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Topical Review

Causality in physiological signals

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Abstract

Health is one of the most important non-material assets and thus also has an enormous influence on material values, since treating and preventing diseases is expensive. The number one cause of death worldwide today originates in cardiovascular diseases. For these reasons the aim of understanding the functions and the interactions of the cardiovascular system is and has been a major research topic throughout various disciplines for more than a hundred years. The purpose of most of today's research is to get as much information as possible with the lowest possible effort and the least discomfort for the subject or patient, e.g. via non-invasive measurements. A family of tools whose importance has been growing during the last years is known under the headline of coupling measures. The rationale for this kind of analysis is to identify the structure of interactions in a system of multiple components. Important information lies for example in the coupling direction, the coupling strength, and occurring time lags. In this work, we will, after a brief general introduction covering the development of cardiovascular time series analysis, introduce, explain and review some of the most important coupling measures and classify them according to their origin and capabilities in the light of physiological analyses. We will begin with classical correlation measures, go via Granger-causality-based tools, entropy-based techniques (e.g. momentary information transfer), nonlinear prediction measures (e.g. mutual prediction) to symbolic dynamics (e.g. symbolic coupling traces). All these methods have contributed important insights into physiological interactions like cardiorespiratory coupling, neuro-cardio-coupling and many more. Furthermore,

we will cover tools to detect and analyze synchronization and coordination (e.g. synchrogram and coordigram). As a last point we will address time dependent couplings as identified using a recent approach employing ensembles of time series. The scope of this review, as opposed to various other excellent reviews like (Hlaváčková-Schindler *et al Phys. Rep.* **441** 1–46, Kramer *et al* 2004 *Phys. Rev.* E **70** 1–10, Lombardi 2000 *Circulation* **101** 8–10, Porta *et al* 2000 *Am. J. Physiol.: Heart and Circulatory Physiol.* **279** H2558–67, Schelter *et al* 2006 *J. Neurosci. Methods* **152** 210–9), is to give a broader overview over existing coupling measures and where to look to find the most appropriate tool for a given situation. The review will comprise a test of one representative of the most important coupling measure groups using a simple toy model to illustrate some essential features of the tools. At the end we will summarise the performance of each measure and offer some advice on when to use which method.

Keywords: coupling direction, time series analysis, cardiovascular system

(Some figures may appear in colour only in the online journal)

1. Introduction

Many people throughout the world suffer from cardiovascular diseases, which are the number one cause of death worldwide (WHO 2010). Their treatment causes enormous costs for the public health care system (Heidenreich *et al* 2011) and is not always successful. These are among the main reasons why the study of the human cardiovascular system plays such a big role in the field of medical science, which can look back on a history of over one hundred years. The comparatively new branch of cardiovascular physics (Wessel *et al* 2007a), which combines methods from linear and nonlinear data analysis and modelling with medical background knowledge, has brought forth a lot of new interesting insights and tools to help in understanding the interactions of the cardiovascular system and thus predicting diseases, assessing risks and providing new clinical parameters (Sands *et al* 1989, Dougherty and Burr 1992, Counihan *et al* 1993, Hohnloser *et al* 1994, Malberg *et al* 2002). The development of noninvasive tools to measure physiological signals, e.g. the ECG and the blood pressure, has led to an enormous amount of data recorded under various conditions. The challenge now lies in analyzing the data, thus trying to understand the underlying mechanisms and their interactions amongst each other, and in the end extracting meaningful parameters usable for diagnostics and risk stratification. For example, heart rate (HRV) and blood pressure variability (BPV) parameters have helped understanding the nervous control mechanisms of the cardiovascular system (Sayers 1973, Lown and Verrier 1976, Akselrod *et al* 1981, Taskforce 1996). However, the many open questions lead to an undampened interest in analyzing the data and developing new sophisticated methods. Due to the complex structure with its many control loops and the strong dependence on internal as well as external conditions, the cardiovascular system exhibits a complicated spatio-temporal behaviour. Thus, a lot of fruitful ideas have been contributed by the field of chaos theory and nonlinear dynamics during the last decades (Voss *et al* 1995, 1996, Malik 1998, Schäfer *et al* 1999, Lombardi 2000, Marwan *et al* 2002, Kiyono *et al* 2004, Stein *et al* 2005, Porta *et al* 2007, Wessel *et al* 2007b). In order to gain a deeper insight into the actual mechanisms purely descriptive linear or nonlinear parameters are not sufficient, mathematical models are needed. Using these it is possible to describe the individual components and their interactions under various conditions, for example during diseases, and finally to draw conclusions about the reality (Cohen and Taylor 2002). Usually, there are two

approaches. The first one uses differential (Grodins 1959, Cavalcanti and Belardinelli 1996, Ottesen 1997, Olufsen *et al* 2000, Kuusela 2004, Kotani *et al* 2005, Zebrowski *et al* 2007) or difference equations (DeBoer *et al* 1987, Rosenblum and Kurths 1995) based on principles of physics, mathematics and, in this case, incorporating knowledge of physiology about couplings between e.g. heart rate, blood pressure, and respiration. The second one employs tools from time series analysis and system identification to model the measured data via autoregressive (AR) models and thus infer mechanisms independent of *a priori* knowledge (Pagani *et al* 1986, Baselli *et al* 1994, Chon *et al* 1997, Matsukawa and Wada 1997, Porta *et al* 2000). A problem with this approach lies in the potentially large number of possible parameters, which might interfere with a physiological interpretation. Also, as most natural processes, the cardiovascular system exhibits highly nonlinear behaviour, impairing the use of linear methods and models without further effort. For this reason, several extensions for nonlinear AR-models to describe HRV and BPV have been proposed in the last years, e.g. bilinear (Armoundas *et al* 2002), functional coefficient (Belozeroff *et al* 2002), nonlinear additive AR-models without (NAAR) (Wessel *et al* 2006) and with external input (NAARX) (Riedl *et al* 2008, Riedl 2009), and AR-models with conditional heteroscedasticity (Kantelhardt *et al* 2003).

For the models to help us in understanding the underlying mechanisms, we need to identify the interactions between the single variables using no or only little *a priori* knowledge. Therefore, a plethora of coupling measures to allow for identifying a complex system's coupling structure, including coupling strength, direction, and occurring time lags, has been developed over the years.

The analysis of effects from coupling in and between systems is important in data-driven investigations as practised in many scientific fields. It allows deeper insights into the mechanisms of interaction emerging among individual smaller subsystems when forming complex systems as in the human circulatory system or the climate system. In the last century and especially during the last 20 years the development and application of coupling measures became more and more important. The correct application of those, requires at least a basic understanding of the concept of causality. Since there is no binding definition of the term causality, two examples roughly based on Russell (1912) are given here.

An event A is said to be causal for an event B if,

- when A happens, B also takes place (necessary criterion),
- A happens chronologically before B,
- and, if A does not happen, B cannot occur either (sufficient criterion).

Based on probability theory also the next definition is possible. A causes B, if

- the probability for A to occur is not zero,
- A happens chronologically before B,
- and the probability for B to happen, when A has occurred before, is larger than the probability of B taking place on its own.

Due to the relativity theory, the second point in both definitions implies also a spatial restriction, which can be neglected for a lot of applications of coupling analyses, however. The utilisation of these definitions for time series analysis is not readily feasible. Often, some measure of *a priori* knowledge is still needed. One attempt of a causality definition for time series analysis was given by Granger (1969). A process X Granger-causes a process Y, if

- X happens chronologically before Y
- and the error when predicting the future of Y is reduced when taking information from X into account.

A lot of coupling measures are based on this definition. However, there are also other measures which employ another definition. A process X influences a process Y, if

- X happens chronologically before Y
- and the processes show similar behaviour.

