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Bivariate phase-rectified signal averaging—a novel technique for cross-correlation analysis in noisy nonstationary signals

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Abstract Signals generated by biologic systems are characterized by a high degree of nonstationarities and noise. Phase-rectified signal averaging (PRSA) was shown to be superior to conventional methods in detection of periodicities in biologic signals. Bivariate phase-rectified signal averaging (BPRSA) is an extension of the PRSA-method for analysis of interrelationships between 2 synchronously recorded biologic signals. Here, we review the methodology of the technique and demonstrate its performance in simulated data. As application to biologic data, we use BPRSA to analyze synchronously recorded time series of systolic arterial blood pressure, RR intervals, and respiratory activity.

Keywords: Autonomic function; Baroreflex; Cross-correlation; Non-stationarity; Sinus arrhythmia

Introduction

Many natural systems generate periodicities at different time scales. Examples can be found in living nature such as in cardiovascular, endocrinologic, or neurologic systems but have also been described for phenomena in nonliving nature, for example, for the El-Niño phenomenon, for sunspot numbers, and ice age periods.[1,2] In living systems, periodic modulations often reflect closed loop regulation processes and therefore provide important insights into the state of health of the system. However, the diagnostic approach to signals generated by biologic systems is limited. Nonstationarities are a major problem in the analysis of biologic signals particularly when recorded for a long period and not in a true experimental setting. Internal and external perturbations continuously affect the system causing interruptions of the periodic behavior. Moreover, almost all biologic signals contain a substantial amount of 1/*f*-noise. Recently, we introduced the method of phase-rectified signal averaging (PRSA) that is capable of detecting and quantifying periodic components in noisy nonstationary time series.[3] The PRSA-based deceleration capacity of heart rate has been shown to be a strong and independent predictor of late mortality after acute myocardial infarction. Its predictive power was shown to be superior to standard measures of heart rate variability and left ventricular ejection fraction.[4]

Here, we review an extension of the PRSA method, the so-called bivariate PRSA (BPRSA), for the study of interrelationships of periodic behavior in 2 or more synchronously recorded biologic signals.[5] We briefly describe the methodology of BPRSA and use simulated data to demonstrate its performance. As application in natural data, we use BPRSA to quantify the interrelationships between periodic modulations of systolic arterial blood pressure, heartbeat intervals, and respiratory activity.

Method of BPRS averaging

Let *X(i)* and *Y(i)* be 2 synchronously recorded time signals, and let us assume that periodic modulations of *X(i)* cause periodic modulations of *Y(i)*. *X(i)* might then be called the *trigger signal* and *Y(i)* the *target signal*. Examples for trigger and target signal might be the series of systolic arterial blood pressure values (SBPs) and the series of heartbeat intervals (RRIs) derived from a synchronously recorded electrocardiogram. Systolic arterial blood pressure values are temporally attributed to prior R waves. Series of

