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Coupled Oscillators Approach in Analysis of Physiological Data

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Abstract—**We discuss the usage of the coupled oscillators approach in analysis of bivariate physiological data, taking the cardio-respiratory interaction as an example. These model-based techniques allow us to detect and quantify the strength and directionality of weak interaction, as well as to estimate the delay(s) in coupling. We present both theoretical description of the technique and its algorithmic implementation.**

I. Introduction

Processing of bivariate (or, generally multivariate) measurements is an important problem of physiological data analysis. Here we discuss several data analysis tools based on the assumption that the bivariate data originate from two coupled self-sustained oscillators. These tools are designed to provide the solutions for the following tasks: (i) to detect and quantify an interaction between the systems, (ii) to reveal the direction of coupling, and (iii) to estimate delay(s) in coupling, provided the following assumptions are fulfilled: (i) we deal with two self-sustained oscillators which can be *weakly coupled,* (ii) we know how to ascribe the signals to systems, and (iii) the signals are appropriate for phase estimation.

Numerous techniques - linear and nonlinear - provide information on an interrelation between two signals. With our analysis we try to go beyond this task and aim at revealing some information about the *system (or systems)*, which generates the data. Certainly, by making such a step one cannot consider the system as a black box, but requires a certain knowledge or assumption about it. Such model-based analysis provides additional information about the systems which generate signals, but this is true if and only if the assumptions about the data source are correct. On the contrary, the non-model-based analysis can always be employed, but the price for this is the reduced information or ambiguity in the interpretation of the results.

We note that we prefer to speak about coupling between the systems and interrelation between the signals, understanding coupling as some physical connection between oscillators which may or may not result in an interrelation between the signals measured at the output of these oscillators.

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II. Phase Dynamics of Weakly Coupled Oscillators

Active systems, capable of producing long-term sustained rhythmical activity, are known in physics as *self-sustained* oscillators. The image of periodic and chaotic self-sustained oscillations in the phase space is a limit cycle and a strange attractor, respectively (see, e.g., [1]-[2] for a discussion). The motion of the phase point along the limit cycle (or along the flow of a chaotic system) is parameterized by a variable, called *phase*. For limit cycle oscillators it is defined as the monotonically growing variable which gains 2π during one oscillation period, $\dot{\varphi} = \omega$, where ω is the natural frequency [1]. The notion of phase and amplitude(s) can be extended, though not rigorously, to some chaotic oscillators [2].

An important theoretical idea, widely explored below, says that a weak interaction of limit cycle oscillators affects only their phases, whereas the amplitudes can be considered as unchanged [1]. Therefore, the description of weakly coupled oscillators can be reduced to the phase dynamics

$$\begin{aligned} \dot{\varphi}_1 &= \omega_1 + f_1(\varphi_1, \varphi_2) + \zeta_1 \\ \dot{\varphi}_2 &= \omega_2 + f_2(\varphi_1, \varphi_2) + \zeta_2, \end{aligned} \quad (1)$$

where $\omega_{1,2}$ are frequencies of uncoupled systems and functions $f_{1,2}$ describe the coupling; obviously they are 2π-periodic with respect to their arguments. This property will play a very important role in the reconstruction of phase equations from data, to be described below, because it naturally restricts the class of test functions for fitting. Note that (1) describe also the dynamics of weakly coupled chaotic systems; in this case the irregular terms $\zeta_{1,2}$ correspond to perturbations to the phase dynamics due to the chaotic nature of amplitudes.

An important consequence of coupling is *synchronization*, when two (or many) weakly interacting systems adjust their phases $\varphi_{1,2}$ and average frequencies $\Omega_{1,2} = \langle \dot{\varphi}_{1,2} \rangle$ where $\langle \cdot \rangle$ denotes averaging over time, so that the following conditions of *phase and frequency locking* are fulfilled:

$$n\Omega_1 = m\Omega_2, \ \ |n\varphi_1 - m\varphi_2| < const.$$

This nonlinear phenomenon [1]-[3] is well-known in the context of interacting cardiovascular and respiratory systems [4]-[8]. It is often convenient, and we use it below, to use instead of continuous time equations (1) a corresponding mapping for phase increments

$$\begin{aligned} \Delta\varphi_1 &= F_1(\varphi_1, \varphi_2) + \xi_1, \\ \Delta\varphi_2 &= F_2(\varphi_1, \varphi_2) + \xi_2, \end{aligned} \quad (2)$$

where the functions $F_{1,2}$ are also 2π -periodic with respect to their arguments.