Of course, these definitions are strongly attenuated versions of the causality definitions above. Therefore, one has to keep in mind, that usually a found coupling in time series can imply a causal connection, but cannot be taken as compelling proof. At least not, if not all variables of a given complex system are known. What is analyzed in most cases, is causality in the sense of Granger causality (Granger 1969), i.e. when the prediction of one system is significantly improved by using knowledge of a second system.

While often classic methods like correlation and coherence are used to define connections between subsystems (compare e.g. Nollo *et al* (2005) and Romero-Garcia *et al* (2014) for cortex networks and the cardiovascular system), today, there are coupling measures originating in different fields comprising Granger causality, methods based on information theory, phase space measures, symbolic dynamics, and synchronisation and coordination, which are able to provide more information about coupling strength and direction. There are several works comparing the different measures and testing their applicability in different situations stemming from neurophysiological and cardiovascular systems (Lungarella *et al* 2007a, Lehnertz 2011, Porta and Faes 2013, Schulz *et al* 2013a). Several models of the cardiovascular system have been proposed based on the results of combining practical and theoretical *a priori* knowledge with insights obtained via coupling analyses (DeBoer *et al* 1987, Porta *et al* 2000, 2002, Stefanovska *et al* 2001a, 2001b, Sheth *et al* 2004). These models usually employ coupled oscillator, biological, and data-driven approaches. In the next section different coupling analysis tools from various fields will introduced to give a rough overview about this vast area of data analysis.

2. Methods for coupling analyses

Today there is an abundance of coupling measures stemming from different fields to be found. In Lungarella *et al* (2007a), Porta and Faes (2013) and Schulz *et al* (2013a) very good reviews of existing tools and their applications to physiological time series can be found. However, the aim of this review is to give a broader scope about the different approaches in the field of coupling analyses without going into too much details. A stronger focus will be given to recent developments in the field of time variant coupling analyses based on an example originating in the area of symbolic dynamics. Table 1 gives an overview the most common coupling measures, their extensions, and their fields of application. The columns labelled 'nonlinear' and 'multivariate' here mean that the tools can be used to also detect nonlinear couplings and are able to incorporate the knowledge of multvariate data, respectively. We arrange the coupling measures regarded into six different groups according to their origin and purpose and will give further information in the next sections. The groups are classical measures, Granger-causality-based methods, entropy-based tools, methods based on nonlinear prediction, approaches stemming from the field of symbolic dynamics, and measures from the field of synchronisation and coordination analyses. From each group an example is chosen and explained and discussed in more detail.

2.1. Classical measures

The classical measures are usually based on a correlation measure (Nollo *et al* 2005, Romero-Garcia *et al* 2014) and display several drawbacks when compared with other coupling analysis

Table 1. Overview of existing coupling measures and their applications.

Group	Subgroup	Nonlinear	Multivariate	References	Applications
Classical measures					
Correlation		No	No	Romero-Garcia *et al* (2014)	Cortex networks
Cross-spectral coherence		No	No	Nollo *et al* (2005)	ECG, blood pressure under head-up-tilt
Granger causality					
Granger causality					
	Classical, conditional	No	Yes	Geweke (1984), Granger (1969)	Financial time series
	Radial basis functions	Yes	No	Ancona *et al* (2004)	Heart rate, breath rate of sleeping subjects
	Conditional GC + embedding	Yes	Yes	Chen *et al* (2004)	
	NAARX	Yes	Yes	Faes *et al* (2008a), Riedl *et al* (2008), (2010), Riedl (2009)	RR, SAP on tilt table; cardiovascular system; women suffering from PE
	Partial GC	No	Yes	Guo *et al* (2008)	Brain activity in sheep
	Polynomial embedding	Yes	Yes	Ishiguro *et al* (2008a)	Gene regulatory networks
	Kernel-based	Yes	Yes	Marinazzo *et al* (2011), (2008a) and (2008b)	EEG fmri data; gene regulatory networks
	Long-term causality	No	Yes	Smirnov and Mokhov (2009)	Climate series
	Nonlinear extensions	Yes	Yes	Ishiguro *et al* (2008b), Hlaváčková-Schindler *et al* (2007)	
Partial directed coherence		No	Yes	Baccalá and Sameshima (2001), Schelter *et al* (2006b), Winterhalder *et al* (2006), (2007)	EEG of sleeping rats; EEG; emg

(*Continued*)

Table 1. (*Continued*)

Group	Subgroup	Nonlinear	Multivariate	References	Applications
Evolution map approach		Yes	No	Bezruchko *et al* (2003), Cimponeriu *et al* (2003), Mrowka *et al* (2003), Musizza *et al* (2007), Rosenblum *et al* (2002), Rosenblum and Pikovsky (2001), Smirnov and Andrzejak (2005), Smirnov and Bezruchko (2003)	Chaotic oscillators; cardiorespiratory data; EEG, meg during paced finger tapping; EEG data from rats under anaesthesia
Entropy					
Mutual information					
Partial mutual information		Yes	Yes	Frenzel and Pompe (2007)	
Transfer entropy		Yes	Yes	Schreiber (2000)	Heart rate, breath rate of sleeping subjects
	Wavelet extension	Yes	Yes	Lungarella *et al* (2007b)	Heart rate, breath rate of sleeping subjects
	Information transfer	Yes	Yes	Verdes (2005)	Cardiorespiratory data
Conditional mutual information		Yes	Yes	Musizza *et al* (2007), Paluš *et al* (2001a), (2001b), (2004), Paluš and Stefanovska (2003), Paluš and Vejmelka (2007), Paluš (1996), Paluš (2007), Quinn *et al* (2011), Vejmelka and Paluš (2008), Vejmelka (2008)	EEG; cardiorespiratory signals; mri; EEG data from rats under anaesthesia; neural spike trains
	Non-uniform embedding	Yes	Yes	Faes *et al* (2011), (2012b)	RR, SAP, respiration on tilt table; EEG
	Causation entropy	Yes	Yes	Sun and Bollt (2014), Sun *et al* (2014a) and (2014b)	Cellular dynamics
Momentary information transfer		Yes	Yes	Pompe and Runge (2011), Runge *et al* (2012a), (2012b) and (2014)	Climate time series, cardiovascular data

(*Continued*)

Table 1. (*Continued*)

Group	Subgroup	Nonlinear	Multivariate	References	Applications
Nonlinear prediction					
Mutual prediction		Yes	No	Le Van Quyen *et al* (1999), Nollo *et al* (2009), Schiff *et al* (1996), Terry and Breakspear (2003)	Motoneuron data; EEG of epilepsy patients; ECG, blood pressure under head-up-tilt; EEG
Interdependence measures	S, H, M, L	Yes	No	Andrzejak and Kreuz (2011), Arnhold *et al* (1999), Chicharro and Andrzejak (2009), Faes *et al* (2008b), Quian Quiroga *et al* (2000), (2002), Schmitz (2000), Smirnov and Andrzejak (2005)	EEG measurements from implanted electrodes in epilepsy patients; heart rate, blood pressure; EEG
Mean conditional recurrence		Yes	No	Romano *et al* (2007)	
Inter-system recurrence networks		Yes	Yes	Feldhoff *et al* (2012)	Palaeoclimate series
Recurrence based		Yes	No	Hirata and Aihara (2010), Marwan *et al* (2013), Ramírez Ávila *et al* (2013), Zou *et al* (2011)	Wind measurements; cardiorespiratory data
Symbolic dynamics					
Symbolic coupling traces		Yes	No	Suhrbier *et al* (2010), Wessel *et al* (2009)	Heart rate, blood pressure (Normal and during sleep)
Symbolic transfer entropy		Yes	Yes	Staniek and Lehnertz (2008), Stausberg and Lehnertz (2009)	EEG of epilepsy patients
Joint symbolic dynamics		Yes	No	Schulz *et al* (2013b)	ECG, blood pressure
Transient interactions					
Symbolic coupling traces		Yes	No	Müller *et al* (2013), Müller *et al* (2014)	Orthostatic test, arousals during sleep
Interdependence measure	H	Yes	No	Andrzejak *et al* (2006)	
Evolution map approach		Yes	No	Wagner *et al* (2010)	Event-related potentials
Symbolic transfer entropy		Yes	Yes	Martini *et al* (2011)	Event-related potentials

