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Symbolic Coupling Traces for Causality Analysis of Cardiovascular Control

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Abstract— **Directional coupling analysis of time series is an important subject of current research. In this paper, a method based on symbolic dynamics for the detection of time-delayed coupling in biosignals is presented. The symbolic coupling traces, defined as the symmetric and diametric traces of the bivariate word distribution, allow for a more reliable quantification of coupling and are compared with established methods like mutual information and cross recurrence analysis. The symbolic coupling traces method is applied to appropriate model systems and cardiological data which demonstrate its advantages especially for nonstationary and noisy data. Moreover, the method of symbolic coupling traces is used to analyze and quantify time-delayed coupling of cardiovascular measurements during different sleep stages. Significant different regulatory mechanisms are detected not only between the deep sleep and the other sleep stages but also between healthy subjects and patients. The proposed method may help to indicate pathological changes in cardiovascular regulation and also effects of continuous positive airway pressure therapy on the cardiovascular system.**

I. Introduction

BIOLOGICAL systems usually consist of several subsystems which are interrelated by feedbacks with time delay. To reveal such time-delayed coupling directions from biosignals is a basic task in understanding such systems [3-5]. Data recorded from these systems reflect biological activities of living beings and are characterized on the one hand by real biological information, including nonstationarities, nonlinearities and intrinsic noise, and on the other hand by measurement noise. Therefore, the analysis of biosignals, especially the detection of coupling directions is complicated. The methods known so far for coupling direction estimation require different assumptions, e.g. linearity or stationarity [6,7]. Biosignals, however, almost never fulfill these requirements. Nevertheless, different methods for the detection of coupling directions, starting from Granger causality via mutual predictability to information-theoretic approaches [8-10] were applied to biosignals. All these methods are able to find directions of interactions. However, due to the nonstationarity and nonlinearity of the biosignals, the conclusions are not homogenous.

Recently new methods based on order pattern analysis appear to circumvent these problems [11-13]. Order patterns result from a coarse graining (symbolization) of the data into two states: increasing or decreasing amplitudes. This symbolic representation of successive amplitudes is not sensitive to nonstationarities. Fig. 1 gives one example showing the potentials of symbolic anylyses: The linear cross correlation analysis obviously is not as applicable as the recurrence quantification analysis with order patterns in the bivariate data set of heart rate and blood pressure. The order pattern approach reveals the lags τ of the time series more clearly (Fig. 1), suggesting the idea that the ordinal structure of nonlinear and nonstationary time series is necessary for the analysis of the dynamics.

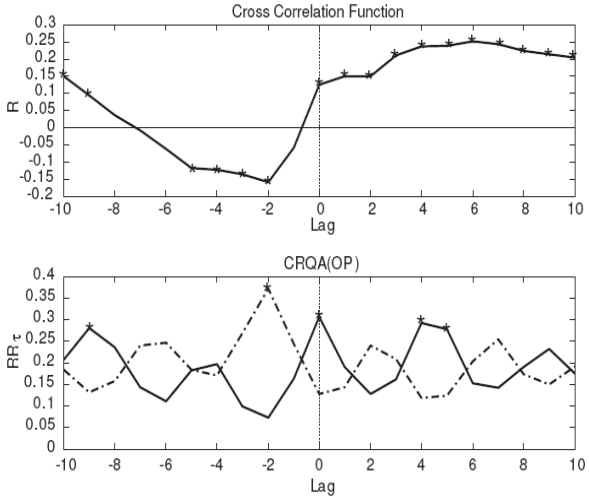

Fig. 1. Linear Cross Correlation Function (R) as well as Recurrence Quantification Analysis (Recurrence rate RR_τ) for the detection of coupling directions of real data. Top: R between heart rate (BBI) and systolic blood pressure (SBP) data. This analysis reveals interrelations between both time series for almost any lag (marked with asterisks) and is, therefore, not very specific. Bottom: Cross recurrence quantification analysis based on order patterns (CRQA(OP)) applied to BBI and SBP data [12,13] reveals the most significant positive interrelation between both time series for lag τ =0 and negative interrelation for lag τ = -2. Solid line: SBP → BBI (positive linkage RR_+ in [11], dotted line: BBI → SBP (negative linkage RR_-). The order patterns are constructed using the dimension m=3 and delay 3.

