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7 Coupled oscillators approach in analysis of bivariate data

Michael Rosenblum[1], *Laura Cimponeriu*[1,2], *and Arkady Pikovsky*[1]

[1] Institute of Physics
Potsdam University
Germany
[2] Department of Medical Physics
Patras University
Greece

We discuss the usage of model-based and non-model-based techniques in analysis of bivariate data. In particular, we consider in detail the coupled oscillators approach for identification of a weak interaction between two oscillators from signals measured at their output. Our framework allows one 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. We illustrate the technique by its application to analysis of the cardiorespiratory interaction.

7.1 Bivariate data analysis: model based vs. non model based approach

Multichannel measurements are ubiquitous in experimental studies in all branches of natural sciences and, hence, processing of bivariate (or, generally, multivariate) experimental records is a typical task of data analysis. This task can include a separate processing of two channels by all possible univariate techniques, as well as an application of a true *bivariate* technique which performs a joint analysis of two channels. The goals of the bivariate analysis can be different. So, for example, there exist numerous techniques – linear and nonlinear – which provide information on an interrelation between two signals. However, quite often the analysis goes beyond this task and aims 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. Typically, one assumes (explicitely or implicitly) that the system can be described by a certain *class of models*, e.g., by an input-output system, a delay line, a set of coupled active oscillators, etc. (We emphasize that we mean exactly a model of the data source, but not a model of signals, like ARMA, etc.) The respective analysis technique that exploits such an assumption can be denoted as *model-based*. The interpretation of the results then crucially depends on the correctness of the assumption concerning the model of the data source.

For illustration let us consider a common and a power tool of the data analysis, the cross-correlation analysis and its frequency domain counterpart – the cross-spectral analysis. It is well-known that this technique provides a complete description of a linear input-output system, namely its transfer function; in this case the interpretation of the results is unambiguous. The technique certainly can (and often must) be used also for the analysis of nonlinear input-output systems, or systems of coupled active oscillators, but the interpretation of the results becomes more complicated and ambiguous. So, in latter complex cases the cross-correlation (spectral) analysis still determines reliably whether certain frequency components of given signals are interrelated (coherent) to a certain degree. However, a computation of the transfer function becomes of a limited, or of no use, and the conclusion about coherence cannot be extrapolated for the case when, say, amplitudes of signals will change.

Another example is related to an estimation of the transmission delay τ. 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. (Sometimes in biomedical literature the delay is obtained from the phase shift at the characteristic frequency, $\tau = \Delta\varphi/\omega$, what implicitly uses an additional assumption that the delay is smaller than the oscillation period.) However, if we are uncertain about the structure of the system under study, then this technique cannot be used, as it does not distinguish between the delay and the phase shift.

Two above considered examples shed light on the main difference between non-model-based and model-based analysis. Note that the same algorithm, e.g. computation of the cross-correlation function, can be used for both non-model-based and model-based analysis. The 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. Otherwise, the results may be misleading. 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.

In this Chapter we discuss several data analysis tools based on the assumption that the bivariate data originate from two coupled self-sustained oscillators (Fig. 7.1). (Below we also discuss the extension of the approach to the multivariate case). These tools are designed to provide the solutions for the following tasks:

- to detect and quantify an interaction between the systems,
- to reveal the direction of coupling,
- to estimate delay(s) in coupling,

provided the following assumptions are fulfilled:

- we deal with two self-sustained oscillators which can be *weakly coupled*
- we know how to ascribe the signals to systems,
- the signals are appropriate for phase estimation.

We emphasize that we prefer to speak about coupling between the systems and interrelation between the signals. Coupling in this context means some physical connection between oscillators which may or may not result in an interrelation between the signals measured at the output of these oscillators.

The Chapter is organized as follows. In the rest of this Section we briefly discuss the main facts of the coupled oscillators theory. Next, we discuss a particular example of bivariate

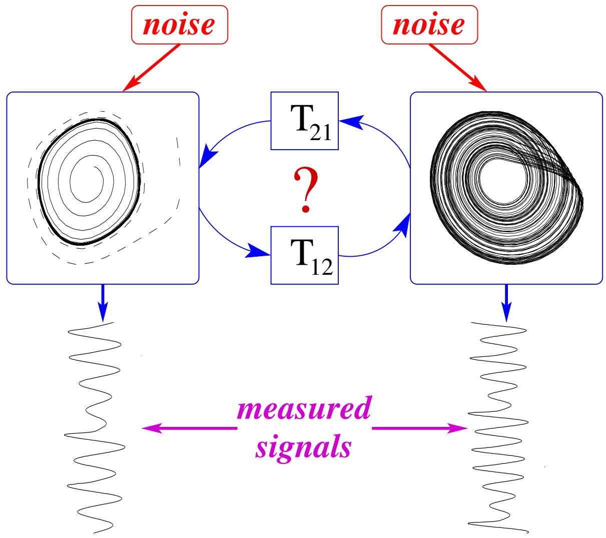

Figure 7.1: Coupled oscillators approach to the analysis of bivariate data explicitely assumes that the data are generated by two weakly coupled self-sustained oscillators. The systems can be either periodic or chaotic and are assumed to be perturbed by independent noise sources. The coupling can be uni- or bidirectional, and can occur with delays T_{21} and T_{12}.

data analysis, namely cardiorespiratory interaction in a healthy baby. In the next Sections we describe techniques of phase estimation and phase dynamics reconstruction from data. Finally, we present the analysis tools and illustrate them by an application to cardiorespiratory data.