III. CARDIORESPIRATORY INTERACTION IN A HEALTHY BABY

We illustrate our theoretical framework using a case study analysis of the interaction between human cardiac and respiratory systems. The experimental data consists of a single segment of bivariate, artifact-free, cardiorespiratory measurements (the cardiac and respiratory signals) recorded from a six-months healthy infant during quiet sleep. The data set has been kindly provided by R. Mrowka and A. Patzak, Department of Physiology, Charité, Humboldt University, Berlin. A detailed description of the experimental setup and data pre-processing can be found in [7]-[9] and for quantitative analysis of the strength of interaction see [7].

A. Reconstruction of phase dynamics from data

The first step in the reconstruction of the phase dynamics is a computation of the bivariate series of phases $\varphi_{1,2}(j)=\varphi_{1,2}(t_j)$, where index $j=1:M$ denotes a discrete set of time points $t_j = j \cdot dt$, see, e.g., [2] for discussion of the methods. The next step depends on whether we want to reconstruct the continuous or discrete phase model (1)-(2). In the first case we have to estimate the time derivatives $\dot{\varphi}_{1,2}$. For this goal we first compute the phase increments $\Delta\varphi_{1,2}$ over the sampling interval. Because the data are noisy, one has to use a smoothening/interpolation technique, based e.g. on a Savitzky-Golay filter [2]. In the second case we just compute $\Delta\varphi_{1,2}$ over a fixed time interval which can be much larger than the sampling interval (e.g., it can be of the order of the oscillation period; certainly, it is a multiple of the sampling interval).

The main and final step is to approximate the dependencies

$$\begin{aligned} \Delta\varphi_1(j) &= \Delta\varphi_1(\varphi_1(j),\varphi_2(j)), \\ \Delta\varphi_2(j) &= \Delta\varphi_2(\varphi_1(j),\varphi_2(j)), \end{aligned} \quad (3)$$

by a model (1) or (2).

Because continuous functions $f_{1,2}$ and $F_{1,2}$ are 2π -periodic in arguments, they admit a natural Fourier series representation, and we can in both cases seek for the dependencies in the form:

$$\Delta\varphi_1(\varphi_1,\varphi_2) = \\ = \sum_{m,n=1}^{N} a_{m,n}\cos(m\varphi_1+n\varphi_2) + b_{m,n}\sin(m\varphi_1+n\varphi_2),$$

and similarly for $\Delta\varphi_2(\varphi_1,\varphi_2)$.

Practically, we can use the standard linear least square regression to fit the data with a truncated Fourier series model. This leads to a minimization problem, which solution is rather sensitive to a choice of parameter N. Therefore, we apply a preliminary estimation of the Fourier coefficients based on the assumption that the noise in the otherwise synchronous oscillators or quasi-periodic dynamics ensures a quite uniform scattering of phase points over the $[0, 2\pi)\times[0, 2\pi)$ square. In this case $a_{m,n}$ and $b_{m,n}$ are just the real and imaginary part of the Fourier transform

$$Q_1(m,n) = \frac{1}{M}\sum_{j=1}^{M}\Delta\varphi_1(j)\exp(i(m\varphi_1(j)+n\varphi_2(j)). \quad (4)$$

In order to make use of the FFT algorithm, the irregularly sampled $\Delta\varphi_2(\varphi_1,\varphi_2)$ should be resampled onto a regular grid, by employing some form of interpolation or, in the presence of noise, estimation. After the FFT has been performed, one can select the dominant modes as the modes with the largest values of $|Q(m,n)|$. Then one can restrict the summation in (3) to these modes only, what significantly improves the reliability of found Fourier coefficients $a_{m,n}$ and $b_{m,n}$.