(*Continued*)

Table 1. (*Continued*)

Group	Subgroup	Nonlinear	Multivariate	References	Applications
Synchronisation					
				Mrowka *et al* (2000), Pikovsky *et al* (2001), Rosenblum *et al* (1998)	Cardiorespiratory data
	Synchrogram			Rosenblum *et al* (2001), Schäfer *et al* (1999), Schäfer *et al* (1998)	Cardiorespiratory data, EOG, EMG
	Partial phase synchronisation			Schelter *et al* (2006a)	
Coordination					
				Raschke and Hildebrandt (1982), Raschke (1986), (1987)	Cardiorespiratory data
	Coordigram			Müller *et al* (2014), Riedl *et al* (2014)	Cardiorespiratory data, apnoea

tools. However, they are usually quite simple to use and do not require too big amounts of data. One of the simplest bivariate coupling measures is based on the so-called Pearson correlation ρ_{XY} (Galton 1886, Pearson 1895), which was developed to quantify the magnitude of linear interrelation between two time series $x(t)$ and $y(t)$. It is given by

$$\rho_{XY} = \frac{\mathrm{Cov}(x(t), y(t))}{\sqrt{\mathrm{Var}(x(t))\mathrm{Var}(y(t))}},$$

where X and Y are the two processes regarded, Cov() and Var() describe the covariance and the variance, respectively. The value of ρ_{XY} lies between $\rho_{XY} = 1$, total positive correlation, and $\rho_{XY} = -1$, total negative correlation, while $\rho_{XY} = 0$ means no correlation. To infer information about possible causal structures, a time lag τ between the time series can be introduced, resulting in the so-called cross-correlation

$$\rho_{XY}(\tau) = \frac{\mathrm{Cov}(x(t), y(t+\tau))}{\sqrt{\mathrm{Var}(x(t))\mathrm{Var}(y(t))}}.$$

Depending on for which choice of τ the value $|\rho_{XY}(\tau)|$ is highest, one can draw conclusions about the predominant coupling structure (e.g. $\tau < 0$ means Y drives X and vice versa). Technically, the results give us only some information about temporal connections between the time series regarded, so inferences about causal connections have to treated cautiously.

2.2. Granger-causality-based tools

Granger causality is probably one of the best known and most often applied methods. The classical Granger causality was introduced in Granger (1969). It is based on estimating AR-models for the data given and checking whether the errors produced by the modelling process are significantly reduced when incorporating information from a second variable. Over the years, several extensions for multivariate data and nonlinear applications have been developed.

Table 2. This scheme shows how to transform time series $x(t)$ and $y(t)$ into word sequences $w_x(t)$ and $w_y(t)$ with $l = 3$ via the symbol series $s_x(t)$ and $s_y(t)$, respectively.

$x(t) =$	…	8	6	9	11	12	8	13	5	…
$y(t) =$	…	7	2	5	3	7	11	10	6	…
						⇓				
$s_x(t) =$		…	0	1	1	1	0	1	0	…
$s_y(t) =$		…	0	1	0	1	1	0	0	…
						⇓				
$w_x(t) =$			…	011	111	110	101	010	…	
$w_y(t) =$			…	010	101	011	110	100	…	

2.2.1. Linear methods. The traditional Granger causality is today a method of choice for a first assessment of couplings in cardiovascular and cardiorespiratory data and has been used as the keystone for several modelling approaches. In the scope of this review we will take a closer look at the conditional Granger causality for set of systems X_i and their representing time series x_i given by the following equations,

$$x_{kj}^{(r)}(t) = \sum_{i=1;i\neq k}^{n_{\text{var}}} \sum_{\tau=0;1}^{\Omega} a_{ij}^{(r)}(\tau) x_i(t-\tau) + \epsilon_{kj}^{(r)}(t),$$

$$x_{j}^{(u)}(t) = \sum_{i=1}^{n_{\text{var}}} \sum_{\tau=0;1}^{\Omega} a_{ij}^{(u)}(\tau) x_i(t-\tau) + \epsilon_{j}^{(u)}(t).$$

The superscript indices (r) and (u) denote the restricted (using only part of the available information) and the unrestricted (using all available information) models. Here, the model itself is a multivariate AR-model defined by the parameters a, the past of the time series x and the error term ε. The number of regarded variables is given by n_{var}, the model order by Ω, and τ represents the time lags. These equations let us determine the influence from X_k to X_j conditioned on $\{X_i; i \notin \{j,k\}\}$ via the term

$$F^{(c)}_{X_k \to X_j | \{X_i; i \notin \{j,k\}\}} = \log \frac{\text{var}(\varepsilon_{kj}^{(r)})}{\text{var}(\varepsilon_{j}^{(u)})},$$

where var() denotes the variance of the error terms. Based on this idea several linear tools to assess the coupling structures in different time series have been developed. These range from applying versions of the classical approach to applications in the frequency domain (see Faes *et al* (2012a), Geweke (1982) and Winterhalder *et al* (2005) for reviews in this field). The time domain approach e.g. has been applied to analyze the baroreflex during anaesthesia and the influence of the respiration (Bassani *et al* 2012, Porta *et al* 2012a). To also identify indirect couplings, there are several extensions for multivariate data (Granger 1969, Geweke 1984, Guo *et al* 2008). Another way to solve this problem is to use a factorisation approach (Porta *et al* 2012b). The spectral version of Granger causality is also known as partial directed coherence and has among others been applied on EEG (Baccalá and Sameshima 2001, Schelter *et al* 2006b, Winterhalder *et al* 2006, 2007) as well as cardiorespiratory data (Faes and Nollo 2010, Milde *et al* 2011).

2.2.2. Nonlinear methods. Several extensions of the concept of Granger causality aim at making the framework applicable to nonlinear data. This includes the use of NAARX-models

(Faes *et al* 2008a, Riedl *et al* 2008, 2010, Riedl 2009), different embedding techniques (Chen *et al* 2004, Ishiguro *et al* 2008b), the use of radial basis functions (Ancona *et al* 2004), and the application of kernel based methods (Marinazzo *et al* 2011, 2008a, 2008b). A comparison of different nonlinear extensions can be found in Ishiguro *et al* (2008a) and Hlaváčková-Schindler *et al* (2007). The applications range from financial data over cardiovascular, neurophysiological, and gene regulatory network data to climate time series. To assess also long-term couplings for example in climate data, in Smirnov and Mokhov (2009) an appropriate approach has been proposed.

Another method is given by the so-called evolution map approach (Rosenblum and Pikovsky 2001) which has been extensively used on theoretic models and EEG as well as cardiorespiratory data (Rosenblum *et al* 2002, Bezruchko *et al* 2003, Cimponeriu *et al* 2003, Mrowka *et al* 2003, Smirnov and Bezruchko 2003, Smirnov and Andrzejak 2005, Musizza *et al* 2007). It is based on modelling the time development of the phases of two time series using finite Fourier series.

