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Synchronisation and Coupling Analysis: Applied Cardiovascular Physics in Sleep Medicine

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Abstract— **Sleep is a physiological process with an internal program of a number of well defined sleep stages and intermediate wakefulness periods. The sleep stages modulate the autonomous nervous system and thereby the sleep stages are accompanied by different regulation regimes for the cardiovascular and respiratory system. The differences in regulation can be distinguished by new techniques of cardiovascular physics.**

The number of patients suffering from sleep disorders increases unproportionally with the increase of the human population and aging, leading to very high expenses in the public health system. Therefore, the challenge of cardiovascular physics is to develop highly-sophisticated methods which are able to, on the one hand, supplement and replace expensive medical devices and, on the other hand, improve the medical diagnostics with decreasing the patient's risk. Methods of cardiovascular physics are used to analyze heart rate, blood pressure and respiration to detect changes of the autonomous nervous system in different diseases. Data driven modeling analysis, synchronization and coupling analysis and their applications to biosignals in healthy subjects and patients with different sleep disorders are presented. Newly derived methods of cardiovascular physics can help to find indicators for these health risks.

I. Introduction

Synchronization and coupling analyses of bivariate time series are important topics in current biomedical signal analysis. We use a method based on symbolic dynamics for detection of time-delayed coupling of time series during sleep in patients with obstructive sleep apnea. More specifically we apply this analysis to the coupling between heart rate and systolic blood pressure [1]. This is of high interest because we know that heart rate and blood pressure are modulated by sleep stages and by sleep pathologies. With each single apnea event we see changes in heart rate and arterial blood pressure during the night. These changes are the consequence of multiple effects and are shown in Fig. 1. In this study the symbolic coupling traces (SCT) analysis is used to investigate characteristics in patients with sleep apnea. A conventional coupling analysis based on cross correlation techniques can only show associations and not directions of the coupling process. However, as can be seen in Fig. 1 the associations are directed [2]. Therefore, a coupling analysis should reveal the direction of coupling as well as the corresponding time lags. This is essential to study the causal relation between cortical arousal and autonomous nervous system arousal. This analysis of direction may reveal a better understanding on the underlying pathophysiological mechanisms of the apnea events itself and thereafter on the effects of treatment. The treatment of first choice is continuous positive pressure ventilation with continuous positive airway pressure (CPAP) devices [3]. This therapy is just a physical support of the collapsing upper airways. The positive pressure keeps the upper airways open so that normal breathing can be maintained even when the upper airways tend to collapse due to low muscle tone [4].

The analysis of heart rate variability (HRV) and its correlation to other physiological rhythms, e.g. respiration, has been developed to investigate the regulation of the autonomic nervous system. One of it's, so far non-fully understood, aspects is the mutual influence of the cardiac and respiratory oscillations on their respective onsets. This cardio-respiratory synchronization (CRS) has been observed previously during normal sleep. CRS has not yet been described during respiratory sleep disorders, involving more active regulatory processes.

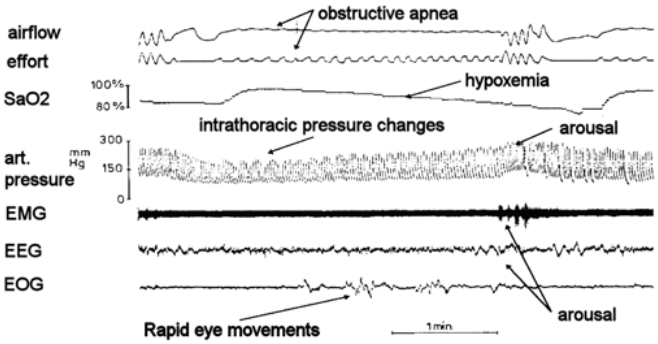

Figure 1. The recording of one long obstructive apnea / hypopnea event is shown together with all influences on arterial blood pressure [2]. The obstructive apnea is characterized by a cessation of airflow. In addition we see respiratory effort movements which make the event an obstructive one. Parallel with obstructive efforts we see small variations in systolic blood pressure. They are caused by intrathoracic pressure changes and are also called pulsus paradoxus. The drop in oxygen leads to hypoxemia. Parallel with hypoxemia we observe an increase in arterial blood pressure. At the end of the apnea event we see an arousal in the EEG and the EMG with a parallel strong increase in blood pressure. Systolic values above 220 mmHg are often observed. At the time of high blood pressure we can observe also cardiac arrhythmias which are well reflected in the blood pressure curve. The lowest curve shows EOG and rapid eye movements which characterizes the entire period as REM sleep. The REM sleep is the reason for the very long duration of this apnea event. Also the REM sleep is the reason for a high level of blood pressure during the entire period.