To exemplify this, a segment of approx. 350 average cardiac cycles length is selected, and the phases of cardiac (φ_h) and respiratory (φ_r) oscillations along with their finite difference approximations $\Delta\varphi_{h,r}$ over time interval 0.05 s are computed. Prior to FFT, we perform a Delaunay-triangulation based cubic interpolation of $\Delta\varphi_{h,r}$ on a uniform grid on the square $[0, 2\pi)\times[0, 2\pi)$ with the grid step $2\pi/128$. In this way the Nyquist theorem provides the upper limit of the frequencies resolved by these data as $M=64$, which, under assumption that the underlying coupling functions are smooth, can be considered as sufficiently large to prevent aliasing.

The next step is the identification of the dominant spatial modes, which will allow us to fit a more parsimonious Fourier series model. For this purpose we employ the surrogate hypothesis testing. Namely, for testing the null hypothesis of no coupling from the respiration to the heart, we compute the Fourier coefficients $Q_h(k_h,k_r)$ for 100 realizations of the randomly shuffled $\Delta\varphi_h$ and take $Q_{h\max}(k_h,k_r) = \langle \max|Q_h(k_h,k_r)| \rangle$ as the threshold value, where $\langle\cdot\rangle$ means averaging over the realizations of surrogates. It means that for the model fitting we use only the terms which satisfy $|Q_h(k_h,k_r)| < Q_{h\max}(k_h,k_r)$. In the same way, we identify the dominant modes of interaction between cardiac and respiratory oscillators.

The results of this analysis are given in Fig. 1. We remind that for the reconstruction we used the phase estimates, which, contrary to true phases do not fulfill (for uncoupled systems) the condition $\dot{\varphi}=\omega$. The oscillation of the estimated phase around a uniform growth is especially pronounced if the Hilbert transformation is used. This reflects in the appearance of the terms $\sin(\varphi_r),\cos(\varphi_r)$ in the equation for $\Delta\varphi_r$ (2).

The appearance of the same terms in the equation for $\Delta\varphi_h$ may, however, have an important physical meaning. Indeed, these terms in addition to the terms $\sin(k_r\varphi_r \pm k_h\varphi_h),\cos(k_r\varphi_r \pm k_h\varphi_h)$ possibly indicate the presence of two mechanisms of interaction - a modulating one and a synchronizing one.

B. Directionality of coupling from phases

In quantification of the directionality from the reconstructed equations of the phase dynamics we follow

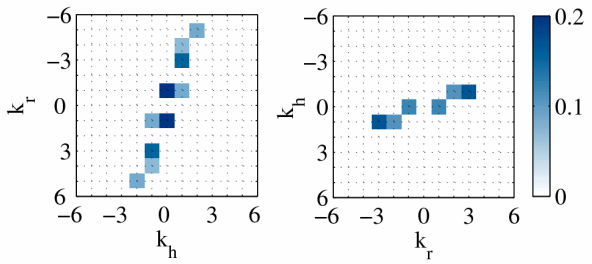

Fig. 1. Two-dimensional Fourier transforms of the resampled $\Delta\varphi_h(\varphi_h,\varphi_r)$ (left) and $\Delta\varphi_r(\varphi_r,\varphi_h)$ (right); gray scales code the absolute value of the corresponding Fourier coefficients.

our previously developed approach [11]-[12]. We emphasize, that there is no unique way to quantify the directionality of coupling, even if (1) is known. One way to quantify the directionality is as follows. We quantify the influence of system *2* on system *1* by the coefficient

$$c_{1,2}{}^2 = \int_0^{2\pi}\int_0^{2\pi}\left[\frac{\partial\Delta\varphi_{1,2}(\varphi_1,\varphi_2)}{\partial\varphi_{2,1}}\right]^2 d\varphi_1 d\varphi_2 .$$

Note that $c_{1,2}$ can be easily obtained from the model coefficients [13], e.g.