2.3. Entropy-based

The methods stemming from the field of information theory are usually based on a form of mutual information (Shannon 1948). The first subgroup is the transfer entropy (Schreiber 2000) with several extensions (Verdes 2005, Lungarella *et al* 2007b, Faes *et al* 2011). It has been mostly applied to cardiovascular data. The second measure, the conditional mutual information (Paluš 1996), bears some similarities with the transfer entropy and is in some cases equivalent. It has been widely applied to neurophysiological and cardiovascular data (Paluš *et al* 2001a, Paluš *et al* 2004, Paluš and Stefanovska 2003, Frenzel and Pompe 2007, Musizza *et al* 2007, Paluš and Vejmelka 2007, Paluš 2007, Vejmelka 2008, Faes *et al* 2011, Quinn *et al* 2011, Sun and Bollt 2014). This approach can also be used on phase time series. An overview about several information theoretic methods can be found in Hlaváčková-Schindler *et al* (2007). Recently, a new approach, the so-called momentary information transfer, has been introduced. It specialises on avoiding spurious couplings by conditioning on certain subgroups of the data points and on how to identify these. It has been successfully applied to climate and cardiovascular data (Pompe and Runge 2011, Runge *et al* 2012a, 2012b, Runge *et al* 2014).

Here, we will regard the coarse-grained transinformation rate (CTIR) from Paluš *et al* (2001a) in more detail. It is based on conditional mutual information and is computed by

$$i_{Y\to X} = \frac{1}{\tau_{\max}} \sum_{\tau=1}^{\tau_{\max}} I(y(t), \Delta_\tau x(t) | x(t)),$$

where $\Delta_\tau x(t) = x(t+\tau) - x(t)$. The parameter $\tau_{\max}$ is chosen in a way that for $\tau > \tau_{\max}$ the mutual information $I(x(t), x(t+\tau)) = 0$ holds approximately true. The advantage of this method is, that influences from the past of a given time series on itself are neglected by conditioning on these. Thus the coarse-grained information rate is less susceptible to indirect coupling effects. Because of the necessity to estimate a probability distribution in order to compute the mutual information, usually longer time series are necessary to obtain meaningful results.

2.4. Nonlinear prediction measures

The nonlinear prediction methods are usually based on mutual prediction using a nearest neighbours approach and comparing prediction errors when incorporating other variables (Schiff *et al* 1996, Le Van Quyen *et al* 1999, Quian Quiroga *et al* 2000). Thus, they are also

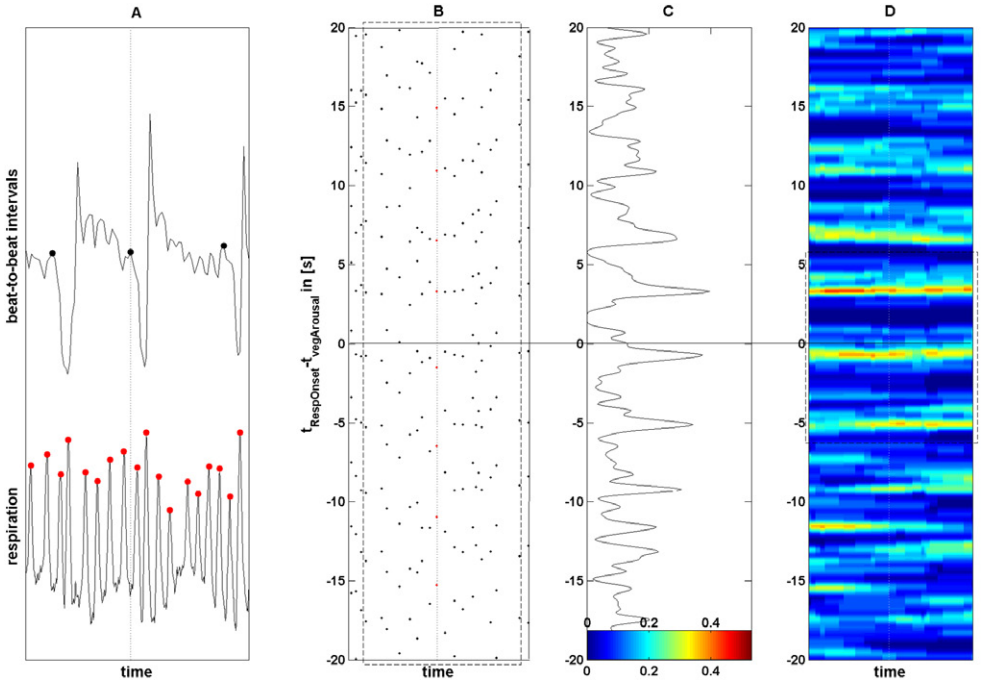


Figure 1. This figure shows how to build the coordigram from two given time series, based on an analysis of vegetative arousals during sleep (beat-to-beat intervals) and the corresponding respiratory signal (Müller *et al* 2014). First the events are marked in each series (A) and the respective time differences are computed (B). Using a Gaussian kernel function, the point distribution is estimated (C) and the dentisty is colourcoded for each time point (D).

based on identifying causalities in the sense of Granger. There are today several refinements of the original measures using e.g. rank statistics, and they have been successfully applied to different nonlinear model systems and neurophysiological as well as cardiovascular data (Arnhold *et al* 1999, Le Van Quyen *et al* 1999, Schmitz 2000, Quian Quiroga *et al* 2002, Terry and Breakspear 2003, Smirnov and Andrzejak 2005, Faes *et al* 2008b, Chicharro and Andrzejak 2009, Nollo *et al* 2009, Andrzejak and Kreuz 2011). A second class in this field consists of recurrence based measures with applications to climate series and the cardiovascular system (Romano *et al* 2007, Zou *et al* 2011, Feldhoff *et al* 2012, Marwan *et al* 2013, Ramírez Ávila *et al* 2013). Among these measures there is also an approach to identify hidden variables to avoid spurious connections (Hirata and Aihara 2010).

2.5. Symbolic dynamics

Among other features, their robustness against noise predestines symbolic approaches for a coupling analysis. They are based on the symbolification of the data using different approaches. The coupling analysis part is usually done by applying another known coupling measure algorithm on the obtained symbol sequences. By choosing the symbol alphabet, word length, and time lags between consecutive 'letter' of a word, one can easily adapt the measures to the needs at hand (e.g. short-term or long-term coupling). Some of the most successful measures are the symbolic transfer entropy (Staniek and Lehnertz 2008, 2009), joint symbolic dynamics (Schulz *et al*

2013b), and the symbolic coupling traces (Wessel *et al* 2009, Suhrbier *et al* 2010), which have all been applied to neurophysiological and cardiovascular data and have delivered promising results.

The symbolic coupling traces (SCT) were introduced by Wessel *et al* (2009) and are an extension of a bivariate joint symbolic dynamics method (Baumert *et al* 2002) which was developed to characterise and interpret the complex and highly nonlinear interactions between heart rate and systolic blood pressure. For both methods a dynamical system represented by two one-dimensional time series $x(t)$ and $y(t)$ is considered, which are then transformed into coarse grained symbolic time series $s_x(t)$ and $s_y(t)$ according to

$$s_z(t) = \begin{cases} 1, & z(t) \leqslant z(t+\vartheta) \\ 0, & z(t) > z(t+\vartheta). \end{cases}$$

The time lag ϑ is usually set to $\vartheta = 1$ but can also be chosen as another number of time steps in order to accommodate *a priori* knowledge about the time scales on which the couplings act. These symbol series in turn are used to construct series of words $w_z(t)$ where each word contains l successive symbols (see table 2). Because of the binary alphabet in this case, this gives $d = 2^l$ different possibilities of words. Larger values of ϑ work like an averaging process across the area defined by ϑ and l.