7.1.1 Coupled oscillators: main effects

Active systems, capable of producing long-term sustained rhythmical activity, are known in physics as *self-sustained* oscillators. These are autonomous nonlinear dissipative systems, which compensate the loss of energy at the expense of an internal non-oscillatory energy source. Mathematically, such systems are described by autonomous differential equations. The image of periodic self-sustained oscillations in the phase space is a closed attracting trajectory, called limit cycle; the image of chaotic self-sustained oscillations is a strange attractor. See, e.g., [1, 2, 3] 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 gain 2π during one oscillation period:

$$\dot{\phi} = \omega \ , \tag{7.1}$$

where ω is the natural frequency. The notion of phase and amplitude(s) can be extended, though not rigorously, to some chaotic oscillators [4, 3]. As will be discussed below, the notion of phase is crucial for a description of interaction between self-sustained systems.

Models of coupled self-sustained oscillators appear in various fields of science and engineering, as well as in live nature. An important effect is *synchronization*, when two (or many) weakly interacting systems adjust their phases $\phi_{1,2}$ and average frequencies $\Omega_{1,2} = \langle \dot{\phi}_{1,2} \rangle$, where $\langle \rangle$ denotes averaging over time, so that the following conditions of *phase and frequency locking* are fulfilled:

$$|n\phi_1 - m\phi_2| < \text{const} , \qquad n\Omega_1 = m\Omega_2 . \tag{7.2}$$

This nonlinear phenomenon [5, 1, 2, 3, 6, 7] is often observed in man-made and natural systems. In the latter case it is found on a level of single cells, physiological subsystems, organisms and even on the level of populations [8, 9, 3]. Sometimes, synchronization is essential for a normal functioning of a system, e.g., for a coordinated motion of several limbs or for the performance of a pacemaker, where many cells fire synchronously, and in this way produce a macroscopic rhythm that governs respiration, heart contraction, etc. Sometimes, the onset of synchrony leads to a severe pathology, e.g., in case of the Parkinson's disease, when locking of many neurons results in the tremor activity. Quite often, the functional role of synchrony is yet unknown, e.g., in the case of cardiorespiratory coordination [10, 11, 12, 13, 14] or in the case of mutual entrainment of respiration and locomotion; possibly its appearance is just a manifestation of a general property of self-sustained oscillators – to adjust their rhythms due to a weak interaction. On the other hand, an onset or a cessation of synchrony reflects variation in the state of the complex system, and therefore may provide important physiological information.

Concept of synchronization can be also applied for description of interaction of noisy self-sustained oscillators (and natural systems are inevitably noisy). In this case the conditions (7.2) are fulfilled only in a statistical sense and the distinction between synchronous and asynchronous regimes is generally ambiguous (see discussion in [3] and references therein). Furthermore, the notions of phase and frequency locking can be extended for a class of chaotic self-sustained systems; in the context of interacting chaotic systems this effect is called phase synchronization [4]. From an experimentalist's viewpoint, the dynamics of weakly coupled noisy and chaotic systems is quite similar, and therefore in the context of data analysis they can be treated in a similar way.

Note that an interaction can result not only in adjustment of frequencies of coupled systems, i.e. in the tendency of the systems to become synchronized, but can also lead to variation of their frequencies (and amplitudes). (It means, that their frequencies are not constant but oscillate with time.) For example, in the context of the cardio-respiratory interaction such a variation of the heart rate with the frequency of respiration is called respiratory sinus arrhythmia. It is, therefore, important to distinguish between two different kinds of interaction. The first one is illustrated in Fig. 7.1; in general, such an interaction can affect the frequencies of systems as well as cause their variation. In the second case, which we denote as *modulation*, the modulating source does not act directly on the system, but only on the channel, where its output is being transmitted (see a discussion in [3]). Obviously, this kind of interaction cannot shift the frequency of the driven system but only cause its modulation. In other words, we denote by modulation the action that is called the phase modulation in the engineering literature. On the other hand, we do not have to separate what is called in engineering the frequency modulation from a general case of interaction treated in the synchronization theory and illustrated in Fig. 7.1. The distinction of two kinds of interaction from data remains an open question and will be not treated here; below we always assume that the coupling acts directly on the systems, in accordance with Fig. 7.1.

7.1.2 Weakly coupled oscillators: phase dynamics description

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]. This happens due to the fact that the amplitude is a variable, corresponding to the direction in the phase space which is transversal to the limit cycle, and, therefore, corresponding to the negative Lyapunov exponents of the dynamical system. Hence, the amplitude is a stable variable and cannot be adjusted by weak forcing or interaction. (For chaotic systems the amplitudes correspond to negative and positive Lyapunov exponents.)

On the contrary, the phase corresponds to the direction along the limit cycle (or to the flow of a chaotic system); this direction is characterized by the zero Lyapunov exponent. As a consequence, the phase is a marginally stable variable that can be adjusted by a very weak interaction. The main conclusion is that the description of weakly coupled oscillators can be reduced to the phase dynamics

$$\begin{aligned} \dot{\phi}_1 &= \omega_1 + f_1(\phi_1, \phi_2) + \xi_1(t) , \\ \dot{\phi}_2 &= \omega_2 + f_2(\phi_2, \phi_1) + \xi_2(t) , \end{aligned} \tag{7.3}$$

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 (7.3) from data, to be described below, because it naturally restricts the class of test functions for fitting. Noise terms in Eqs. (7.3) are considered as phase-independent. Note that Eqs. (7.3) describe also the dynamics of weakly coupled chaotic systems; in this case the irregular terms $\xi_{1,2}$ correspond to perturbations to the phase dynamics due to the chaotic nature of amplitudes.