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Here we report an extension of bivariate symbolic dynamics [14] that greatly improves the detection of coupling directions in biosignals. Signals from coupled biological processes tend to move in the same direction or in opposing directions. We show that this type of relationship is reliably indicated by the symmetric and diametric bivariate word distributions. Our very intuitive measure is tested on paradigmatic models and applied to cardiovascular data, especially to bivariate time series consisting of the beat-to-beat systolic blood pressure and heart rate variability values. Revealing the coupling relations for the latter data enables us to quantify the short term regulation of the cardiovascular system, and thus to quantify the risk of cardiovascular disorders. In the following we develop the theory and give examples of *symbolic coupling traces* (SCT) which is also based on the analysis of structural patterns but easier to interpret and less computational intensive.

Moreover, the SCT are applied to coupling analysis of heart rate and systolic blood pressure during different sleep stages. The cardiovascular consequences of disturbed sleep are of particular high medical interest for sleep physicians because they present a risk factor for cardiovascular disorders such as hypertension, cardiac ischemia, sudden cardiac death, and stroke. Our new derived measures may help to detect pathological mechanisms for these health risks during sleep. Understanding these cardiovascular mechanisms during sleep may be useful to predict effects of treatment in subjects with disordered breathing during sleep as well as in other sleep disorders and effects of ageing in healthy subjects.

II. Symbolic Coupling Traces

To introduce the SCT method, we consider a dynamic system represented by two paired one-dimensional time series *x(t)* and *y(t)*. They are first transformed into two symbol sequences $s_x(t)$ and $s_y(t)$ via the transformation rule

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

Next, we construct series of words $w_x(t)$ and $w_y(t)$ containing $l=3$ successive symbols from the time series $s_x(t)$ and $s_y(t)$, respectively. Hence, eight different patterns ($d=2^l=8$) are possible. These patterns are invariant with respect to an arbitrary, increasing transformation of the amplitude. Afterwards, the bivariate word distribution (BWD) $(p_{ij})_{\ i=1,..,8,\ j=1,...,8}$ is estimated [14]. p_{ij} is the joint probability that the words W_i and W_j occurs at the same time t in the word sequences $w_x(t)$ and $w_y(t)$, respectively. To measure the delay-time probability matrix that the word W_i occurs in w_x at time t and W_j occurs in w_y at time $t+\tau$, we introduce

$$p_{ij}(\tau) = P\big(w_x(t) = W_i, w_y(t+\tau) = W_j\big),$$

In order to consider short time-delayed dependencies in the cardiovascular system, we choose the lag τ between -20 and 20. With the given binary symbol transformation we take a loss of amplitude information, however, in time series with moderate noise and nonstationarities these information can be unreliable. Through symbolization, word transformation and symmetric bivariate selection of the diagonals we can exclude random effects and include significant coupling information only. In this paper, SCT is based on differences, which is sufficient for many applications but the symbol transformation can also be adapted for further use.