From the word sequences generated in this way for time series $x(t)$ and $y(t)$, a bivariate word distribution can now be estimated as

$$\Pi_{ij} = P(w_x(t) = W_i, w_y(t) = W_j).$$

Here, W_i and W_j denote certain words out of the whole vocabulary of $d = 2^l$ different words and Π_{ij} is the joint probability of words W_i and W_j appearing at the same time t in the word series w_x and w_y, estimated over all values of t. To later be able to determine the coupling direction and the occurring lags, a time lag τ between the two word sequences w_x and w_y is introduced, resulting in the matrix

$$(\Pi(\tau))_{ij} = P(w_x(t) = W_i, w_y(t+\tau) = W_j).$$

One way to characterise this matrix could be to regard the joint Shannon entropy (Shannon 1948) for each lag τ. However, studies in Wessel *et al* (2009) showed, that using Shannon entropy does not clearly reveal the correct time lags. Instead, the results improve a lot, when regarding only the difference between the occurrences of symmetric (e.g. $w_x(t) = w_y(t+\tau)$) and diametric words (e.g. $w_x(t) =$ '1 1 1' and $w_y(t+\tau) =$ '0 0 0'). The symmetric word frequency is represented by

$$T(\tau) = Tr(\Pi(\tau)) = \sum_{i=j} (\Pi(\tau))_{ij} \tag{1}$$

and the diametric word frequency by

$$\bar{T}(\tau) = \sum_{i=1,\ldots,d; j=d+1-i} (\Pi(\tau))_{ij}, \tag{2}$$

where $\mathrm{Tr}(\Pi(\tau))$ is the trace of the matrix $\Pi(\tau)$ and $d = 2^l$ is the number of the possible different words. The difference $\Delta T = T - \bar{T}$ has proved to be an effective parameter to identify the coupling structure of bivariate systems. To assess the significance of the results thus obtained, an empiric test based on a simulation with bivariate white noise for different signal lengths has been developed (Suhrbier *et al* 2010). For the significance level $\alpha = 0.01$ the critical values of ΔT are given as

$$\Delta T_{\mathrm{crit}}(N) = \pm\, 2.7005 \cdot N^{-0.5179},$$

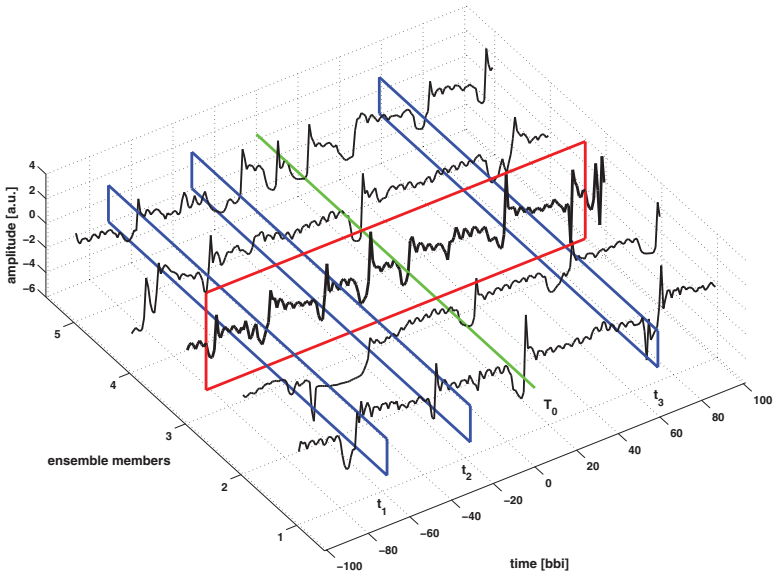


Figure 2. This figure illustrates the ensemble approach for the analysis of transient interactions. The ensemble here consists of five members synchronised at time point T_0. Instead of regarding the time average for one series (red rectangle), the measures can be evaluated at specific time points (e.g. t_1, t_2, and t_3) via ensemble averaging (blue rectangles). The example time series here are again beat-to-beat intervals.

where N is the number of data points regarded. Now, the coupling direction can be determined via the occurring time lags τ where ΔT is significant. The coupling strength is related to $|\Delta T|$ and $\mathrm{sgn}(\Delta T)$ tells us whether symmetric or diametric behaviour is dominant. Further insight into the systems in question might be gained by looking at the results of the SCT when using the absolute value of the time series as input.

2.6. Synchronization and coordination tools

Synchronisation (Pikovsky *et al* 2001) is an effect which usually renders the detection of coupling directions impossible, since in a completely synchronised state two systems cannot be distinguished anymore. A second tool, the synchrogram (Schäfer *et al* 1998), allows for a graphical interpretation of synchronised states in bivariate systems. It has been mainly used on cardiorespiratory data (Rosenblum *et al* 1998, 2001, Schäfer *et al* 1999, Schäfer *et al* 1998, Mrowka *et al* 2000, Schelter *et al* 2006a). Since this measure is used to detect phase synchronisation, it is not a coupling measure *per se*, but still has delivered interesting insights. However, another method based on a similar approach, namely the coordigram (Riedl *et al* 2014), can be used to infer coupling directions. As opposed to the synchronisation, which describes a phase-based relationship between systems, the coordination describes a time-based connection (e.g. between the time points of the onsets of respiratory cycles and the heart beats) and has been shown to play an important role for example in cardiorespiratory mechanisms (Raschke and Hildebrandt 1982, Raschke 1986, 1987).

The coordigram is based on recurring events in the two signals regarded, for example the onsets of inhalation in respiratory signals and the R-peaks of the ECG. To build it (compare also figure 1) the time points of these events are denoted by t_{z1j} (the reference cycle, e.g. the jth respiratory onset) and t_{z2k} (the second cycle, e.g. the time index of the kth R-peak during the respiratory cycles directly before and after t_{z1j}). To build the coordigram the time differences Δt between

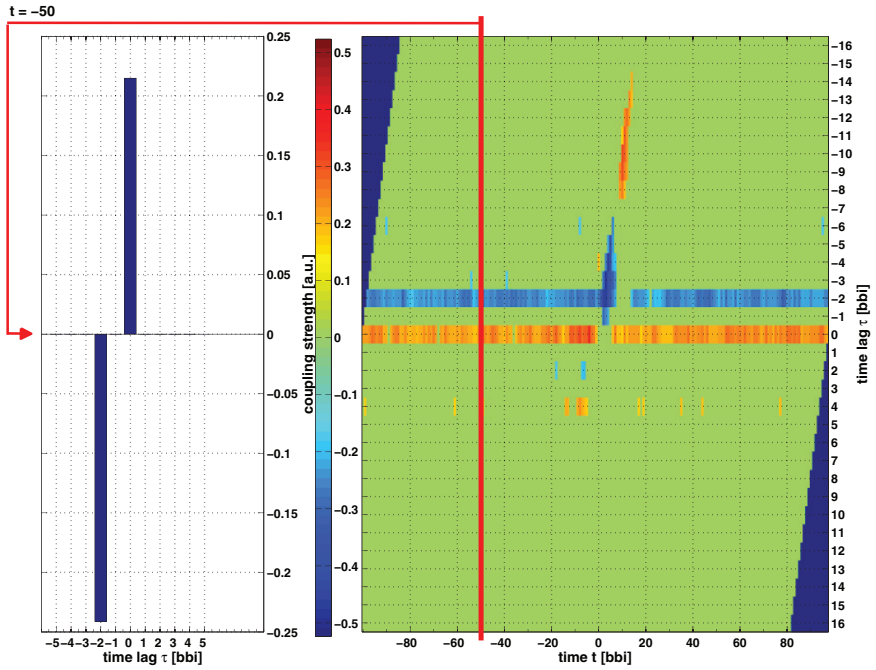
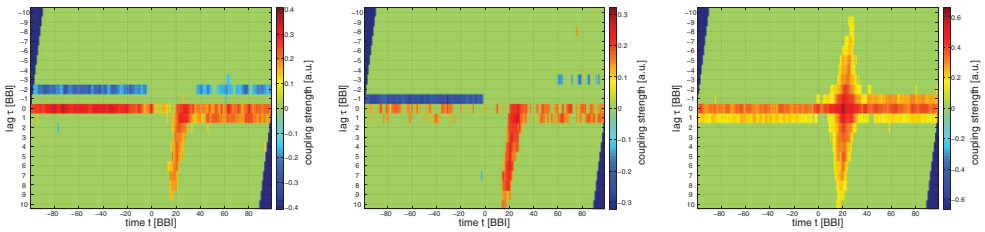


Figure 3. The figure shows how to read the results of the ESCT method. For any given time point the result can be displayed as for the classic SCT, positive values depicting symmetric coupling, negative values diametric coupling. The absolute values represent the coupling strength in some way. In the ESCT the sign and the absolute values of the results are colour coded (red—symmetric, blue—diametric). The coupling direction is determined via the occurring time lags τ. The time series for this example are beat-to-beat intervals and systolic blood pressure for vegetative arousals during sleep (Müller *et al* 2014).