It is often convenient (in particular, it will be used below for estimations of directionality and delay in coupling) to use instead of continuous time equations (7.3) a corresponding mapping for phase increments $\Delta\phi_{1,2}(t) = \phi_{1,2}(t + \Delta t) - \phi_{1,2}(t)$:

$$\begin{aligned} \Delta\phi_1 &= F_1(\phi_1, \phi_2) + \zeta_1(t) , \\ \Delta\phi_2 &= F_2(\phi_2, \phi_1) + \zeta_2(t) , \end{aligned} \tag{7.4}$$

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

7.1.3 Estimation of phases from data

Prior to the analysis of phase relations we have to estimate phases from data. There exist three main approaches to the problem. One is based on the construction of the complex *analytic signal* $\zeta(t)$ [15] from a scalar experimental time series $s(t)$ via the Hilbert transform (HT)

$$\zeta(t) = s(t) + is_H(t) = A(t)e^{i\phi(t)} , \qquad s_H(t) = \pi^{-1}\text{P.V.} \int_{-\infty}^{\infty} \frac{s(\tau)}{t - \tau} d\tau , \tag{7.5}$$

where $s_H(t)$ is HT of $s(t)$. Equation (7.5) unambiguously provides an instantaneous phase $\phi(t)$ and an amplitude $A(t)$. (We use the same notation ϕ for the true phase satisfying Eq. (7.1) and its estimate obtained from a scalar time series.) Note that HT is parameter free. Practical hints for computation and usage of the HT, as well as further citations can be found in [16, 3]. Here we briefly mention the crucial points:

- Mathematically, HT is defined for an arbitrary signal. However, $\phi(t)$ and $A(t)$ admit a clear physical interpretation only for narrow band signals. If the signal has no well-expressed peak in its power spectrum, then the computation of the phase and application of the synchronization approach is highly doubtful. We recommend to perform always a simple test, namely to plot $s_H(t)$ vs. $s(t)$ and to look whether the trajectory in this presentation always rotates around the origin; only in this case one can meaningfully compute the instantaneous phase. (Note that often the origin should be shifted to a point different from zero).
- A complex, broad band, signal that can be considered as a mixture of several narrow band processes should be first decomposed into oscillatory components which can be then considered as signals with slowly varying amplitude and frequency; as the next step, the phases of these components can be obtained via HT. (Note that sometimes it is difficult to decide whether a peak in the spectrum represents another process or a harmonic.) Decomposition can be done by means of a band-pass filter or by more sophisticated techniques like independent component analysis.
- Determination of $\phi(t)$ is very sensitive to low-frequency trends, what makes the preprocessing of the data a crucial step in the analysis.

The second approach exploits the wavelet analysis with a complex wavelet function and provides a phase (and an amplitude) as functions of time for a certain spectral frequency band [17, 18]:

$$A(t;f)e^{i\phi(t;f)} = \int_{-\infty}^{\infty} s(\tau)\Psi^*(t,\tau;f)d\tau \ , \tag{7.6}$$

where $\Psi(t,\tau;f)$ is the Morlet, or Gabor, wavelet:

$$\Psi(t,\tau;f) = \sqrt{f}\exp\left(i\cdot 2\pi f(\tau-t)\right)\exp\left(-\frac{(\tau-t)^2}{2\sigma^2}\right) .$$

This procedure is equivalent to a band-pass filtration and subsequent HT of the signal $s(t)$ [19]. The central frequency of the filter is f, and its width is determined by the parameter σ.

Third, the phase can be very easily introduced for processes that can be treated as a series of well-defined events taking place at times t_k (point processes). Examples include signals characterizing heart contraction or neuron firing. If the interval between two events can be considered as a cycle, then it is natural to say that the phase increment between the events is exactly 2π. Hence, we can assign to the times t_k the values of phase $\phi(t_k) = 2\pi k$, and for an arbitrary instant of time $t_k < t < t_{k+1}$ take

$$\phi(t) = 2\pi k + 2\pi\frac{t-t_k}{t_{k+1}-t_k} \ . \tag{7.7}$$

We emphasize that the definition and the practical determination of a phase of a complex signal in the context of the synchronization analysis remains an open problem. One approach, called locking-based frequency measurement was suggested in [20]. The idea of this approach is to use the signal under study in order to drive a set of uncoupled limit cycle oscillators with different natural frequencies. A subset of these probe oscillators can be entrained by the common forcing, and therefore synchronize in between; the frequency and the phase of these locked oscillators can be taken as an estimate of the frequency and the phase of the original signal.

Note that in theoretical studies of coupled systems the phase can be rigorously defined only for limit cycle oscillators, whereas a rigorous definition of the phase of noisy/chaotic oscillators remains a theoretical challenge. For an autonomous limit cycle oscillator the phase is defined as a uniformly growing function of time, cf. Eq. (7.1) [1, 3]. However, phase estimates according to Eqs. (7.5-7.7) generally do not meet this requirement. As a result the estimated phase obeys (if we neglect numerical errors)

$$\dot{\phi} = \omega + \tilde{f}(\phi), \tag{7.8}$$

where the function $f(\phi)$ reflects the nonuniformity of the motion of the phase along the limit cycle, and the equation for the coupled systems read (cf. Eqs. (7.3)):

$$\begin{aligned} \dot{\phi}_1 &= \omega_1 + \tilde{f}_1(\phi_1) + \hat{f}_1(\phi_1, \phi_2) + \xi_1(t) \ , \\ \dot{\phi}_2 &= \omega_2 + \tilde{f}_2(\phi_2) + \hat{f}_2(\phi_2, \phi_1) + \xi_2(t) \ , \end{aligned} \tag{7.9}$$

where the coupling is described by the functions $\hat{f}_{1,2}$. Similarly, if we want to describe the coupled system system by a discrete mapping, then the mapping obtained from phase estimates differs from the mapping Eq. (7.4) for true phases.

Finally, we note that, theoretically, phase is defined on the real line. In the following we call such a phase "unwrapped", while the phase defined on the $(0, 2\pi)$ interval is called "wrapped". The use of wrapped or unwrapped phase depends on the application and is often a crucial point.

