Causal Coherence Detects Causality in the Closed Loop Relationship Between Heart Period and Systolic Arterial Pressure Variability Series

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Abstract

Coherence is not able to evaluate the strength of the link between two interacting signals in a specific causal direction as it merges both feedback and feedforward arms of the closed loop describing the relationships between them. We propose a method to evaluate the degree of linear dependency between two variables at each frequency without losing causality. It is based on the definition of two causal coherence functions. The approach is tested on heart period and systolic arterial pressure beat-to-beat series recorded in 7 heart transplant recipients less than 14 months after heart transplantation. In healthy subjects these variables interact in closed loop but in heart transplant recipients the neural feedback path (from arterial pressure to heart period) is cut due to surgical procedure, while the mechanical path (from heart period to arterial pressure) is preserved. The significance of the coupling is assessed by means of a surrogate data approach.

1. Introduction

Given two signals, the squared coherence function measures the degree of correlation between corresponding frequency components. It ranges from 0 (no correlation) to 1 (full correlation). The evaluation of the degree of coupling between two signals is not useful to assess the strength of the link in a specific causal direction. Indeed, a strong correlation between two signals can be found in open loop conditions when either one signal acts onto the other or viceversa (the latter affects the former). However, also closed loop conditions, consequence of the contemporaneous activation of feedforward and feedback paths, can produce a high correlation. The possibility to distinguish among these three situations should allow one to model more precisely the interactions between two biological signals and to derive indexes more closely related to specific physiological mechanisms.

The aim of this study is to propose a measure of the degree of correlation in a specific causal direction at each frequency. The measure, referred to as causal coherence, is simply derived from the estimate of the coherence function based on bivariate autoregressive (AR) process [1]. The method tests the significance of coherence and causal coherence using a surrogate data approach [2].

The technique is validated on the beat-to-beat variability series of heart period (RR interval) and systolic arterial pressure (SAP) extracted from heart transplant recipients less than 14 months after transplantation [3]. These two signals usually interact in closed loop in healthy subjects. On the contrary, in heart transplant recipients the pathway from SAP to RR interval is cut due to cardiac denervation as a result of the surgical procedure, thus opening the RR-SAP loop and imposing causality from RR interval to SAP.

2. Methods

2.1. Autoregressive bivariate process

Given two zero mean series y_1 and y_2, the bivariate AR process $y=|y_1\ y_2|'$ is defined as

$$y(t) = A(z)\cdot y(t) + w(t)$$

where $w=|w_1\ w_2|'$ is the column vector of uncorrelated white noises and A(z) is a 2x2 matrix of polynomials describing the interactions between the two signals. The polynomials on the main diagonal

$$A_{ii}(z) = \sum_{k=1}^{p} a_{ii,k} z^{-k}$$

represent the dependency of y_i on its own p past samples (z^{-1} represents the one delay operator), while the polynomials out of the main diagonal

$$A_{ij}(z) = \sum_{k=0}^{p} a_{ij,k} z^{-k}$$

describe the influence of p+1 samples of y_j (p past values plus the current one) on y_i. Fig.1 depicts the linear interactions between y_1 and y_2 [1] and represents the model structure underlying the bivariate AR process.

2.2. Coherence and causal coherence

The 2x2 transfer function matrix linking w to y is

$$N(z) = (I - A(z))^{-1}$$

where I is identity matrix. The auto-spectra $S_{ii}(f)$ and the cross-spectra $S_{ij}(f)$ are obtained from the 2x2 matrix

$$S(f) = N(z) \cdot \Lambda \cdot N'(z^{-1})\Big|_{z=e^{j2\pi\Delta tf}}$$

where $N'(z^{-1})$ is the transpose of $N(z^{-1})$, Λ is the variance matrix containing the variance of w_1 and w_2 on the main diagonal and zeroes out of the main diagonal due to the uncorrelation between w_1 and w_2 and Δt is the sampling period.

The coherence function is defined as

$$K_{1,2}^2(f) = \frac{|S_{12}(f)|^2}{S_{11}(f) \cdot S_{22}(f)}$$

As both cross-spectrum $S_{12}(f)$ and power spectra $S_{11}(f)$ and $S_{22}(f)$ depend on feedback and feedforward paths represented by the blocks A_{12} and A_{21}, the two causal directions are both taken into account, thus preventing the evaluation of the coupling in a specific causal direction. The evaluation of the strength of the link in a predefined causal direction is performed in two steps: i) the coefficients of the closed loop model (i.e. A_{11}, A_{22}, A_{12} and A_{21}) are identified via a least squares method (here the Cholesky decomposition); ii) the coefficients of the blocks describing the dependency of one signal on the other (A_{12} and A_{21}) are separately forced to 0, thus virtually opening the loop. For example, if one wish to evaluate the strength of the coupling $K^2_{1\rightarrow 2}(f)$ in the causal direction from y_1 to y_2, $K^2_{1,2}(f)$ should be calculated by setting $A_{12}(z)=0$ and leaving $A_{21}(z)$ as it results from the identification procedure.