$$c_1{}^2 = \sum_{n=1}^{N} n^2 (a^2{}_{m,n} + b^2{}_{m,n}).$$

The coefficient c_1 is an integrative measure of how strongly oscillator 1 is driven and how sensitive it is to the driving. Computing in the same way c_2, we quantify asymmetry in interaction by one number

$$d_{2\to 1} = \frac{c_2 - c_1}{c_2 + c_1},$$

that we call *directionality index*. It varies from +1 in the case of unidirectional coupling ($1 \to 2$) to -1 in the opposite case ($1 \leftarrow 2$), while intermediate values correspond to a bidirectional coupling configuration. If two oscillators are structurally identical and they differ only by their natural frequencies, then $f_1(\cdot) = f_2(\cdot)$ and $d_{2\to 1} = (\varepsilon_2 - \varepsilon_1)/(\varepsilon_2 + \varepsilon_1)$. Alternative solutions of the directionality estimates have been discussed and experimentally verified in [11], [14], [9].

We emphasize that the presented algorithm fails if the oscillators are phase locked, which mathematically corresponds to the appearance of a functional dependency between the two phase variables. On the other hand, if the coupling is too weak, so that the systems cannot be distinguished from uncoupled ones, the directionality cannot be estimated, as well. Note also that coefficients $c_{1,2}$ are always overestimated; indeed, if the first coefficient is zero, its estimate $\sqrt{\langle(\partial\Delta\varphi_1/\partial\varphi_2)^2\rangle}$ is positive. A way to correct the estimate was suggested in [13].

We remark that in the quantification of the directionality we are not interested in the mostly exact reconstruction of the model equations, but only in the recovery of interdependencies in the phase dynamics. In this context it is more appropriate to work with discrete mappings (1). Computation of a phase increment over a relatively large time interval (it can be of the order of oscillation period) helps to reduce the effect of noise, see discussions in [10]-[12] for more details. Application of the directionality algorithms to cardiorespiratory data can be found in [9]-[11]. Here we present the results for the sample data set. The directionality index obtained from coefficients of the model (3) is $d_{h\to r} \approx -0.42$. This means that the coupling is bidirectional, though not symmetrical: the action from respiration to the cardiac system dominates over the reverse action. However, in the interpretation of the results it is important to have in mind that in case of *n:m* coupling with *equal* strength, the coefficients c_1 and c_2 are generally different. For an illustration, let us consider a simple model

$$\dot\varphi_1 = \omega_1 + \varepsilon\sin(3\varphi_2 - \varphi_1),$$
$$\dot\varphi_2 = \omega_2 + \varepsilon\sin(\varphi_1 - 3\varphi_2).$$

It is easy to see that $c_1 = 3\,c_2$, what gives $d_{2\to 1} \approx 0.5$.

C. *Delay in coupling from data*

We consider now the last problem, namely an estimation of the delay in coupling. First we note that if there is an *a priori* knowledge that two signals represent the input and the output of a delay line, then the delay can be estimated from the position of the maximum of the cross-correlation function (*CCF*). Sometimes, in the biomedical literature the delay is estimated from the phase shift at the characteristic frequency, what implicitly uses an additional assumption, that the delay is smaller than the oscillation period. However, as discussed below, in case of coupled oscillators this technique fails, as it does not distinguish between the delay and the phase shift.

There are two ways to estimate the delay. First, one can compute from the time series of phases the synchronization index, then shift the first series with respect to the second one and compute the index for different, positive and negative values of the shift parameter τ. It is natural to expect that the *shift-dependent synchronization index* [15]

$$\rho^2(\tau) = \langle\cos(\varphi_1(t) - \varphi_2(t-\tau))\rangle^2 + \langle\sin(\varphi_1(t) - \varphi_2(t-\tau))\rangle^2$$

maximizes when the shift corresponds to the (unknown) delay in coupling. The index can be easily generalized to the case of *n:m* coupling (see Fig. 2). The second, model based approach, exploits a generalization of the models (1) and (2)

$$\dot\varphi_1 = \omega_1 + \varepsilon f_1(\varphi_1(t), \varphi_2(t - T_1)) + \zeta_1(t),$$
$$\dot\varphi_2 = \omega_2 + \varepsilon f_2(\varphi_1(t - T_2), \varphi_2(t)) + \zeta_2(t),$$