Parts of this study had been published recently in A. Suhrbier, et al. Chaos 20, 045124 (2010), T. Penzel, et al. Conf Proc IEEE Eng Med Biol Soc., 1475-8 (2011), Müller et al., Somnologie, 16: 24-31 (2012).

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II. METHODS

A. 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] (cf. Fig. 2). 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 lose amplitude information, however, in time series with moderate noise and nonstationarities this 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.

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

(i) The trace T of the matrix $(p_{ij})(\tau)$ is defined as

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

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

(ii) The parameter

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

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. 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.

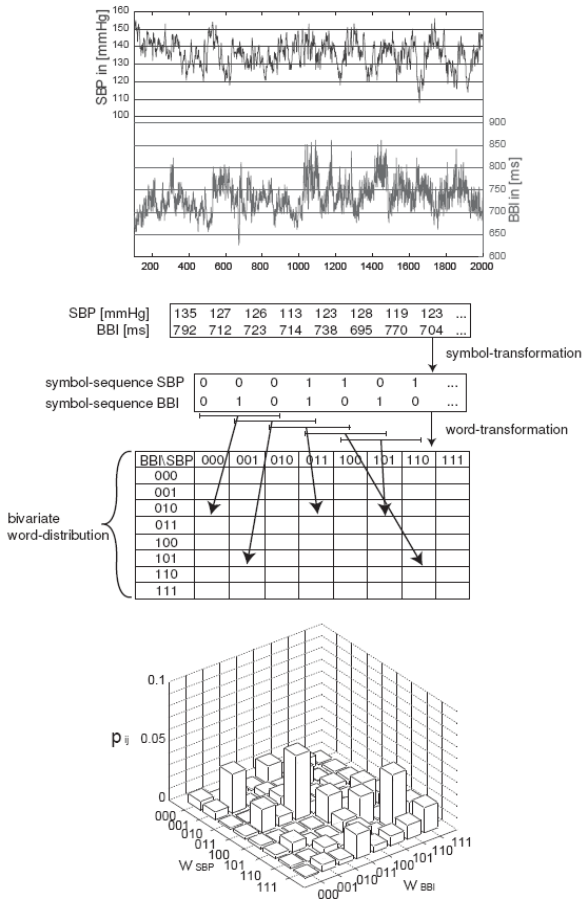

Figure 2. Scheme for calculating the bivariate word distribution. Starting from two time series (e.g. SPB and BBI upper part, syst. Blood pressure and beat-to-beat intervals resp.), a two-dimensional symbol sequence (middle part) is calculated by a symbol transformation which leads then to the bivariate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

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.

B. Cardio-respiratory Synchronization

In many studies the heart beat time series as well as the respiration time series during sleep were investigated in a univariate manner. We are, however, also interested in the synchronization between them. It is assumed that a high degree of synchronization indicates a high ergonometric optimization of respiration and the heart beat. A function of deep sleep is physical recreation with very low consumption of energy, and therefore an ergonometric optimization is favored. If during sleep this synchronization is lost than this might indicate a lowered physical recreation. The analysis of respiration and heart beat using a synchrogram shows the loss of phase synchronization during these episodes with repetitive apneas. In the synchrogram method the momentary phase of the breathing signal RES_i is reconstructed by calculating $\varphi(t_i) = 2\pi(t_i - t_k)/(t_{k+1} - t_k) + 2\pi k$ with $t_k \le t_i < t_{k+1}$. t_k is the begin of the k-th respiratory cycle characterized by

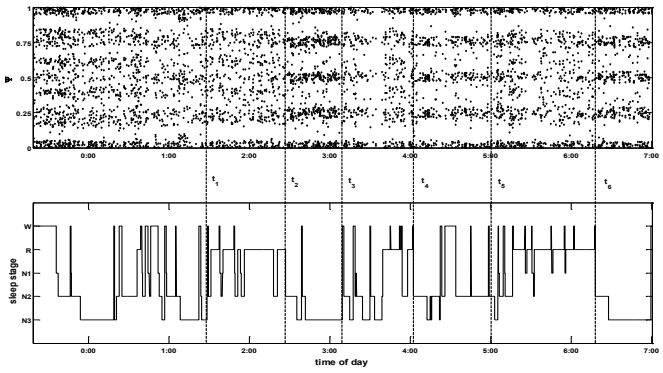

Figure 3: Cardiorespiratory synchrogram with the associated hypnogram of a healthy subject. In the first two hours no clear synchronization can be seen, although already deep sleep occurs. In the area of t1-t2 no synchronization occurs because the patient is in REM sleep. Between t2 and t3 one (4:1)-synchronization can be seen, which corresponds to a long deep sleep phase. In t3 - t4 this is interrupted by light and REM sleep phases. Between t4 and t5, again synchronization is observed, which is temporarily disturbed by a short period of wakefulness. Between t5 - t6 the test subject is mainly during REM sleep, which means that no synchronization occurs. From t6 to the end of the measurement (4:1)-synchronization occurs during deep sleep.

