of the current model may be as follows. In a first approximation, the interaction between the heart and respiratory oscillations is due to a unidirectional influence of the respiratory oscillator on the heart rhythm. The effect of coupling to the rest of the system can be taken into account by allowing for the fluctuations. This simplified situation can be modelled as a singled-out nonlinear oscillator driven by periodic and random forces. The model can be further simplified. By introducing a slowly varying phase difference between the phase of oscillator and the phase of the driving force $\phi(t) = \Phi(t) - \Psi(t)$, and by assuming a constant amplitude approximation [29], we have

$$\dot{\phi} = \Delta + K \sin(\phi) + \psi(t), \tag{11}$$

where Δ is the detuning $n\omega_1 - m\omega_2$, K is a function of the system parameters, ϕ is the slowly varying phase of the cardiac oscillations and ψ is a new zero-mean random Gaussian variable.

It can be seen that small values of Δ correspond to a small slope of the wash-board potential corresponding to (11), leading to the locking of the phase ϕ at the bottom of one of the potential wells. On the other hand, relatively large values of Δ correspond to a large slope of the wash-board potential, to the disappearance of the local potential well, and hence to the absence of synchronization. In the presence of weak noise two distinct effects can be expected. For small Δ, noise can induce transitions of the phase between different potential wells. In this regime the system will stay mainly in a state of synchronization but, from time-to-time, phase steps $\propto 2\pi$ will occur. The other possible regime for relatively large (but not too large) values of Δ is that the system may stay mainly in the desynchronized state modulated by noise. If however large rare fluctuations have the effect of temporarily decreasing the value of Δ, short epochs of synchronization will occur, as observed. This hypothesis can in principle be verified using methods for the direct analysis of the fluctuational dynamics [30].

Note that our simulations have implemented a simplified version of the original [5, 9] model. In particular, we have taken no account of the description of the flow along the vessels in terms of partial differential equations, as proposed in Eqs. (8). Apart from being difficult, it would arguably have been inappropriate to do so at this early stage in the modelling, given that the model structure and the parameter values still need to be optimised. However, the influence of spatially distributed flow on the dynamics has in a sense already been included through our addition of noise, which was not considered in the original model.

We conclude that our preliminary results support the model of five coupled oscillators suggested and justified in physiological experiments ([5] and references therein). In particular, the model is able to reproduce some basic features of the cardio-respiratory interactions observed in physiological time series including e.g. heart rate variability, synchronization phenomena and the general shape of the power spectra. Moreover, the preliminary analyses suggest that the information obtained from these time series is complementary to that from the physiological measurements, in that it will allow one to determine at least approximately the type and strength of coupling. One of the most important and unexpected conclusions is that the interplay between the synchronization and frequency modulation can be taken into account by adding noise to the system.

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