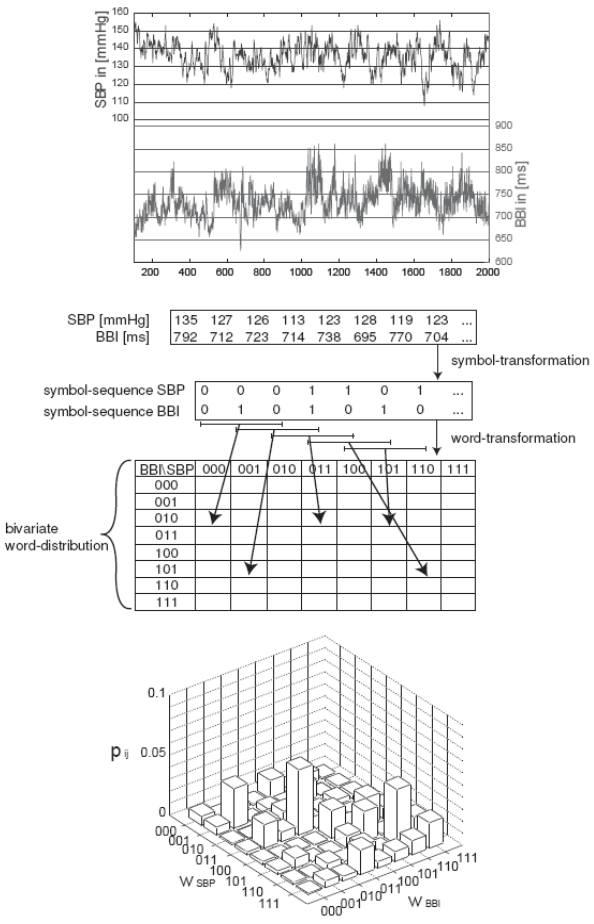

Fig. 2. Scheme for calculating the bivariate word distribution. Starting from two time series (e.g. SPB and BBI upper part), a two-dimensional symbol sequence (middle part) is calculated by a symbol transformation which leads then to the bivariate word distribution (lower part) as the basis of parameter calculation.

Significant coupling information is quantified by two parameters based on the BWD-diagonals:

(i) The trace T of the matrix P(τ) is defined as

$$T(\tau) = \sum_{i=j} p_{ij}(\tau) \cdot$$

It represents the fraction of both time series, which are structurally equivalent to each other at lag τ.