the *k*-th lokal minima in the original signal. t_i is the time of the *i*-th heartbeat. To obtain the synchrogram, the relative cyclic phase $\psi_m(t_i) = \left(\varphi(t_i) \bmod 2\pi m\right)/2\pi$ is plotted versus the times t_i of the heartbeats. In this contribution we used $m = 1$ - in Fig. 3 all heart beats within one respiratory cycle are plotted. Phase synchronization in synchrograms is characterized by parallel horizontal lines.

C. Nonparametric data-driven modeling

Modeling cardiorespiratory phase synchronization and the loss of synchronization may help to diagnose sleep apnea better in terms of risk prediction. A nonparametric modeling approach will be used here based on data driven functions.

Optimal transformations and the associated concept of maximal correlation provide a nonparametric procedure to detect and determine nonlinear relationships in bivariate data sets. Let *X* and *Y* denote two zero-mean data sets and

$$R(X,Y) = \frac{E[XY]}{\sqrt{E[X^2]E[Y^2]}}$$

their (normalised) linear correlation coefficient, where *E[.]* is the expectation value. The basic idea of this approach is to find such transformations $\Theta(Y)$ and $\Phi(X)$ that the absolute value of the correlation coefficient between the transformed variables is maximised. This leads to the *maximal correlation*.

$$\Psi(X,Y) := \sup_{\Theta,\Phi} \left| R(\Theta(Y), \Phi(X)) \right|$$

The functions $\Theta(Y)$ and $\Phi(X)$ for which the supremum is attained are called *optimal transformations*. $\Psi(X,Y)$ quantifies nonlinear dependencies of the form

$$\Theta(Y) = \Phi(X) + \eta \,.$$

Especially, if there is complete statistical dependence, i.e., *Y* is a function of *X* or vice versa, the maximal correlation attains unity. Here we are mainly interested in the estimation of the optimal transformations for the multivariate regression problem

$$\Theta(Y) = \Phi_1(X_1) + \ldots + \Phi_m(X_m) + \eta$$

This is an additive model for the (not necessarily independent) input variables $Y, X_1, \ldots, X_m$. To estimate them nonparametrically, we use the *Alternating Conditional Expectation* (ACE) algorithm. This iterative procedure is nonparametric because the optimal transformations are estimated by local smoothing of the data using kernel estimators.

The maximal correlation and optimal transformation approach were applied recently to nonlinear dynamic systems to identify delay in lasers and partial differential equations in fluid dynamics. The ACE algorithm turned out to be a very efficient tool for nonlinear data analysis. A more detailed introduction to the ACE-algorithm is given in Wessel et al. 2007 [5].

D. ECG-Derived Respiration

There are several techniques to obtain the respiration signal from an electrocardiogram. On the one hand, there are techniques measuring the transthoracic impedance from the ECG electrodes, on the other hand, there are some techniques using the ECG signal itself. The latter are based on the beat-to-beat variations of the RR intervals (respiratory sinus arrhythmia) and on the morphological ECG changes due to respiration (P-wave, T-wave, PR-interval, Q-peaks, QRS area, myogram, baseline wandering). The reason for these changes is that the positions of ECG electrodes on the chest surface move relative to the heart, while transthoracic impedance varies, as the lungs fill and empty. We are applying a new algorithm which combines all of these changes into one integrative signal before estimating the ECG-derived respiration (cf. Fig. 4).

III. Results

Considering the standard parameters, we obtain the following results. There are significant differences between the sleep stages in the parameters HF-S and LF-S (high and low frequency bands in SBP) in the normotensive (NT) diagnostic night (DD) group as well as in HF-B and LF-B (high and low frequency bands in HRV) in the hypertensive (HT) DD group ($p<0.05$, Kruskal–Wallis test). Interestingly, these differences are not present under CPAP therapy and in healthy controls, pointing to sleep disturbances such as snoring and/or apneas as the main cause for these differences. In the normotensive group, differences between the DD and the therapy CPAP night can be detected for HF-S in light and deep sleep as well as baroreceptor sensitivity (BRS) in light sleep. For the NT group, differences are present for HF-S in light and deep sleep, for LF-B and LF-S in light sleep, as well as for BRS in deep sleep. Comparisons of patient groups with the control group (C) show significant differences in HF-S, light and deep sleep (NT DD versus C), in HF-S, LF-S during REM (NT CPAP versus C), as well as in LF-S during light sleep and HF-S during REM (HT CPAP versus C). The SCT results are compared to other standard