7.1.4 Example: cardiorespiratory interaction in a healthy baby

We choose the study of the cardiorespiratory interaction as a primary example for the illustration of the applicability of our theoretical framework and techniques for experimental data analysis, for two reasons. The first is based on the *a priori* physiological evidence that the two vital rhythms are self-sustained and interact rather weakly. The second reason is that, despite extensive investigations at both theoretical and experimental level, the nature of cardiorespiratory interaction remains controversial. In particular, it remains an open question whether the effects of interaction (e.g. the frequency and the phase entrainment between the two rhythms) can be solely attributed to the well-known modulation of the heart rate by the respiratory rhythm (the so-called respiratory sinus arrhythmia), or a reciprocal form of coupling may coexist. To gain insight into this question, appropriate modeling and experimental data analysis tools are needed.

In the following sections, our framework is presented 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 preprocessing can be found in [13, 21]. For the computation of the phase of the cardiac signal we assume that the time occurrence of each R-wave in the electrocardiogram (ECG) marks the onset of a new cardio-cycle and that during each cardio-cycle the phase increases in a monotonic uniform way. This translates into the computation of instantaneous phase ϕ_h of the cardiac signal by linear interpolation between successive R-wave peaks (cf. Eq. (7.7)). Whereas the cardiac phase has thus a unique determination from R-wave timings, we face several alternatives in determination of the phase of the respiratory signal. It is known that, in normal physiological conditions, measurements of respiration during the quiet sleep provide a narrow-band signal, characterized by a certain degree of breath-to-breath variability in both amplitude and timing of the onset of the inspiration/expiration. In order to get a signal well-behaved with respect to Hilbert transform, and therefore having well-defined instantaneous attributes, a smoothing filter must be employed. The choice of the filter and its parameters results in a compromise between signal distortion due to an excessive filtering (which may provide an almost sinusoidal waveform) and smoothing (measurement noise suppression). With a correct choice of filter parameters, the instantaneous phase computed via HT preserves the information about cycle-to-cycle variability. Alternatively, the instantaneous phase of the respiratory signal can be obtained in a fashion similar to the way the phase of the cardiac signal has been determined. For the respiratory oscillator, the onset time of inspiration/expiration may serve as a physiologically relevant marker event. Figure 7.2 shows the instantaneous phase of the cardiac signal and the phase of the respiration derived via both HT and marker events for the data set considered for the analysis. Note that although the estimates obtained in two different ways differ on the time scale of one cycle, they provide same average frequencies.

7.2 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 $\phi_{1,2}(j) = \phi_{1,2}(t_j)$, where index $j = 1 \dots M$ denotes a discrete set of time points $t_j = j \cdot \delta t$, with the help of one of the algorithms described in Section (7.1.3). The next step depends on whether we want to reconstruct the continuous or discrete phase model (see Eqs. (7.3) and Eqs. (7.4)). In the first case we have to estimate the time derivatives $\dot{\phi}_{1,2}$. For this goal we first compute the phase increments $\Delta\phi_{1,2}$ 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, see an Appendix in [3]. In the second case we just compute $\Delta\phi_{1,2}$ 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 $\Delta\phi_1(j) = \Delta\phi_1(\phi_1(j), \phi_2(j))$, $\Delta\phi_2(j) = \Delta\phi_2(\phi_1(j), \phi_2(j))$ with a model (7.3) or (7.4). Because continuous functions $f_{1,2}$ and $F_{1,2}$ are 2π periodic in arguments, they admit a natural Fourier series representation, and

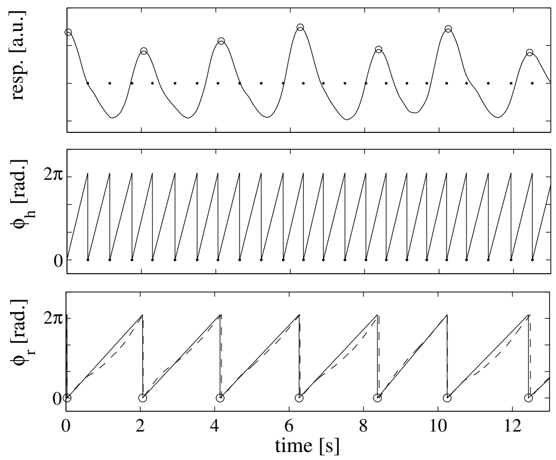

Figure 7.2: Top panel: respiratory signal. Middle panel: phase of the cardiac signal ϕ_h linearly increases and grows by 2π between two heart beats. Bottom panel: phase of respiration ϕ_r obtained via the Hilbert transform (dashed line) and via the linear interpolation of the time between two onsets of expiration.

we can in both cases seek for the dependencies in the form

$$\Delta\phi_1(\phi_1,\phi_2) = \sum_{m=0,l=-N}^{N} a_{m,l}\cos(m\phi_1 + l\phi_2) + b_{m,l}\sin(m\phi_1 + l\phi_2)\ , \tag{7.10}$$

and similarly for $\Delta\phi_2(\phi_1,\phi_2)$.