(ii) The parameter

$$\overline{T}(\tau) = \sum_{i=1,..,d,\, j=d+1-i} p_{ij}(\tau)$$

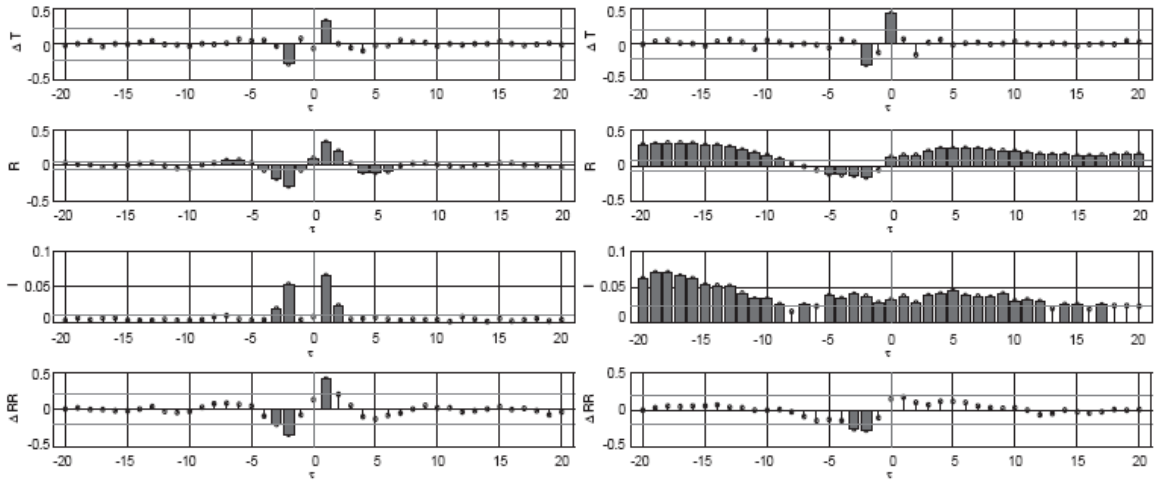

Fig. 3. Comparison of the calculated SCT parameter $\Delta T = \overline{T} - T$, *R*, the mutual information *I* and the recurrence rate difference ΔRR for a simulation (left, $x_i = ax_{i-1} + by_{i-\tau 1} + \varepsilon_i$ and $y_i = cy_{i-1} + dx_{i-\tau 2} + \nu_i$, two coupling terms coupling $y_{i-\tau 1}$ and $x_{i-\tau 2}$, ε=N(0,0.1), ν=N(0,0.1), a=0.3, b=0.7, c=0.3, d=0.7) and experimental data of a healthy volunteer (right) at different lags *τ*. Significant lags are drawn as boxes, insignificant as stems. A simulation with symmetric coupling at $\tau = 1$ as well as diametric coupling at $\tau = -2$ is indicated on the left. The exact detection of the lags by ΔT is obvious. This is also true if nonstationarities, such as additive trends or heteroscedasticy are present. *R* and *I* as well as ΔRR help to draw conclusions about the lags, but do not show them clearly. On the right, the most significant lags in the real data are revealed by ΔT at $\tau = 0$ and $\tau = -2$, i.e. BBIs correspond diametrically $\tau = -2$ and symmetrically $\tau = 0$ with SBP. The parameters *R*, *I* and ΔRR do not show these lags as clearly as ΔT resp. show false significant lags.

describes the fraction of both signals, which are structurally diametric at lag *τ* (*d* is the number of different patterns). Both parameters vary from 0 to 1 and comprise the diagonals of the BWD only. Other measures such as the Shannon-entropy as a possible parameter to quantify the complete BWD are tested, too. However, it does clearly not reveal the correct lags in the theoretical model. Finally, the difference $\Delta T = \overline{T} - T$ of the above parameters is the most appropriate choice.

Apart from the cross recurrence and SCT parameters, the classic cross correlation function *R* and the mutual information *I* are calculated for comparison. The cross correlation function reveals information about symmetric $R(\tau) > 0$ and diametric $R(\tau) < 0$ behavior in the time series. The mutual information, as a parameter of information theory, does not reveal any information about symmetric and diametric behavior in the time series, but is based on estimated distributions.

III. Results

To study significance limits for all methods introduced above, the parameters are calculated for randomized time series. For the latter one no coupling should exist. Therefore, the maximum and minimum of the parameters in the group of simulations represent the border of significant coupling. To validate the new method, the simplest approach is used: Simulations of coupled 2D autoregressive (AR) processes (cf. Fig. 3 left part). The coefficients of the AR models are varied in order to study the influence of varying coupling strengths and of noise. For an example with model-specified lags at $\tau = -2$ and $\tau = 1$ (Fig. 3 left part), all lags are SCT, the other three methods are not able to localize these lags exactly. The SCT-parameters detected the lags in case of delayed coupling with autocorrelation more clearly than cross correlation, mutual information and recurrence plot based on order pattern. This way up to 4 lags can be detected correctly by the SCT-parameters. For higher noise-levels this advantage decreases, however, for cardiological time series autocorrelation with certain coupling have to be expected. Consequently, the SCT parameters are suitable for analyzing the coupling of these signals (cf. Fig. 3 right part). For a further validation, we also applied it to nonlinear coupled models, e.g. SETAR (self-exciting threshold autoregressive model) systems and got similar results.

For the data of the different sleep stages [2], *R* and *I* are calculated also for differential time series to have a more appropriate comparison. Nevertheless, both parameters still have problems to detect time-delayed couplings in oscillating signals with noise interaction which results in additional coupling terms [2]. For all groups and for all sleep stages we obtain the same characteristic pattern of τ=-2 for diametric coupling and τ=0 for symmetric coupling as one can see in Fig. 4. Moreover, there are additional lags in light and deep sleep which reaches from -8 to +4. The hypertensive DD group was the only group with other detected lags beside 0 and -2 in the wake and REM stages (Fig. 4} wake (d)). As quantified by the Kruskal-Wallis test, there are significant differences in the strength of the detected lags 0 and -2 (stars in Fig. 4). The most prominent difference can be seen between REM and deep sleep, except in the NT CPAP group Fig. 4 (c).