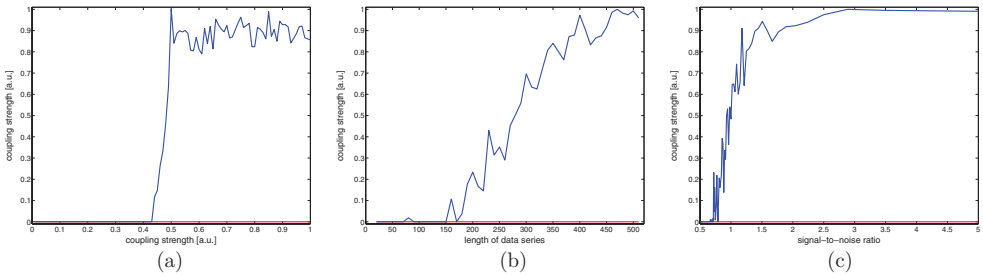


(a) (b) (c)

Figure 4. The figure shows the significant results of the ESCT for the analysis of transient events (Müller *et al* 2013) for the coupling structure between beat-to-beat intervals and systolic and diastolic blood pressure during an orthostatic test (Müller *et al* 2013). (a) BBI—SBP. (b) BBI—DBP. (c) SBP—DBP.

these points plotted above each other for every t_{z1j}. Horizontal lines in the resulting diagram depict coordination. Lines in the negative part ($\Delta t < 0$) show an influence from t_{z2k} to t_{z1j} and vice versa for the positive part ($\Delta t > 0$). The lines can be quantified using a windowed evaluation based on a Gaussian kernel. The point distribution for the ith onset of the first cycle is given by

$$f_i(\Delta t) = \frac{2\pi}{2w+1} \sum_{j=i-w}^{i+w} \sum_{k=1}^{N_j} K\left(\frac{\Delta t - (t_{z2k} - t_{z1j})}{b}\right),$$



(a) (b) (c)

Figure 5. The figure shows the significant results of the lagged cross-correlation for the coupling structure of the coupled logistic maps depending from left to right on coupling strength, length of the data series, and strength of noise. The red colour depicts coupling from X to Y and blue vice versa. (a) Coupling strength. (b) Length of data series. (c) Noise.

where

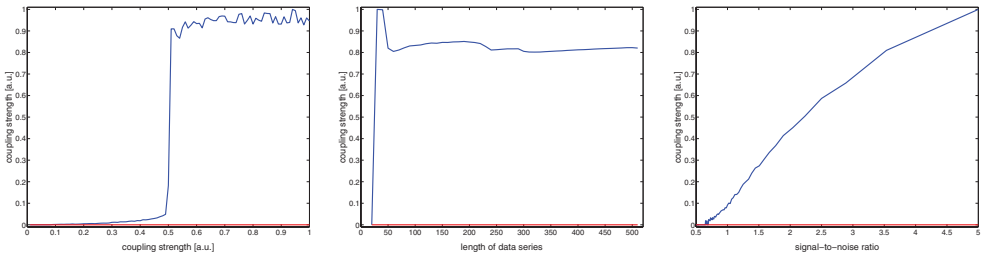
$$K(x) = \frac{1}{\sqrt{2\pi}} \exp\left(-\frac{x^2}{2}\right).$$

$K(x)$ is the Gaussian kernel, $2w + 1$ the window size, N_j the number of onsets of the second cycle regarded around t_{z1j} and b is the band width. Using a colour coding to depict the height of the distribution function, the lines can be emphasised visually. The window size is chosen as a compromise between a valid estimation of the distribution function and the fast changes in the regarded signals. For the analysis of cardiorespiratory coordination (Müller *et al* 2014, Riedl *et al* 2014) $w = 1$ was chosen, while in the analysis of vegetative arousals (Müller *et al* 2014) it was set to $w = 10$ due to a lower signal-to-noise ratio. The band width was in both cases chosen as $b = 0.2s$ as double the sampling time of the respiratory signal.

2.7. Transient interactions

The detection of time-variant coupling structures is an important research issue, since many systems from fields encompassing physics, physiology, neuroscience, chemistry, biology, climate research, economy, etc display dynamic changes in the system structure. These changes might be based on internal or external disturbances, like for example shocks or crises in economy, large-scale events (e.g. El Niño or volcanic events) in climate research (Malik *et al* 2012, Radebach *et al* 2013), event-related potentials in neuroscience (Callaway *et al* 1978), and sleep apnoea in physiology (Leung and Bradley 2001), or on inherent transitions between different regimes, like changes of sleep stages (Iber *et al* 2007), or seasons in the climate. Often, the time periods before and after such a transition are analyzed in order to study differences in dynamic behaviour, coupling structure, etc, but the transition itself is regarded as an undesirable complication. This is because it usually happens on a much shorter time scale than adequately resolved by the data on hand and generally destroys any stationarity assumptions. Thus, also a windowed analysis approach would not work.

In order to overcome this problem, methods based on multiple realisations of a given process have been developed to e.g. detect transient chaos (Jánosi and Tél 1994, Dhamala *et al* 2001), to denoise transient signals (Effern *et al* 2000, Stausberg and Lehnertz 2009), and also to characterise couplings (Kramer *et al* 2004, Andrzejak *et al* 2006, Ishiguro *et al* 2008b, Komalapriya *et al* 2008, Leski and Wójcik 2008, Wagner *et al* 2010, Martini *et al* 2011). The idea bears resemblance to the ergodic theorem of thermodynamics (Birkhoff 1931) where a



(a) (b) (c)

Figure 6. The figure shows the significant results of the conditional Granger causality (Geweke 1984) for the coupling structure of the coupled logistic maps depending from left to right on coupling strength, length of the data series, and strength of noise. The red colour depicts coupling from X to Y and blue vice versa. (a) Coupling strength. (b) Length of data series. (c) Noise.

time average of one particle can be exchanged for a space average of an ensemble of particles at one time point. So, instead of estimating a given coupling measure over a time period, the averaging process is conducted across an ensemble of multiple realisations of the time series in question (see figure 2)). The ensemble could either be built by repeatedly performing a measurement of the same experiment on possibly several subjects, like for example an orthostatic test (Barantke *et al* 2007, 2008) (head-up tilt or standing up after lying down for an elongated period of time), or by using inherent repeating events in a single time series, like several apnoea (cessation of airflow) during sleep (Leung and Bradley 2001, Gapelyuk *et al* 2011, Penzel *et al* 2012, Camargo *et al* 2014, Riedl *et al* 2014). This approach is applicable to many existing coupling measures, of course keeping in mind the requirements and limitations of the respective methods.