Practically, we can use the standard linear least square regression [22] to fit the data with a truncated Fourier series model. A minimization of

$$\sum_{j=1}^{M}\left(\Delta\phi_1(j) - \sum_{m=0,l=-N}^{N} a_{m,l}\cos\left(m\phi_1(j) + l\phi_2(j)\right) + b_{m,l}\sin\left(m\phi_1(j) + l\phi_2(j)\right)\right)^2$$

leads to a linear system

$$\sum_{s=0,n=-N}^{N} a_{s,n}A_{snml} + b_{s,n}B_{snml} = D_{ml}\ , \qquad \sum_{s=0,n-N}^{N} a_{s,n}B_{mlsn} + b_{s,n}C_{snml} = E_{ml}\ ,$$

where

$$A_{snml} = \sum_{j=1}^{M} \cos(s\phi_1(j) + n\phi_2(j)) \cos(m\phi_1(j) + l\phi_2(j)) \ ,$$

$$C_{snml} = \sum_{j=1}^{M} \sin(s\phi_1(j) + n\phi_2(j)) \sin(m\phi_1(j) + l\phi_2(j)) \ ,$$

$$B_{snml} = \sum_{j=1}^{M} \sin(s\phi_1(j) + n\phi_2(j)) \cos(m\phi_1(j) + l\phi_2(j)) \ ,$$

$$D_{ml} = \sum_{j=1}^{M} \Delta\phi_1(j) \cos(m\phi_1(j) + l\phi_2(j)) \ ,$$

$$E_{ml} = \sum_{j=1}^{M} \Delta\phi_1(j) \sin(m\phi_1(j) + l\phi_2(j)) \ .$$

Generally, a solution of this problem 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 matrices A and C are diagonal and B vanishes. This assumption is reasonable only when noise in the otherwise synchronous oscillators or quasiperiodic dynamics ensures a quite uniform scattering of phase points over the $[0, 2\pi) \times [0, 2\pi)$ square. In this case $a_{m,l}$ and $b_{m,l}$ are just the real and imaginary part of the Fourier transform

$$Q(m, l) = \frac{1}{M} \sum_{j=1}^{M} \Delta\phi_1(j) e^{i(m\phi_1(j)+l\phi_2(j))} \ . \tag{7.11}$$

In order to make use of the FFT algorithm, the irregularly sampled $\Delta\phi_{1,2}$ should be resampled onto a regular grid, by employing some form of interpolation or, in the presence of noise, estimation. After the transform (7.11) have been performed, one can select the dominant modes as the modes with the largest values of $|Q(m, l)|$. Then one can restrict the summation in (7.10) to these modes only, what significantly improves the reliability of found Fourier coefficients $a_{m,l}$ and $b_{m,l}$.

To exemplify this approach to phase dynamics model reconstruction, we take for the analysis the bivariate cardiorespiratory data set mentioned in the previous Section. A segment of ≈ 350 average cardiac cycles length is selected (see Fig. 7.4), and the phases of cardiac ϕ_h and respiratory ϕ_r oscillations along with their finite difference approximations $\Delta\phi_{h,r}$ over time interval 0.05 s are computed. In order to make use of the FFT algorithm for the $2D$ Fourier transform, we perform a Delaunay-triangulation based cubic interpolation of $\Delta\phi_{h,r}$ 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 $|\tilde{Q}(k_h, k_r)|$ for 100 realizations of the randomly shuffled $\Delta\phi_h$ and take $\langle \max(|\tilde{Q}(k_h, k_r)|) \rangle$ as the threshold value, where $\langle\rangle$ means averaging over the realizations of surrogates. It means that for the model fitting we use only the terms which satisfy $|Q(k_1, k_2)| \geq \max(|\tilde{Q}(k_h, k_r)|)$. In the same way, we identify the dominant modes of interaction between cardiac and respiratory oscillators. The results of this analysis is given in Fig. 7.3.

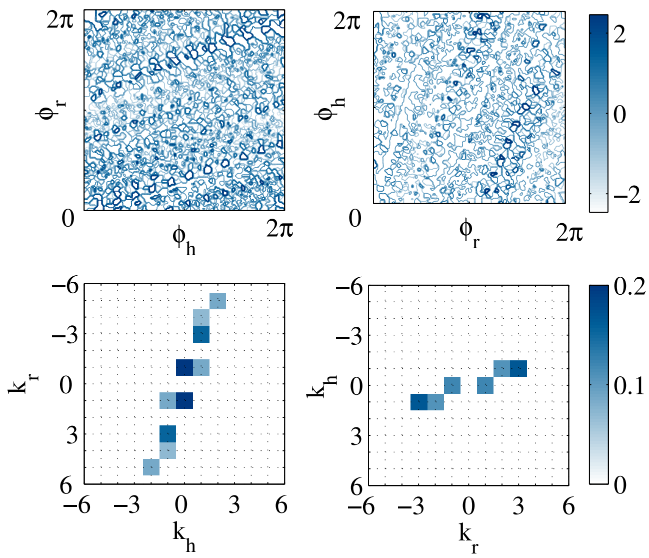

Figure 7.3: Top panel: Two-dimensional contour plots of the resampled $\Delta\phi_h(\phi_h, \phi_r)$ (left) and $\Delta\phi_r(\phi_r, \phi_h)$ (right). Bottom panel: Their corresponding two-dimensional Fourier transforms; gray scales code the absolute value of the corresponding Fourier coefficients.

The reconstructed model for the specified segment of the cardiorespiratory data reads (we use here notations $\phi_1 = \phi_h$ and $\phi_2 = \phi_r$):

$$\begin{aligned}
\Delta\phi_h \quad &\approx \quad 0.078 + 0.039\sin(\phi_r) + 0.481\cos(\phi_r) \\
& \quad -0.017\sin(\phi_r - \phi_h) + 0.133\cos(\phi_r - \phi_h) \\
& \quad -0.248\sin(3\phi_r - \phi_h) + 0.031\cos(3\phi_r - \phi_h) \\
& \quad -0.064\sin(5\phi_r - 2\phi_h) + 0.036\cos(5\phi_r - 2\phi_h)\ , \\
\Delta\phi_r \quad &\approx \quad 0.11 - 0.572\sin(\phi_r) - 0.114\cos(\phi_r) \\
& \quad +0.004\sin(\phi_h - 2\phi_r) + 0.172\cos(\phi_h - 2\phi_r) \\
& \quad +0.073\sin(\phi_h - 3\phi_r) + 0.339\cos(\phi_h - 3\phi_r)\ .
\end{aligned} \tag{7.12}$$

We remind that for the reconstruction we used the phase estimates, which, contrary to true phases do not fulfill (for uncoupled systems) the condition $\dot{\phi} = \omega$. 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 $\sim \sin(\phi_r)$, $\sim \cos(\phi_r)$ in the equation for $\Delta\phi_r$, cf. Eqs. 7.8. The appearance of the same terms in the equation for $\Delta\phi_h$ may, however, have an important physical meaning. Indeed, these terms in addition to the terms $\sim \sin(n\phi_r \pm m\phi_h)$, $\sim \cos(\phi_r \pm \phi_h)$ possibly indicate the presence of two mechanisms of interaction - a modulating one and a synchronizing one.