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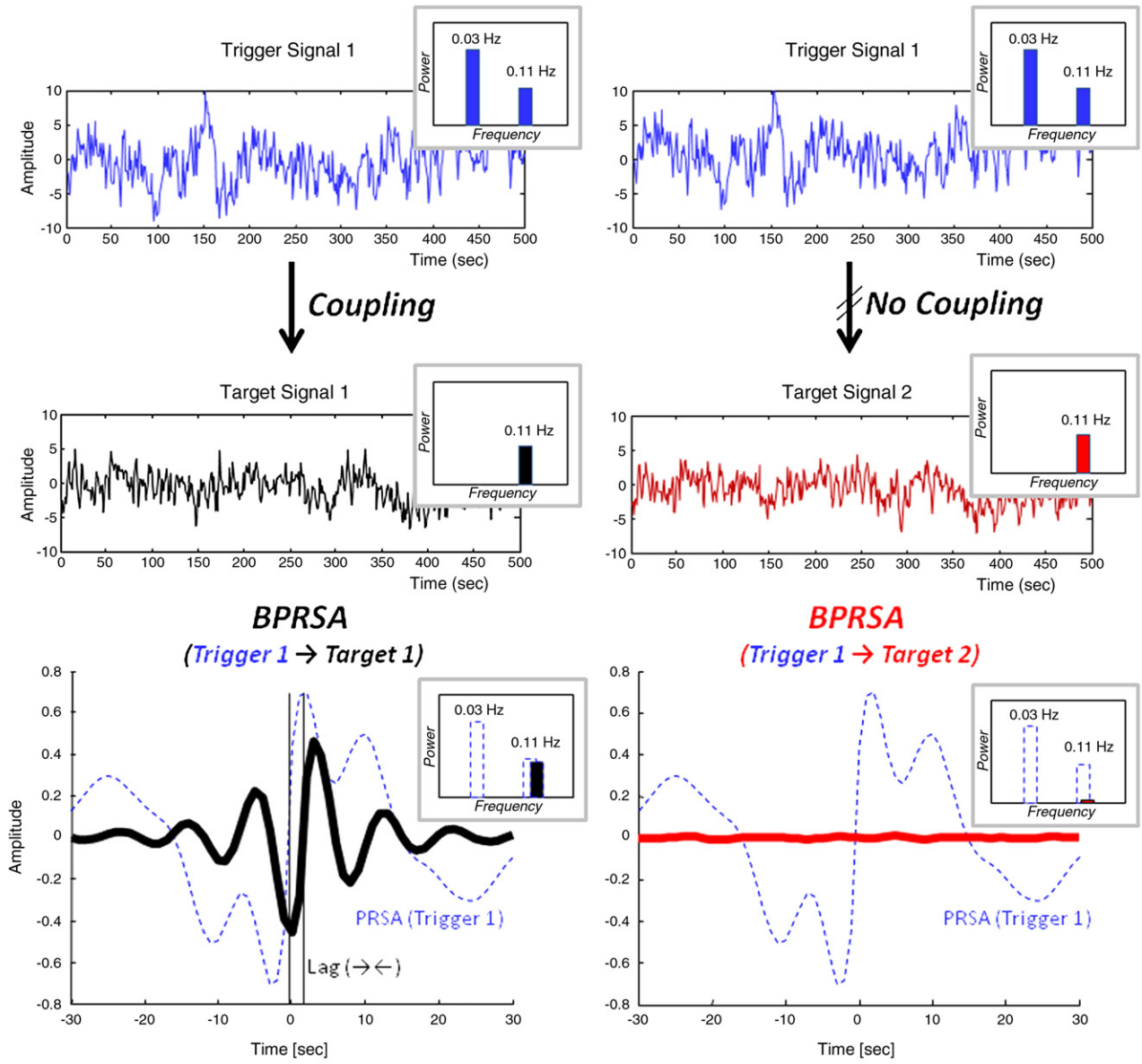

Fig. 1. Application of BPRSA to simulated data with and without coupling. The upper 2 rows show trigger and target signal with (left) and without coupling (right). Only the first 500 of 10 000 seconds are shown. The power spectra in the small boxes were calculated from the signals using Fourier transformation. For the sake of clarity, only the peaks of the power spectra are visualized by bars. The lower graphs show the resulting monovariate and bivariate PRSA signals. The time axis denotes the distance to the anchor (see text for explanations).

heartbeat intervals are calculated as distances from the R wave to the following R wave.

In the first step, RRIs are identified that occur when SBP increases.

$$SBP\,(i) > SBP\,(i-1)$$

Such RRIs are called *anchors*. Typically, nearly one half of all RRIs are identified as anchors. Alternatively, one may define anchors by comparing averages of T values of SBP,

$$\frac{1}{T}\sum_{j=0}^{T-1} SBP\,(i+j) > \frac{1}{T}\sum_{j=1}^{T-1} SBP\,(i-j)$$

T can be used to filter out high frequent oscillations of SBP and RRI and thus works as low-pass filter. As it can be shown mathematically, BPRSA is most sensitive for detection of oscillations with frequencies of $f = 1/(2.5T)$.

In the second step, segments of length $2L$ are defined around the anchors. Anchors close to the beginning or the end of the target signal, where no full surroundings of length $2L$ are available, are disregarded. L is freely definable and depends on the lowest frequency that shall be visualized. Note that most segments overlap. If we denote the positions (indices) of all regarded anchors by (i_v), $v = 1, \ldots, M$, the points in segment number v will be

$$x(i_v - L), x(i_v - L + 1), \ldots, x(i_v), \ldots, X(i_v + L - 2), X(i_v + L - 1)$$