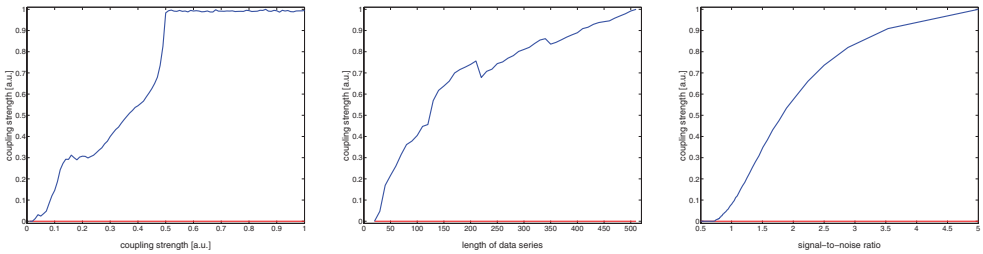
After it has been built, it is important to time rectify the ensemble. This can usually be done by aligning the individual ensemble members by means of a synchronisation point T_0, e.g. the beginning of the event regarded. Corrections can be done by slightly shifting the ensemble measures against each other and looking for the shifting parameter where a maximum correlation can be achieved. Next, the respective coupling measures can be computed by substituting the time average by the ensemble average. The time resolution to be expected with the ensemble extension depends on the coupling measures used, since the estimations often are done over a short range of time points.

As an example we regard here the ensemble symbolic coupling traces (ESCT) (Müller *et al* 2013, Müller *et al* 2014) (see figure 3). Since the ensemble approach for the SCT takes only hold after the word sequences $w_x^{(m)}(t)$ and $w_y^{(m)}(t)$ have been built for the whole ensemble (index m), we only need to regard the following steps. When estimating the probability distribution of the word occurrences, the histogram is now computed over the whole ensemble resulting in the time dependent matrix

$$(\Pi^{(m)}(t,\tau))_{ij} = P(w_x^{(m)}(t) = W_i, w_y^{(m)}(t+\tau) = W_j).$$

The index m here stands for averaging across the ensemble and t represents a fixed point in time. In the end, the symmetric and diametric word frequencies are again given by

$$T^{(m)}(t,\tau) = \mathrm{Tr}\big(\Pi^{(m)}(t,\tau)\big) = \sum_{i=j}\big(\Pi^{(m)}(t,\tau)\big)_{ij}$$



(a) (b) (c)

Figure 7. The figure shows the significant results of the CTIR (Paluš *et al* 2001a) for the coupling structure of the coupled logistic maps depending from left to right on coupling strength, length of the data series, and strength of noise. The red colour depicts coupling from X to Y and blue vice versa. (a) Coupling strength. (b) Length of data series. (c) Noise.

and

$$\bar{T}^{(m)}(t,\tau) = \sum_{i=1,\ldots,d;j=d+1-i} \left(\Pi^{(m)}(t,\tau)\right)_{ij}.$$

Via $\Delta T^{(m)}(t,\tau) = T^{(m)}(t,\tau) - \bar{T}^{(m)}(t,\tau)$ the coupling structure can be determined as before. In this case the same empirical approach to assess the significance of the results should hold true. The choice of the word length determines the expected time resolution of this method.

In figure 4 the time-dependent coupling structure between beat-to-beat intervals and systolic and diastolic blood pressure during an orthostatic test as detected by the ESCT can be seen. It is clearly visible how the blood pressure affects the heart rate during the test and how the stationary structure is broken up.

2.8. Significance testing

For some coupling measures their own significance tests have been developed. There is for example the Granger–Sargent test (Hlaváčková-Schindler *et al* 2007), which is based on an F-test, for Granger causality or an empirical test developed for the symbolic coupling traces (Suhrbier *et al* 2010). However, the most often applied methods to test the significance of the results are surrogate methods. What kind of surrogate is used, depends on the type an amount of data available. For an overview about surrogate methods for coupling analyses see Vejmelka and Paluš (2008). Unfortunately, these methods might not be applicable in the case of the ensemble approach for transient interactions. Due to the definition of the ensembles, surrogates across these will all display the same behaviour during the event and would classify all results as not significant. In these cases, specially for the coupling measures developed significance tests or empirical tests should be applied.

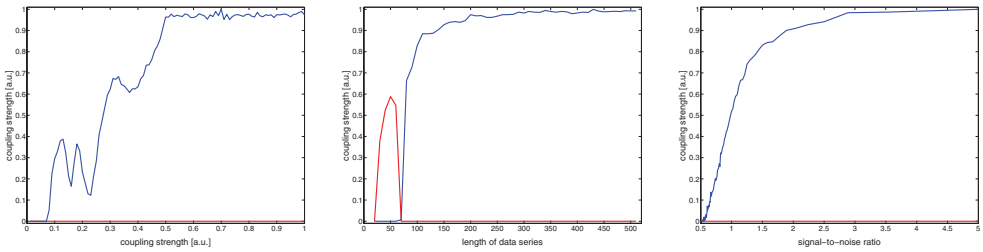
3. Results and discussion

To test some of the measures mentioned above, we will use the well-known logistic map as a model system. A system of two coupled logistic maps is for example given by

$$x(t) = (1-c)\cdot 4\cdot x(t-1)\cdot(1-x(t-1)) + c\cdot y(t-3),$$

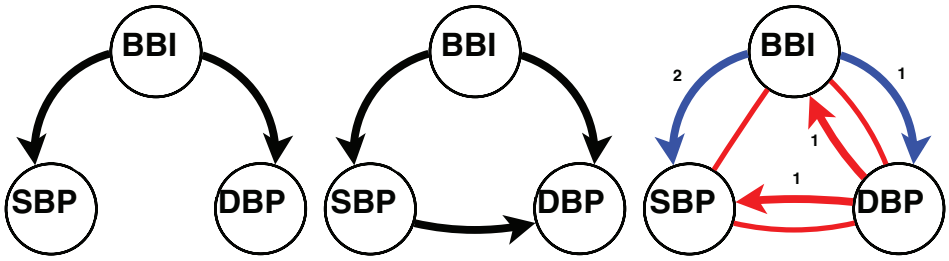
$$y(t) = 4\cdot y(t-1)\cdot(1-y(t-1)).$$

For this choice of parameters the system displays chaotic behaviour. The coupling is realised via the parameter c. We test the performance of the tools depending on different values of c,



(a) (b) (c)

Figure 8. The figure shows the significant results of the symbolic coupling traces (Wessel *et al* 2009) for the coupling structure of the coupled logistic maps depending from left to right on coupling strength, length of the data series, and strength of noise. The red colour depicts coupling from X to Y and blue vice versa. (a) Coupling strength. (b) Length of data series. (c) Noise.



(a) (b) (c)

Figure 9. The figure shows the significant ($p = 0.1$) results of the CTIR method (Paluš *et al* 2001a), the conditional Granger causality (Geweke 1984), and the symbolic coupling traces (Wessel *et al* 2009) for the coupling structure between beat-to-beat intervals and systolic and diastolic blood pressure during a measurement at rest in a supine position just before an orthostatic test (Müller *et al* 2013). The results show the average over 341 subjects regardless of age and gender. For the SCT the blue colour represents diametric coupling, while the red colour depicts symmetric coupling. Black arrows depict just the direction without information on the nature of the coupling. The numbers show the lags at which the couplings occurred and lines without arrows indicate couplings at lag 0. (a) CTIR. (b) Granger. (c) SCT.

on the length of the data series, and on the strength of additive noise. If not otherwise stated the coupling strength is chosen as $c = 0.5$, the length of the time series as $N = 1000$, and the variance of the noise is set to zero. For a better visualisation the results of each coupling measure are normalised in a way, that they lie between 0 and 1, although the measures themselves might actually show values outside this range. Significance tests with $p = 0.1$ have been performed for each measure using multiple realisations of the model data. Surrogates have been formed by using permutations of the realisation indices of the data and pairing the time series of one variable with an original index with another time series of the second variable with a permutated index. The results are given in figures 5–8.