7.3 Characterization of coupling from data

Having estimated the phases of interacting objects from bivariate data we can proceed with characterization of the intensity and the directionality of interaction as well as of the delay in coupling. Generally speaking, there are two ways to do it. On the one hand, we can directly analyze relations between the phases. On the other hand, we can reconstruct phase equations (7.3) and use their parameters in order to quantify the coupling. The latter, truly model based approach, is more dependent on the correctness of the assumptions made, but can be more informative, e.g., providing a more precise estimate of the delay, as shown below.

7.3.1 Interaction strength

We have assumed that the interaction between the systems tend to synchronize them, i.e. to lock their phases and frequencies (cf. Eq. 7.2). The degree of $n : m$ locking and therefore (indirectly) the degree of interaction can be characterized by a *synchronization index*. A convenient choice is to use the parameter-free index computed as [17, 16]:

$$\rho_{n,m}^2 = \langle\cos(n\phi_1 - m\phi_2)\rangle^2 + \langle\sin(n\phi_1 - m\phi_2)\rangle^2 , \tag{7.13}$$

where $\langle\rangle$ denotes time average. The index varies from zero (independent phases) to one (see Fig. 7.4). The latter case corresponds to a constant phase difference, what is a more strict condition than that in Eq. (7.2). Generally, the phase difference in a synchronous state oscillates around a constant (especially if the phases are estimated from data). Hence, the index is less than one even in the synchronous state. Therefore, if the goal of the analysis is to detect a very weak interaction, then it is advisable to use the *stroboscopic approach*. The stroboscopic approach is an application of the well-known in nonlinear dynamics method of Poincaré section to data analysis. It implies that one fixes some value of the phase $\tilde{\phi}$ and observes the phase of, say, second system at the times when ϕ_1 attains $\tilde{\phi}$. Next, for these stroboscopically observed values of ϕ_2 one computes.

$$\lambda_{\tilde{\phi}} = \langle\cos(\phi_2)\rangle^2 + \langle\sin(\phi_2)\rangle^2 .$$

Averaging $\lambda_{\tilde{\phi}}$ over $\tilde{\phi}$ one obtains a stroboscopic synchronization index λ which attains the unit value in the synchronous state even if the phase difference in this state strongly oscillates. Discussion of the stroboscopic index of order $n : m$ and the related graphical tool called "synchrogram" (Fig. 7.4) can be found in [12, 16, 13, 3].

Synchronization index quantifies the end effect of interaction, but not exactly the strength of coupling. The latter is directly related to the amplitudes (norms) of functions $f_{1,2}$ in Eqs. (7.3), while the degree of phase locking is determined both by these amplitudes and

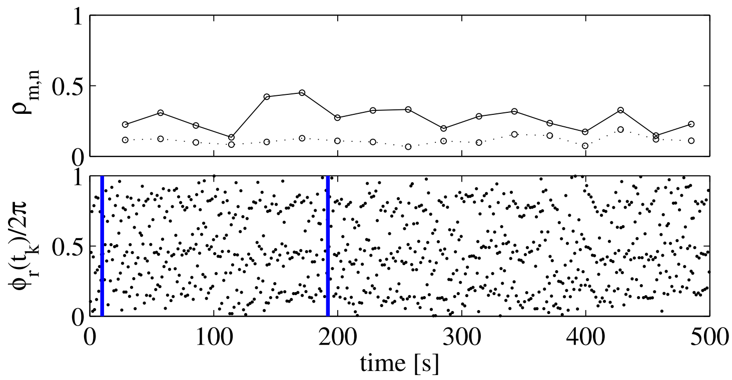

Figure 7.4: Top panel: synchronization indices $\rho_{1,3}$ (solid line) and $\rho_{2,5}$ (dotted line) for the cardiorespiratory data of a baby. The indices are computed in a running window and therefore are plotted as the functions of time (window length is equal to 100 average cardiocycles, windows overlap by 50%). Bottom panel: cardiorespiratory synchrogram. In this representation the phase of the respiration (wrapped to $(0, 2\pi)$ interval) is shown at the instances of appearance of R-peaks in the electrocardiogram, i.e. when the phase of the cardiac systems attains 2π. Note three stripes in the time interval $130 \lesssim t \lesssim 180$s: this is an indication of an interaction that tends to induce the $1:3$ locking. Note also the increase of the $\rho_{1,3}$ index in this time interval. Similar stroboscopic observation of the respiratory phase wrapped to the interval $(0, n \cdot 2\pi)$ can help to reveal an $n:m$ interaction. Vertical lines mark the segment of data used for modeling and identification of coupling.

the frequency mismatch, i.e. the relation between the frequencies of the system. A more detailed information about the strength of interaction may be obtained from the analysis of the coefficients of the reconstructed phase model. This approach is tightly related to quantification of directionality of coupling, described below. It is also important to emphasize that a synchronization index can be high not only in the case of an interaction that may lead to synchronization, but also in the case of a modulating interaction. Hence, a computation of the index alone does not allow one to draw the conclusion about the synchrony in the coupled system but rather demonstrates the presence of an interaction. The distinction between two types of interactions may be probably done from the analysis of the reconstructed model.

