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Separating the effect of respiration on the heart rate variability using Granger's causality and linear filtering

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ABSTRACT

Heart rate variability (HRV) plays an important role in medicine and psychology because it is used to quantify imbalances of the autonomic nervous system (ANS). An important manifestations of the ANS on HRV is also directly related to respiration and it is called respiratory sinus arrhythmia (RSA). This is a controlled phenomenon that leads to a synchronized coupling between respiration and instantaneous heart rate. Thus, the portion of HRV that is not related to respiration, and could potentially contain undiscovered diagnostic value, is overlapped and remains hidden in a standard HRV analysis. In such cases, a decoupling procedure would deliver a discriminated HRV analysis and possible new insights about the regulation of the cardiovascular system. In this work, we propose an algorithm based on Granger's causality to measure coupling between respiration and HRV. In the case of significant coupling, we estimate and cancel the respiration driven HRV component using a linear filtering approach. We tested the method using synthetic signals and prove it to deliver a reliable coupling measurement in 96.3% of the cases and reconstruct respiration free signals with a median correlation coefficient of 0.992. Afterwards, we applied our method to signals recorded during paced respiration and during natural breathing. We demonstrated that coupling is dependent on respiratory frequency and that it maximizes at 0.3 Hz. Furthermore, the HRV parameters measured during paced respiration tend to level among subjects after decoupling. The intersubject variability of HRV parameter is also decreased after the separation process. During natural breathing, coupling is notoriously lower to non-existing and decoupling has little impact on HRV. We conclude that the method proposed here can be used to investigate the diagnostic value of respiration independent HRV parameters.

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1. Introduction

The continuous change and adaptation of the instantaneous heart rate to internal and external factors is called heart rate variability (HRV). The regulation of the heart rate is carried out by the two complementary branches of the autonomous nervous system (ANS), the sympathetic and parasympathetic nervous system [1]. A healthy heart that is regulated in the proper manner is characterized by a strong HRV [2]. This principle is used in many fields of medicine and psychology for diagnostic purposes [3,4]. Scientific studies dealing with topics such as the quantification of risk of sudden cardiac death in patients with chronic heart failure or the assessment of mental workload when performing a given cognitive task, have been approached using the analysis of standard HRV parameters [5,6].

It is well known that HRV is strongly related to respiration [7,8]. There are two major reasons for this fact. First, respiration, heart rate and blood pressure are all part of a greater cardiorespiratory system that is also regulated by the ANS in the form of a coupled feedback control system [9]. Therefore, internal or external perturbations in one of the members of the system have a direct impact on the others. So for example, heart rate tends to increase as a response to hypoxia or hypercapnia in healthy subjects [10]. Another example is the baroreceptor reflex in which a change in blood pressure affects heart rate through negative feedback [11]. Second, a phenomenon called respiratory sinus arrhythmia (RSA),

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in which heart rate increases during inspiration and it lowers during expiration, leads also to a notorious synchronized coupling between the breathing pattern and heart rhythm. As a matter of fact, RSA is the most important manifestation of the ANS directed to the heart and recorded non-invasively from the heart period [12]. Even though RSA is not fully understood, it is believed to minimize mechanical work done by the heart while maintaining a healthy concentration of gases in the blood and to optimize gas exchange while breathing by matching perfusion to heart rate [13–15]. Since the impact of RSA can change depending on different factors such as age, breathing frequency, tidal volume or general health condition of the subject [16–18], it is hard to quantify its effect on the HRV parameters. For this reason, other authors have tried to control the effect of respiration on HRV and have evaluated if this procedure can increase the diagnostic power of HRV parameters [19,20].

In a study presented in 2011 [21], the authors addressed the problem of detecting mental stress during a cognitive task using HRV. For this purpose, a transfer function, that described the cardiorespiratory coupling, was estimated and the respiration related fluctuations of the heart rate were subtracted. It was shown that separating the HRV analysis and removing the respiration driven part of it, leads to a residual HRV that is more suited for discrimination between mental stress and resting state. This conclusion has been ratified in other studies dealing also with stress classification and applying similar procedures [22,23].

The algorithms used to separate respiration from HRV presented in literature lack two important aspects. First, they do not quantify the strength of coupling between respiration and HRV. Thus, in the case that no significant coupling is present, a separation is still carried out. This has the risk of generating wrongly decoupled time series. In addition, the strength of the cardiorespiratory coupling could deliver more information about the state of health of the subject. Second, even though the methods presented in the past have been validated empirically, no validation on a theoretical basis has been carried out. Since the golden truth about the respiration related part of heart rate is not known, it is hard to evaluate the correctness and performance of the separating method itself.