Since in this case the system is nonlinear but the coupling itself linear, all regarded coupling measures perform reasonably well, i.e. are able to identify the correct coupling structure for certain domains of coupling strengths, noise levels, and amounts of data. The lagged cross-correlation (figure 5) needs a comparatively high coupling strength ($c = 0.5$) and a rather high amount of data (≈300 data points) to give a clearly identifiable outcome. It is quite robust

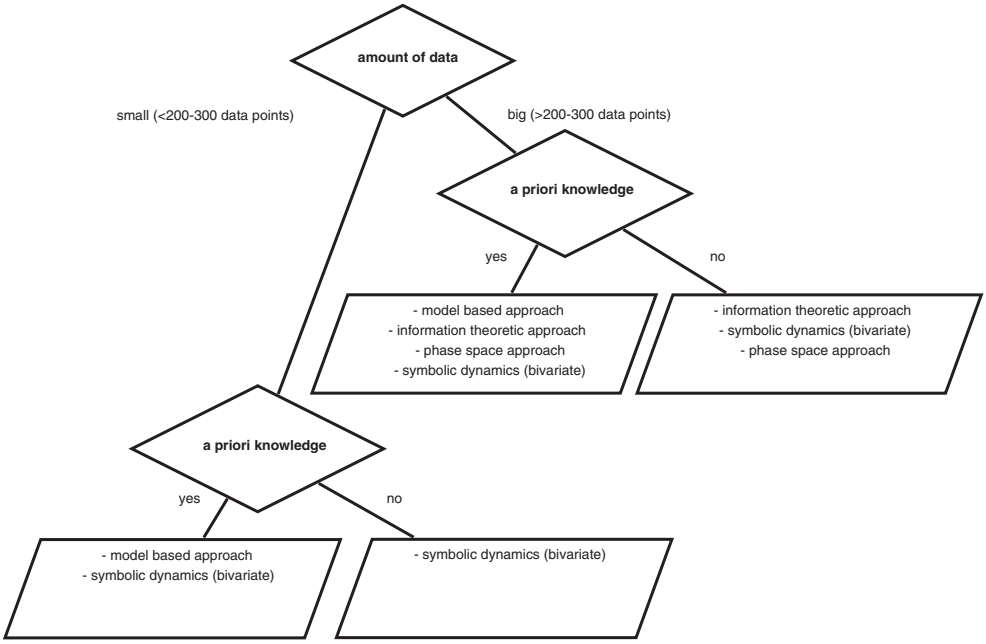


Figure 10. The figure gives some hints on when to look in which field of coupling measures depending on the data to be analyzed.

under the presence of noise, giving the correct results for a signal-to-noise ration higher than one. Granger causality also needs a coupling strength of $c \geqslant 0.5$ before showing the correct couplings but does so also for time series consisting only of 30 data points upward. For the regarded model the employed version of conditional Granger causality is quite susceptible to noise. The representative of the coupling measures stemming from the field on information theory, the CTIR, correctly identifies the coupling structure already for lower coupling strengths and still shows the correct results for noisy data. However, this tool also needs at least 200–300 data points per time series to work. The symbolic coupling traces are able to correctly identify the coupling structure in all categories, delivering usable results already for low coupling strengths and needing only about 70 data points. They also are robust under the influence of noise.

The symbolic coupling traces are easily adaptable to various forms of real world data. Via the choice of the time lag between consecutive symbols (ϑ) it can be applied to either short term analysis to show immediate effects or to longer effect time series analysis. Nonstationarity in the time domain can be handled by the previously described ensemble method. The SCT method and its ensemble form cannot easily be applied to highly nonlinear couplings where additional preprocessing of the data is required. They are also unable to show causality or a possible indirectness of a coupling. Their flexibility and low requirements on data length, however, makes up for these drawbacks and predestines them for physiological data analysis.

In summary, the lagged cross-correlation is outperformed by all other measures. Using the conditional Granger causality the correct coupling structure can already be clearly identified when using less than 50 data points. However, when regarding the dependence on coupling strength or noise, the coupling structure becomes clearer for lower strengths and higher noise levels when using the CTIR or SCT methods. The best performance under the presence of

noise, i.e. giving the clearest correct picture of the couplng structure, is delivered by the SCT. The quality of the results for different coupling strengths are similar between CTIR and SCT.

As a second test we applied the tools mentioned above to cardiovascular time series. The data stems from a study (Barantke *et al* 2008) analyzing amongst other things the influence of an orthostatic test on variables like heart rate and blood pressure. We used the stationary part of the beat-to-beat intervals and the systolic and diastolic blood pressure measurements of 341 subjects of different ages and both genders female and male. As this is only an exemplary example the results (see figure 9) are presented as the average over all measurements regardless of age and gender. The lagged cross correlation showed no usable results and is therefore not shown.

All measures, the CTIR, Granger causality, and the SCT, concur in the found coupling directions between beat-to-beat intervals and the two blood pressure signals. The SCT delivers additional information about the kind of coupling (symmetric or diametric) and the occurring time lags. A coupling between systolic and diastolic blood pressure is only found by Granger causality and the SCT. However, the results contradict each other. In former studies (e.g. Runge *et al* (2014)) the results of the SCT have been confirmed by tools stemming from the field of information theory. The lag-2 connection between beat-to-beat intervals and systolic blood pressure depicts the sympatho-vagal feedback via vasoconstriction and vasodilation due to respiratory movements, while the lag-1 between the blood pressure signals shows the Frank-Starling mechanism. The lag-0 connections go back to mechanically induced fluctuations also based on respiratory movements. In Runge *et al* (2014) it was suggested that the lag-2 coupling might actually be a spurious coupling manifesting via the two lag-1 couplings. However, as the measures regarded here are only working on a bivariate basis, we cannot account for such possibilities. Only the Granger causality might be able to find these spurious couplings, but is in the classical form (detecting only linear connections), according to the results, not well suited for this kind of data which contains nonlinearities.

4. Conclusion

Today there is a plethora of coupling measures, all with their own advantages and drawbacks. Here we give some conclusive remarks and hints on when to look into which field of coupling measures (see also figure 10). The most versatile for systems one does not know much about stem from the field of information theory. The measures are able to identify linear and nonlinear couplings and there are extensions to reliably analyze multivariate data and detect indirect and hidden relations. The drawback is the usually high amount of data needed to estimate the probability distributions in order to compute the entropies. However, with a sufficient amount of data these would be the methods of choice. When data is scarce, a suitable method is probably given by the symbolic coupling traces. Their robustness against noise and low amounts of data needed gives good results for linear and nonlinear couplings. Unfortunately, there is no extension for multivariate data, yet. If there is already some *a priori* knowledge about the system at hand, Granger causality can give deeper insights. The Granger approach is easily adaptable to many different model approaches and there are already extensions for nonlinear and multivariate analyses. The amount of data needed to estimate Granger causality depends on the kind of model used. The classical method detects only linear interactions, but does not need much data. The phase space methods offer another model-free approach to detect linear and nonlinear data. Even some extensions for multivariate analyses exist. Nonetheless, not for all systems delay-embedding can be used in a meaningful way. In these cases, other ways of building the embedding vectors have to be used. Due to the embedding, these methods also

require higher amounts of data, but shine with their versatility. Synchronisation and coordination analyses as well as certain extensions of other coupling measures only work on systems which can be regarded as oscillators. If that is the case, these methods deliver usually good results with even smaller amounts of data. The same strengths and restrictions apply to the measures when extended for the analysis of transient events using the ensemble approach.

The field of coupling analysis is a very active field and new measures keep on getting developed. The areas of application have also broadened in the last years, so that now in almost any discipline coupling analyses can be found. They give deeper insight into the interactions of complex systems than classical correlation analyses or similar tools. However, while the application of these methods is often straightforward, the interpretation of the results requires some additional thinking. For example, one should always keep in mind that coupling in data analysis and causality might be two different things.

Acknowledgment

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