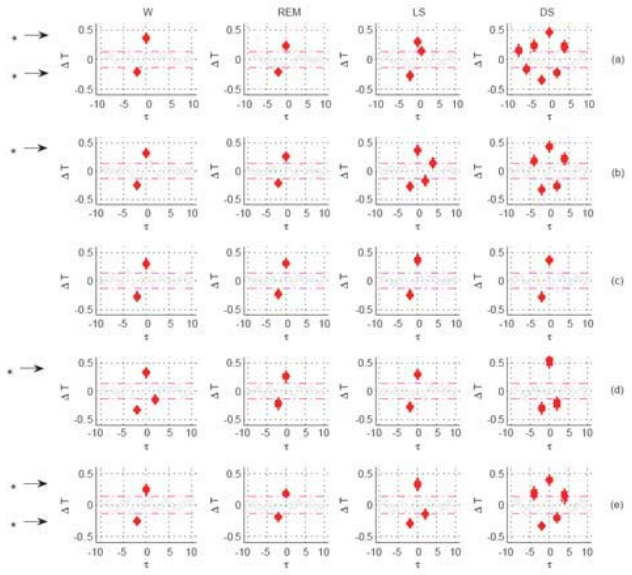

Fig. 4. The comparison between the sleep stages (wake=W, REM−sleep=REM, light sleep=LS, deep sleep=DS) and the different patient groups [healthy controls (a), normotensive DD (b), normotensive CPAP (c), hypertensive DD (d), hypertensive CPAP (e)] clearly shows the short-term asymmetry in the coupling during wake and REM characterized by lags τ =−2 and τ=0. This asymmetry becomes less in light sleep and is lost in deep sleep when periodic breathing leads to a modulation of B_i and S_i. Significant differences in the coupling strength at τ =0 and τ=−2 between the sleep stages are indicated by * ($p<0.05$, Kruskal–Wallis test). Differences exist at both lags in the control patients group as well as hypertensive CPAP. In normotensive DD and hypertensive DD, only the lag τ=0 is significantly different between the sleep stages.

IV. Discussion

The time-delayed coupling analysis of the theoretical models and our measurements demonstrates the advantage of the SCT in comparison to standard methods. We find significant lags at τ =-2 and τ =0 for all groups. This strengthens the prevailing opinion about the cardiovascular short term regulation. The symmetric lag at τ=0 reflects the respiratory induced arterial pressure and heart rate fluctuations, whereas the diametric lag at τ=-2 represents the vagal feedback from heart rate to systolic blood pressure. Moreover, we show that this coupling pattern does not change generally in different sleep stages; however, the strength of interactions may differ. During deep sleep only, we see a loss of heart rate and blood pressure asymmetry as well as an effect of CPAP therapy on the cardiovascular coupling.

We demonstrate that the SCT is more specific than standard methods regarding the detection of delays and directions of interactions. Nevertheless, for the general assessment of coupling directions in time series, both new and established methods should be used. Coupling in stationary data with strong noise can be well detected via mutual information and cross correlation, whereas in deterministic data cross recurrence should be preferred. The parameters of the SCT method and cross recurrence based on order pattern close the gap in the coupling analysis of nonstationary time series with strong autocorrelation and moderate noise, where cross correlation, mutual information and other methods are not sufficient to localize the lags exactly. The prevailing opinion about the cardiovascular short term regulation is based on antagonistic nervous control via vagus and sympathicus. Here, we confirm the results of [1] with significant lags at τ =-2 and τ = 0. Moreover, we show that this coupling pattern does not change generally in different sleep stages; however, the strength of interactions may differ. The highest amplitudes for ΔT we find for deep sleep, the lowest for REM (cf. Fig. 4). This relation can be explained with a reduced sympathetic activity during deep sleep, leading to more pronounced respiratory influence and an increased vagal feedback. Again during deep sleep, where many physiological regulatory mechanisms such as cerebral blood flow and cerebral metabolic rate are reduced, we find an increased heart rate and blood pressure symmetry leading to multiple lags of τ =-2 and τ = 0. Summarizing, the proposed method of the symbolic coupling traces may help to indicate pathological changes in cardiovascular regulation and also effects of continuous positive airway pressure therapy on the cardiovascular system.

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