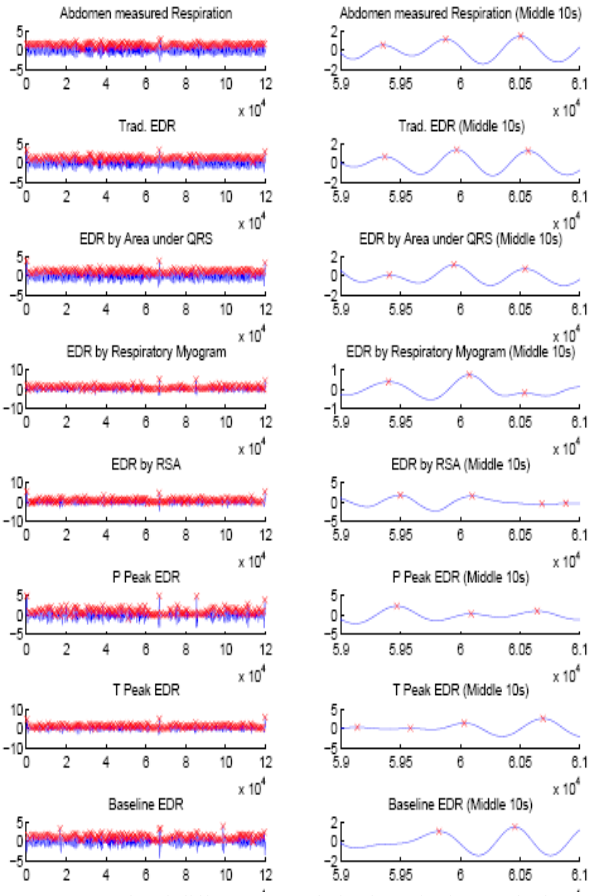

Figure 4. Example of different ECG derived respiration methods. A combination of all techniques was combined in an integrative algorithm for ECG-based apnea detection (cf. text).

methods such as cross correlation R, mutual information I, and recurrence quantification by means of linear as well as nonlinear autoregressive models [6]. 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. In our data, we see R and I detecting too many lags, whereas the SCT and ΔRR consistently detect the lags 0 and 2. In addition, the SCT detects also lag +2 for that example of deep sleep.

Regarding the synchronization analysis using synchrograms, we were able to detect different behavior depending on the sleep stages. Cardiorespiratory synchronization occurs during light and deep sleep but not in REM-sleep. We also could show that subjects suffering from sleep disorders like apnea were not able to attain a state of cardiorespiratory synchronization during sleep. Using the model-based approach we simulated cardiorespiratory synchronization. Short segments of cardiorespiratory synchronization are found only for regular breathing and dominant model functions.

Finally, we applied our algorithms for estimating ECG-derived respiration to blindly estimate an apnea-index comparable to the widely used AHI (Apnea-Hypopnea Index). We achieved a Pearson correlation coefficient of 0.833 comparing our index to an index based on apneas as scored by qualified technicians.

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 confirm the results of [6] where SCT detects significant lags at $\tau = -2$ and $\tau = 0$ for all subjects. This strengthens the opinion about cardiovascular short-term regulation. The symmetric lag at $\tau = 0$ reflects the respiratory induced pressure and heart rate fluctuations, whereas the diametric lag at $\tau = -2$ represents the vagal feedback from heart rate to systolic blood pressure. We show that the coupling does not change 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.

Applying the synchrogram method to identify epochs of synchronization during sleep showed distinct behavior of the cardiorespiratory synchronization. The observation that subjects suffering from sleep disorders usually cannot attain synchronization during sleep corresponds with the finding that cardiorespiratory synchronization in waking can be achieved through concentration or deep relaxation. These findings show promise that a synchronization analysis might help defining a clinical measure of bodily and mental stress in humans. Using our nonparametric data-driven modeling approach we were able to show that both regular breathing and dominant coupling functions are necessary but not sufficient to obtain cardiorespiratory synchronization.

While ECG-derived respiration is currently mostly used to estimate respiration rates, we show that an integration of multiple such signals is much more resilient to noise and can be used to estimate apneas based on signal morphology.

Summarizing, our newly derived methods from cardiovascular physics: Data driven modeling analysis, synchronization and coupling analysis may help to find indicators for health risks of sleep disorders.

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