7.3.2 Directionality of coupling

An estimation of directionality and causality in coupling is an important issue of data analysis. Many techniques used for this goal go back to the Granger's causality concept [24], which can be briefly formulated as follows: if, say, signal 1 depends on signal 2, i.e. there is a directional relation $2 \to 1$, then the future of 1 can be better predicted if the information on 2 is taken into account; if 2 does not depend on 1, there will be no predictability improvement. Different algorithms, related to this approach, can be found in [26, 27, 28]. An extension of this idea in terms of entropy measures has been performed by T. Schreiber [25]; in particular, he applied this approach to the analysis of cardiorespiratory from the bivariate series of the breath rate and the instantaneous heart rate of a sleeping human suffering from sleep apnea.

Another approach, arising from studies of generalized synchronization, exploited the idea of mutual predictability in the phase space: it quantified the ability to predict the state of the first system from the knowledge of the second one [29, 30]. While both approaches are rather complicated to implement and interpret, neither requires any assumptions on the systems under investigation.

Before presenting the algorithms of the coupled oscillators approach, let us make several notes on the concepts of directionality and causality. First, we note that the assumption of weakly coupled oscillators implies that coupling, say from 2 to 1, is not a cause of oscillation of 1, but a weak perturbation to this oscillation. A second important issue is that *quantification of directionality is generally ambiguous*. While everything is clear in the case of unidirectional driving, the definition of symmetric interaction in bidirectionally coupled systems

$$\mathbf{X} = f_1(\mathbf{X}) + p_1(\mathbf{Y}) \,, \qquad \mathbf{Y} = f_2(\mathbf{Y}) + p_2(\mathbf{X}) \,,$$

cannot be unique. Indeed, is the coupling symmetric if $p_1 = p_2$ but $f_1(\cdot) \neq f_2(\cdot)$? Obviously, this question cannot be answered in a unique way, and, hence, different measures of directionality can be proposed and used in different experimental situations.

Directionality from phases: mutual predictability approach

In the case of weakly coupled oscillators the concept of mutual predictability can be very easily implemented, because we have to deal with two scalar signals only, namely with the time series $\phi_{1,2}$. Let us take one series, say, $\phi_1(t_k)$, and use some scheme to predict a future of its points. For the kth point we compute the *univariate prediction error* $E_1(t_k) = |\phi_1'(t_k) - \phi_1(t_k + \tau)|$, where $\phi_1'(t_k)$ is the τ-step ahead prediction of the point $\phi_1(t_k)$; note that phases are unwrapped. Next, we repeat the prediction for $\phi_1(t_k)$, but this time we use both signals ϕ_1, ϕ_2 for construction of the predictor. In this way we obtain the *bivariate prediction error* $E_{12}(t_k)$. If system 2 influences the dynamics of system 1, then we expect $E_{12}(t_k) < E_1(t_k)$, otherwise (for sufficient statistics) $E_{12}(t_k) = E_1(t_k)$. The root mean squared $E_1(t_k) - E_{12}(t_k)$, computed over all possible k and denoted by I_{12}, quantifies the *predictability improvement* for the first signal. This measure characterizes the degree of influence of the second system on the first one. Computing in the same way I_{21}, we end with the directionality index

$$p_{(1,2)} = \frac{I_{21} - I_{12}}{I_{12} + I_{21}} \,. \tag{7.14}$$

This approach has been suggested and applied to cardiorespiratory interaction in [31]. The same algorithm formulated in terms of conditional mutual information has been later used in [32].

Directionality from phases: model based approach

In quantification of the directionality from the reconstructed equations of the phase dynamics we follow our previously developed approach [33, 31]. We remind, that there is no unique way to quantify the directionality of coupling, even if Eqs. (7.3) are known. One way to quantify the directionality is as follows. We quantify the influence of system 2 on system 1 by the coefficient

$$c_1^2 = \|\partial\dot{\phi}_1/\partial\phi_2\| ,$$

where the norm $\|(\cdot)\| = \iint_0^{2\pi} (\cdot)^2 d\phi_1 d\phi_2$. Note that $c_{1,2}$ can be easily obtained from the model coefficients, e.g. $c_1^2 = \sum n^2(a_{m,n}^2 + b_{m,n}^2)$ [34]. 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

$$d_{(1,2)} = \frac{c_2 - c_1}{c_1 + c_2} , \tag{7.15}$$

that we call *directionality index*. It varies from 1 in the case of unidirectional coupling ($1 \rightarrow 2$) to -1 in the opposite case ($2 \rightarrow 1$), while intermediate values correspond to a bidirectional coupling configuration. If two oscillators are structurally identical and differ only by natural frequencies then $f_1(\cdot) = f_2(\cdot)$ and $d^{(1,2)} = (\varepsilon_2 - \varepsilon_1)/(\varepsilon_1 + \varepsilon_2)$. Alternative solutions of the directionality estimates have been discussed and experimentally verified in Ref. [31, 35].

We emphasize that the presented algorithm fails if the oscillators are phase locked, which mathematically corresponds to the appearance of a functional dependence 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 coefficient is zero, its estimate $\sqrt{\langle(\partial\dot{\phi}_1/\partial\phi_2)^2\rangle}$ is positive. A way to correct the estimate was suggested in Ref. [34].

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 (cf. Eqs. (7.4)). Computation of a phase increment over a realtively large time interval (it can be of the order of oscillation period) helps to reduce the effect of noise, see discussions in [33, 23] for more details.