2.3. Testing the significance of coherence

Following the approach set by De Boer et al [4] the coherence function should be considered significant above 0.5. Unfortunately, the value above which the coherence should be considered significant depends mainly on the sequence length and number of degrees of freedom (it is strictly related to the bivariate AR model order p). In this study the sequence length was kept fixed in all the analyses, while the model order p was varied accordingly to the Akaike's figure of merit for bivariate processes [1]. Therefore, the choice to keep a fixed threshold to accept the hypothesis that coherence was larger than 0 was unreliable, thus inducing to the use of a surrogate data approach. According to Palus et al [4] the two series y_1 and y_2 were phase-randomised with two independent realisations of whites noises, thus generating surrogate uncorrelated pairs with the same variance and power spectral density as the original series. After creating 15 surrogate uncorrelated pairs, the threshold to accept the hypothesis that coherence was significant (i.e. larger than 0) was derived as $av[K^2_s(f)]+2 \cdot sd[K^2_s(f)]$

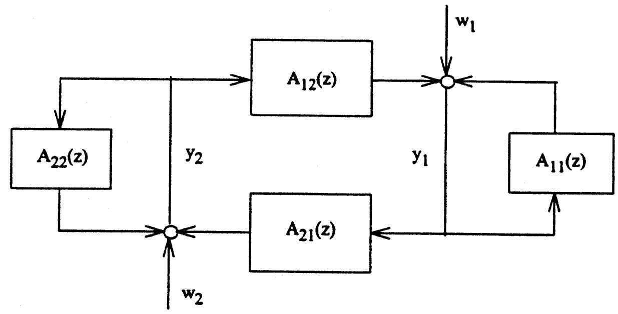

Figure 1. Block diagram describing the interactions between y_1 and y_2 in a bivariate autoregressive process.

where $av[K^2_s(f)]$ and $sd[K^2_s(f)]$ represent the average and standard deviation at a given frequency over the 15 coherence functions calculated on the surrogate data set. If the coherence calculated over the original pair $K^2_o(f)$ exceeded the threshold, the two series were significantly coupled ($p<0.05$) at the considered frequency [5]. The formula to calculate the threshold was applied both to coherence and causal coherence functions.

3. Experimental protocol and data analysis

Seven heart transplant recipients (6 male, 1 female, age: 57±7, mean±sd) less than 14 months after transplantation were studied at rest in supine position. After transplantation all the subjects had normal left ventricular ejection fraction (range:50-62%) and were free of moderate or severe rejection (they all underwent standard immunosupppression teraphy). We recorded the surface ECG (lead II), arterial pressure (Portapres, TNO, Amsterdam, The Netherlands) and respiration (Respitrace, Ambulatory Monitoring, NY, USA).

The heart period was approximated with the distance between two consecutive R peaks detected on the ECG (RR interval). SAP was calculated as the maximum of the arterial pressure signal inside the RR interval. As the i-th RR interval cannot affect the i-th SAP measure (RR interval was not ended yet), one beat delay was introduced on the causal block describing the influences of RR interval onto SAP (the mechanical path). No delay was a priori inserted in the causal block describing the causal effects of SAP on RR interval (the baroreflex path). The respiratory signal was sampled once per cardiac beat to extract the respiratory frequency.

According to the guidelines of cardiovascular variability analysis [6] we classified the oscillations in two frequency bands: low frequency (LF, from 0.04 to 0.14 Hz) and high frequency (HF, ±0.04 Hz around the respiratory rate). The coherence and causal coherence functions were sampled at the central frequency of LF and HF oscillations (i.e. $K^2(LF)$ and $K^2(HF)$) detected using monovariate AR power spectral decomposition technique [1] on the RR series and sampled respiratory