where the coupling function in the first equation (map) contains a retarded value of the phase of the second oscillator, and vice versa. The idea is to reconstruct the model, as discussed in the previous Sections, fit it to the bivariate data where one series is shifted with respect to the other, and to quantify the fit quality by the root mean square errors $E_{1,2}$ for different shifts τ (errors $E_{1,2}$ describe the quality of modeling of $\dot\varphi_{1,2}$). The dependencies $E_{1,2}(\tau)$ should take a minimum at $\tau_{1,2} = T_{1,2}$. Note that for our goal it is not required to reconstruct the phase dynamics very precisely, because we are not interested in the absolute value of $E_{1,2}(\tau)$, but only in its variation with τ.

Analytical and numerical treatment of these two

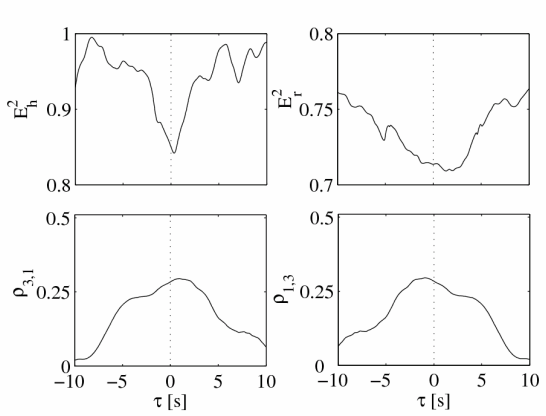

Fig. 2. Estimation of the delays in bidirectional cardiorespiratory coupling. Top panels show the (normalized) errors of fit versus the time shift between the series. Minima of the dependence indicate the values of delays. Bottom panels show the $\rho_{(1,3)}$ ($n=1$, $m=3$) synchronization index. Dependence of the synchronization on shift (bottom panels) is not efficient in delay estimation.

approaches, performed in [10], shows that the position of the maximum of the dependence of the synchronization index ρ on the time shift τ systematically overestimates the delay. Moreover, in the case when the oscillators are far from synchrony, the synchronization index is small for all shifts τ and therefore does not yield the estimate of the delay. Thus, the advantages of this approach, namely its simplicity and absence of parameters, are accompanied by several drawbacks which can be overcome by the technique based on the model reconstruction. On the other hand, if the systems are very close to synchrony, then the model reconstruction fails due to a functional relation between the phases and only the method based on the synchronization index can be used.

The results of the analysis for the cardiorespiratory data set are shown in Fig. 2. The values of delay, estimated from the positions of the minima of the dependence $E_{1,2}(\tau)$ are $\tilde{T}_1 \approx 0.4$ s (delay in coupling from respiration to heart) and $\tilde{T}_2 \approx 1.4$ s (delay in coupling from heart to respiration). As the system is far from synchrony, dependence of the synchronization on shift is not efficient in delay estimation. Our estimate of the time delay in coupling between the respiratory and cardiac oscillators falls well within the range of documented [16] latencies in the human cardiac baroreflex response.

We note that the mostly common tool that can be tested for the detection of the delay is the cross-correlation function. If the fluctuations of the amplitudes of signals are small, then the cross-correlation function $CCF(\tau)$ has a very simple relation to the synchronization index, namely $\rho(\tau)$ is the envelope of $CCF(\tau)$ [10]. Hence, analysis of $CCF(\tau)$ provides the biased estimate of the delay as well.

IV. CONCLUSIONS

We have presented a model-based approach for identification and quantification of an interaction between two coupled systems from experimental data. The approach relies on the assumption that we deal with weakly interacting self-sustained oscillators, and that the measured signals represent the dynamics of different oscillatory systems. We discussed in detail, how to estimate the phase data, the object of the analysis, and how to quantify the main characteristics of the interaction, namely, the strength, the directionality and the delays in coupling. The methods have been exemplified by examining the nature of the interaction between the cardiac and respiratory oscillators of a healthy infant.

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