Need of Causal Analysis for Assessing Phase Relationships in Closed Loop Interacting Cardiovascular Variability Series

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Abstract

The phase spectra obtained by the classical closed loop autoregressive model (2AR) and by an open loop autoregressive model (ARXAR) were compared to shed light on the need of introducing causality in the assessment of the delay between RR and arterial pressure oscillations. The reliability of the two approaches was tested in simulation and real data setting. In simulation, the coupling strength of a bivariate closed loop process was adjusted to obtain a range of working conditions from open to closed loop. In open loop condition, 2AR and ARXAR phases were comparable and in agreement with the imposed delay. In closed loop condition, ARXAR model returned the imposed delays, while 2AR showed an intermediate value of delay. Real data were chosen to represent comparable physiological condition. The use of cross spectrum for calculating the delay from arterial peressure to RR oscillations seems adequate only in particular condition of open-loop relationship as it happens during head up tilt in young healthy subjects.

1. Introduction

The spontaneous fluctuations in arterial pressure and heart rate have been subject to many studies aimed to quantify strength and nature of the coupling between cardiovascular signals [1,2]. Cross-Spectral techniques were introduced for estimating the linear transfer function and specifically for assessing the gain function as baroreflex sensitivity has been demonstrated to be useful for stratifying risk in post MI patients [3]. However, for fully disclosing the nature of the linear relationship between arterial blood pressure fluctuations and cardiac cycle changes the phase function has to be accounted too.

Although heart period and systolic arterial pressure strongly interact in closed loop, gain and phase spectra calculated from the cross-spectral matrix have been for a long time considered as a measure of the baroreflex function, thus disregarding the contribute of the feedforward mechanism to the regulatory loop. Causality was therefore recently introduced for quantifying the information exchange on a specific path of the regulatory loop. While linear and non linear causal models were introduced for estimating strength [4-6] and gain [7] of feedback and feedforward mechanisms, till now no studies have dealt with the estimation of the phase lag between cardiovascular fluctuations with appropriate causal approach. Thus, this study aims to shed light on the need of a causal approach for estimating phase relationships in cardiovascular fluctuations. A parametric linear causal model (ARXAR) is exploited for estimating the phase spectra on the baroreflex regulatory path (feedback phase), and the results are compared with those obtained by a closed loop bivariate autoregressive model (2AR). Simulations and examples from real data, reproducing closed and open loop interactions, are presented to mimic different working conditions of the regulatory system.

2. Methods

2.1. Phase estimation by traditional bivariate approach

The classical method for assessing the phase relationship between two variability series x and y is based on representing their interaction by an input-output model and then calculating in the frequency domain the angle of their transfer function $H_{xy}(f)$:

$$\Phi(f) = \arg\left(\frac{P_{xy}(f)}{P_x(f)}\right) \tag{1}$$

where $P_x(f)$ is the spectral density function of x and $P_{xy}(f)$ is the cross-spectrum between x and y.

When cross-spectral estimation is performed by the parametric autoregressive (AR) approach [8], the interactions between x and y are modeled by the 2AR model shown in Figure 1, which is described by the two equations:
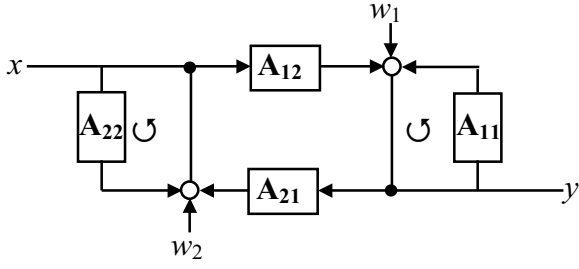
Figure 1. Block diagram of the autoregressive bivariate (2AR) model for the closed loop description of the interactions between two time series.
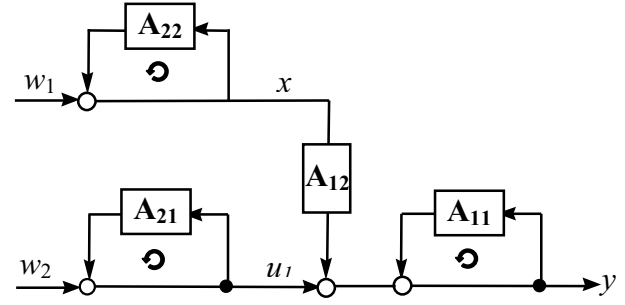

Figure 2. Block diagram of the autoregressive bivariate model with exogenous input (ARXAR) for the open loop description of the interactions between two time series.

$$y(t) = \sum_{k=1}^{P} a_{11}(k)y(t-k) + \sum_{k=0}^{P} a_{12}(k)x(t-k) + w_1(t) \quad (2)$$

$$x(t) = \sum_{k=1}^{P} a_{22}(k)x(t-k) + \sum_{k=0}^{P} a_{21}(k)y(t-k) + w_2(t) \quad (3)$$

where w_1 and w_2 are uncorrelated zero-mean white noises with variance σ_2^2 and σ_2^2. The blocks:

$$A_{ij}(z) = \sum_{k=0}^{P} a_{ij}(k)z^{-k} \quad , \quad i,j = 1,2$$

where z^{-1} represents the one-lag delay operator, describe the dependence of a series on its own past for $i{=}j$ (with $a_{11}(0){=}a_{22}(0){=}0$), and the dependence of a series on the samples of the other for $i{\neq}j$. The transfer function from x to y is calculated by substituting in (1) the spectra obtained from (2) and (3):

$$H_{xy}(f) = \frac{(1-A_{22}(z))A_{21}(z^{-1})\sigma_1^2 + A_{12}(z)(1-A_{11}(z^{-1}))\sigma_2^2}{|A_{21}(z)|^2 \sigma_1^2 + |(1-A_{11}(z))|^2 \sigma_2^2}$$

for values of the complex variable z belonging to the unitary circle (i.e., $z{=}e^{j2\pi fT}$, where T is the sampling period).