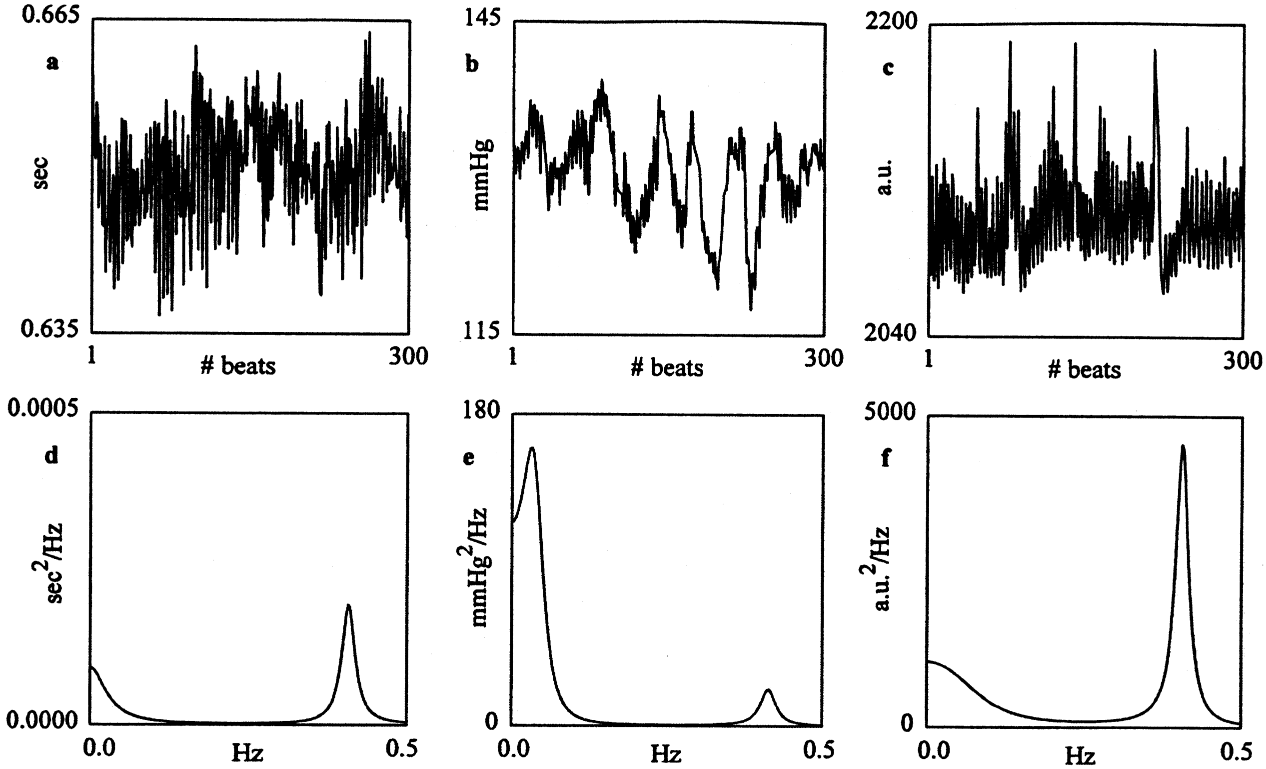

Figure 2. Example of RR, SAP and sampled respiratory series (a,b,c respectively) obtained from a heart transplant recipient. Their relevant monovariate autoregressive spectral densities are shown in d,e,f.

signal respectively. Segments of 300 cardiac beats were analysed.

4. Results

The mean RR interval was 781±136 ms, while the mean SAP was 131±27 mmHg. As expected, the RR variance was dramatically small (32±54 ms^2). On the contrary, SAP series maintained its variability (the SAP variance was 16±12 mmHg^2). The respiratory rate was 0.32±0.06 Hz. In RR series no LF oscillation was found (in only one subject a small LF component was detected) and the RR variability was mainly concentrated at HF (23±38 ms^2, HF was detected in all the subjects). The SAP series exhibited an important LF component at 0.08±0.03 Hz (7.9±12 mmHg^2) and a smaller HF oscillation (1.8±1.9 mmHg^2) in all the subjects. A typical example of RR interval, SAP and sampled respiration series and their relevant monovariate AR power spectra is