Application of the directionality algorithms to cardiorespiratory data can be found in [31, 21, 36]. Here we present the results for the sample data set. The mutual prediction algorithm provides the directionality index

$$p_{h\rightarrow r} \approx -0.84 .$$

The directionality index obtained from coefficients of the model (7.12) is

$$d_{h\rightarrow r} \approx -0.42 .$$

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 $\dot{\phi}_1 = \omega_1 + \varepsilon\sin(3\phi_2 - \phi_1)$, $\dot{\phi}_2 = \omega_2 + \varepsilon\sin(\phi_1 - 3\phi_2)$. It is easy to see that $c_1 = 3c_2$, what gives $d_{(1,2)} = 0.5$.

7.3.3 Delay in coupling from data

We consider now the last problem, namely an estimation of the delay in coupling. There are two ways to treat this problem. First, one can compute from the time series of phases the synchronization index according to Eq. (7.13), then shift the first series with respect to the second one and compute the index for different, positive and negative, shifts τ. It is natural to expect that this *shift-dependent synchronization index* [37]

$$\rho^2(\tau) = \langle \cos(\phi_1(t) - \phi_2(t-\tau)) \rangle^2 + \langle \sin(\phi_1(t) - \phi_2(t-\tau)) \rangle^2 \tag{7.16}$$

maximizes if the shift corresponds to the (unknown) delay in coupling.

The second, model based approach, exploits a generalization of the models (7.3) and (7.4):

$$\begin{aligned} \dot{\phi}_1 &= \omega_1 + \varepsilon f_1(\phi_1(t), \phi_2(t - T_{21}) + \xi_1(t) \ , \\ \dot{\phi}_2 &= \omega_2 + \varepsilon f_2(\phi_1(t - T_{12}), \phi_2(t)) + \xi_2(t) \ , \end{aligned} \tag{7.17}$$

and

$$\begin{aligned} \Delta\phi_1(t) &= F_1(\phi_1(t), \phi_2(t - T_{21})) + \zeta_1 \ , \\ \Delta\phi_2(t) &= F_2(\phi_2(t), \phi_1(t - T_{12})) + \zeta_2 \ , \end{aligned} \tag{7.18}$$

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 $\dot{\phi}_1$ and $\dot{\phi}_2$, respectively). The dependencies $E_{1,2}(\tau)$ should take a minimum at $\tau = T_{12}$, $\tau = T_{21}$. 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 approaches performed in [23] 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. 7.5. The values of delay, estimated from the positions of the minima of the dependence $E_{1,2}(\tau)$ are $\mathcal{T}_1 \approx 0.4$ s (delay in coupling from respiration to heart) and $\mathcal{T}_2 \approx 1.4$ 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 in Ref. [38] 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,

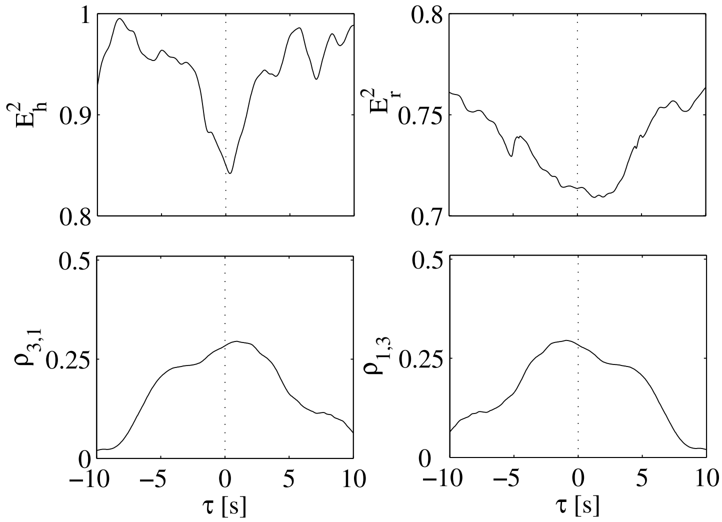

Figure 7.5: Estimation of the delays in bidirectional cardiorespiratory coupling. Top panels show the (normalized) errors of fit vs time shift between the series. Minima of the dependence indicate the values of delays. Bottom panels show the $\rho_{1,3}$ synchronization index. Dependence of the synchronization on shift (bottom panels) is not efficient in delay estimation.

then the cross-correlation function $C(\tau)$ has a very simple relation to the synchronization index, namely $\rho(\tau)$ is the envelope of $C(\tau)$ [23]. Hence, analysis of $C(\tau)$ provides the biased estimate of the delay as well.

7.4 Conclusions and discussion

In this Chapter 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.

Several remarks on the applicability of the presented modeling framework and potential pitfalls of the presented methods for data analysis are in order. First, one should verify whether the assumptions about the data generating processes are valid. Then, an attention must be paid to the preprocessing of signals (e.g., filtering) required for computation of the phases. In particular, a careful search for optimal filter parameters must be undertaken, especially for signals with non-sinusoidal shape and/or cycle-to-cycle variability (e.g., in the case of respiratory signal). Non-optimal filtering can greatly affect the accuracy of the derivative approximation and of the model reconstruction process. Finally, we remind that the model reconstruction and the subsequent application of the algorithms for directionality and time delay estimation requires that the interaction between two observed oscillator is not strong enough in order to bring them to synchrony. At the other extreme, when the interaction is too week (on the level of noise) the estimation of the directionality and the delay becomes impossible, too.

Although in this Chapter we focused on the study of interaction between two oscillators, a natural question arises about the possibility to exploit the presented approach for the study of several interacting systems. A preliminary analysis performed in [31, 36] demonstrates that a study of multivariate data can be partially accomplished by a pairwise analysis of bivariate data and the main effects of interaction can be identified. However, a clear distinction between direct and indirect interactions cannot be made in a straightforward manner, and a further work on the extension of our approach is required.

We conclude by expressing our belief that the presented theoretical and methodological framework of interacting self-sustained oscillators provides a useful basis for further development of techniques of the multivariate data analysis.

7.5 Acknowledgements

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