In order to address these issues, we developed a method to quantify coupling between respiration and HRV using Granger's causality and defined a threshold to detect significant coupling. The algorithm then continues with the separation of the respiration induced part of the HRV. Special procedures were created for paced respiration at different frequencies and natural breathing. The residual HRV unrelated to respiration is achieved using linear filters such as an optimal notch filter (for paced respiration) and an ARMAx filter (for natural breathing). Similar methodologies used for related applications have been presented in the past in [24,21]. For the purpose of testing the method on a theoretical basis, we also carried out a simulation study using synthetic signals that resembled the ones measured for this work. Finally, after demonstrating the validity of the developed algorithm, we use it to separate the influence of respiration on the HRV in a data set recorded during paced respiration and in another one with natural breathing.

2. Methods

2.1. Data

2.1.1. Synthetic signals

In order to test the algorithms developed in this work at a theoretical level, we carried out a simulation study using synthetic signals. Respiration, RR time series (which is reciprocal of the instantaneous heart rate) and their coupling were modeled to resemble the real measured signals in the time and frequency domain. The block diagram shown in Fig. 2a displays the complete simulation scheme that includes the generation of realistic time series, the way these signals are coupled, the decoupling algorithm and the evaluation of the reconstruction. In this work, we call *intrinsic* the part of HRV that is not related to respiration, because it cannot be recorded independently and might be overlapped by other larger influences such as RSA. The intrinsic RR time series $RR_{intri}(n)$ is modeled using pink Gaussian noise [25]. This series resembles the theoretical RR time series that is free of any influence from respiration. The respiration signal $resp(n)$ is modeled using a harmonic function with time varying frequency. In order to model coupling, the respiration signal is first filtered by a moving average (MA) system $G(k)$ and added to the intrinsic RR time series [21]. The resulting signal represents the measured RR time series $RR_{meas}(n)$ that would have been computed from the recorded ECG. This model is characterized by an open-loop configuration allowing an external input. This is a specific case of the more general family of multivariate dynamic adjustment (MDA) models [26].

Mathematically speaking, the signals are modeled in the following way:

- The intrinsic RR time series is modeled by random Gaussian pink noise. It is characterized by a spectral power density that is proportional to the reciprocal of the frequency $S_{RR_{intri}}(f) \propto 1/f$ and by a normal amplitude distribution $\mathcal{N}(0;\sigma)$ in the time domain. This signal can be achieved by filtering white Gaussian noise with a low pass filter [27].
- Respiration is modeled with a harmonic function of the general form $resp(n) = A \cdot cos(\varphi(n))$. The time varying phase of the cosine function is defined as a time discrete approximation of the integral of the time varying frequency $f(n)$:

$$\varphi(n) = 2\pi \sum_{k=0}^{n} \frac{f(k)}{f_s}$$

where f_s is the sampling frequency in Hz used in the real signal processing algorithm. In our study, f_s was set to be 4 Hz, which is a typical value used in literature [28]. The time varying frequency $f(n)$ is defined using the hyperbolic tangent (tanh) function which has a sigmoid shape. The function is parametrised to have lower and upper bounds $f_0 - f_1$ and $f_0 + f_1$ and time discrete constant $f_s \cdot T$. It is centered at the sample point n_0:

$$f(n) = f_0 + f_1 \cdot \tanh\left(\frac{n - n_0}{f_s \cdot T}\right)$$

The parameters A, f_0, f_1, T and n_0 can be freely chosen by the user to recreate different scenarios. In this work, we investigated two types of respiration signals, the constant and the natural breathing. In the case of constant breathing, the frequency f_0 comes randomly from the interval $f_0 \in [0.1;0.6]$ Hz and $f_1 = 0.005$ Hz is chosen fixed to ensure that spectral power is localized around f_0. In the case of natural breathing, the frequency f_0 is also randomly chosen from the interval $f_0 \in [0.1;0.6]$ Hz and f_1 is an aleatory variable from the interval $f_1 \in [0;0.1]$. For both types of signals, the other parameters present in the sigmoid function were randomly chosen from the following intervals: $A \in [0.2;5]$, $n_0 = [180;540]$, $T \in [10;30]$ s and a signal length of $N = 720$ sample points, or three minutes, was set fixed. A large number of repetitions was performed and statistics were carried out for evaluation purposes. The simulation study is presented in detail in Section 3.

The chosen parameters are in accordance with the signals included in the two studies presented in this work, which facilitates the comparability between results obtained from simulation and real measurements. Furthermore, the parameters are

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