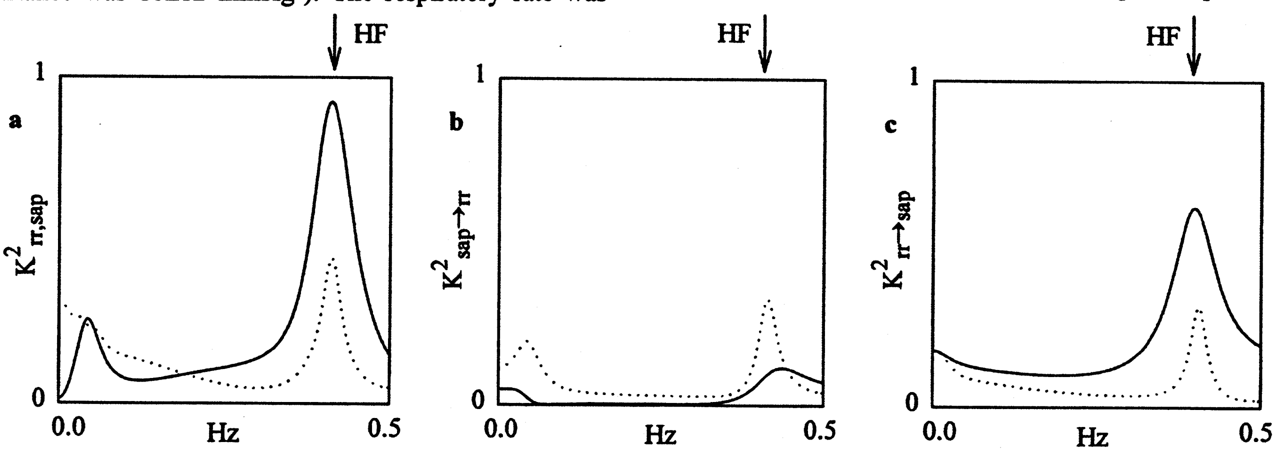

Figure 3. Example of coherence $K^2_{rr,sap}$ (a) and causal coherences $K^2_{sap\rightarrow rr}$ and $K^2_{rr\rightarrow sap}$ (b,c respectively) calculated over the RR interval and SAP beat-to-beat series depicted in Fig.2. The solid line is relevant to the coherence calculated over the original series, while the dotted line represents the threshold above which the coherence is significant (i.e. the two series are significantly correlated at that frequency). HF indicates the respiratory rate.

shown in Fig.2.

The RR and SAP series were highly correlated at HF: indeed, as shown in Fig.3a, the $K^2_{rr,sap}(HF)$ calculated over the original series (solid line) is close to 1 and largely significant (above the threshold represented by the dotted line). This result was found in all the subjects. The mechanical path (from RR to SAP) was responsible for this large coupling as the causal coherence on this path at HF (i.e. $K^2_{rr\rightarrow sap}(HF)$) is significant in 6 out of 7 subjects (in Fig.3c the solid line is largely above the dotted line at HF). On the contrary, the strength of the link on the reverse path (from SAP to RR), measured by $K^2_{sap\rightarrow rr}(HF)$, was 0 in 6 out of 7 subjects (in Fig.3b the solid line is below the dotted line at HF).

5. Discussion

This study proposes a method to measure the strength of the linear coupling between two signals in a specific causal direction at each frequency. This measure can be carried out using the coherence function only after introducing peculiar modifications in its definition. Indeed, the bivarate autoregressive identification procedure correctly estimates the coefficients of the feedforward and feedback paths but, in the usual definition of the coherence function, the two causal paths are mixed together. Similarly, this occurs in the definition of another function measuring the degree of coupling [7]. This explains why, in heart transplant recipients in presence of an ineffective baroreflex feedback due to the neural cardiac denervation (it should produce uncoupling between the two variables), we observe an high coherence between heart period and systolic arterial pressure series at the respiratory rate. To calculate causal coherence from one series to the other (e.g. on the feedback) is sufficient to open the loop by setting to zero the coefficients of the block representing the reverse path (e.g. the feedforward). The proposed causal coherence functions allow us to find out that, as expected, the high correlation between heart period and systolic arterial pressure in heart transplant recipients arises from the presence of an intact mechanical path setting the influences of heart period on arterial pressure, while the baroreflex path is opened.

Also the surrogate data approach utilized to test the hypothesis that the correlation at each frequency is significantly different from 0 (i.e. the two signals are coupled at that frequency) deserves some comments. According to this approach, the threshold defining the value of coherence above which the two signals can be considered significantly coupled is a function of the frequency and it is unreliable to fix it to a predefined value. For example, the threshold in Fig.3a (dotted line) reaches a value very high and close to 0.5 at HF but it can be even largely smaller (e.g. at LF). Therefore, we propose an approach testing the significance of the coupling on a case-by case basis instead of an approach fixing an arbitrary, even though large, threshold [4].

6. Conclusions

The proposed approach to the evaluation of the degree of coupling in a specific causal direction allow one to assess indexes of statistical link between two variables more specific than those derived from traditional coherence function definition. As in many cases the loss of correlation between variables is considered an index of pathology, the method might have useful clinical applications. Indeed, the method permits to detect cases of uncorrelation in a specific causal direction in presence of a global high correlation deriving from a high correlation on the reverse causal path. The surrogate data approach appears to be suitable for the identification of a threshold defining the value of coherence above which the coupling can be considered significant (i.e. the two series are significantly correlated at that frequency).

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