2.2. Phase estimation by causal approach

The ARXAR model [9] represented in Figure 2 was introduced to assess the phase lag between the two series x and y by accounting for the causality of their interactions. The model is defined by the equation:

$$y(t) = \sum_{k=1}^{P} a_{11}(k)y(t-k) + \sum_{k=0}^{P} a_{12}(k)x(t-k) + u_1(t)$$

where the colored noise u_1 and the exogenous input x

are described as AR processes with w_1 and w_2 zero-mean white noises. The ARXAR model is able to elicit the causal dependence of the output y over the input x from the other contributions which influence y without affecting x (modeled by the u_1 signal).

The transfer function from x to y is obtained from the ARXAR model as follows:

$$H_{xy}(f) = \left. \frac{A_{12}(z)}{1 - A_{11}(z)} \right|_{z=e^{j2\pi fT}}$$

2.3. Simulations

The two methods for assessing the phase relationships between two time series were tested on the bivariate process described by the equations [4]:

$$s(t)=-0.7r(t\text{-}2)+\gamma \cdot w_1(t)$$
$$r(t)=0.7s(t)+\delta \cdot w_2(t)$$

where w_1 and w_2 are uncorrelated white noises with zero mean and unitary variance. When $\delta{=}0$ with $\gamma{=}1$, the relationship from s to r is deterministic (with lag equal to 0) and thus its causal link is magnified with respect to that of the relationship from r to s. On the contrary, when $\gamma{=}0$ with $\delta{=}1$ the relationship from r to s overwhelms the link from s to r, with a 2-samples delay. The strength of the coupling on the two paths is equalized when $\delta{=}\gamma{=}1$.

Simulations were repeated by varying one of the two parameters δ and γ from 0 to 1, step 0.1, while keeping equal to 1 the other parameter. A realization of the bivariate process (300 points) was generated for each combination of γ and δ, and phase spectra were computed by the traditional bivariate approach and by the proposed causal approach. In causal analysis, the phase was estimated on both pathways from r to s and from s to r.

2.4. Real data

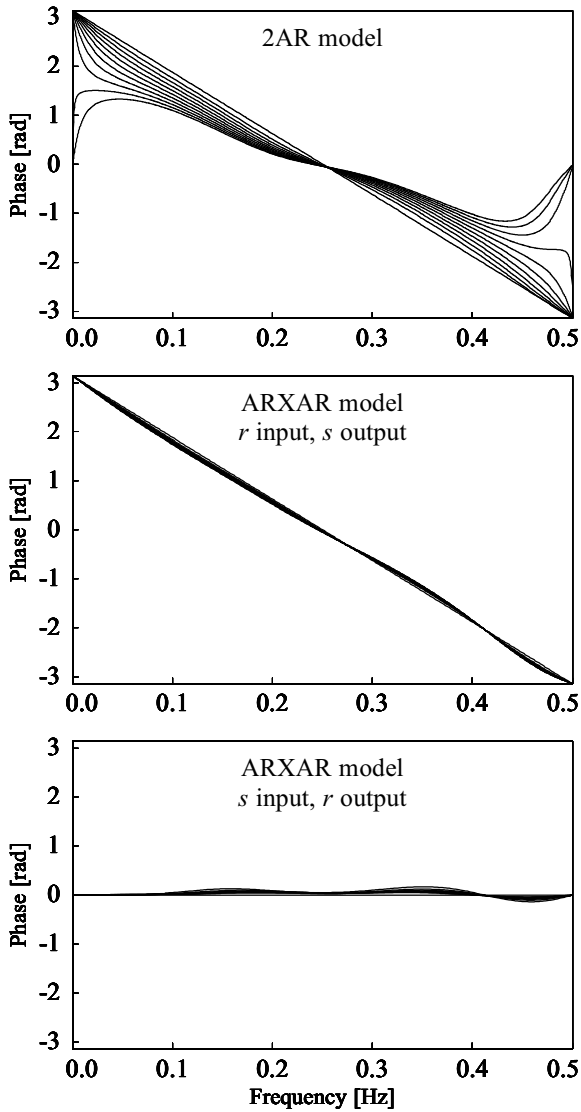One lead ECG and noninvasive arterial pressure (Finapres, Ohmeda) were acquired in a healthy young

Figure 3. Phase spectra obtained by 2AR model and ARXAR model applied to the simulated series, at varying values of the parameter γ.

Figure 4. Phase spectra obtained by 2AR model and ARXAR model applied to the simulated series, at varying values of the parameter δ.

subject (M, 29 years) during rest and head-up tilt. The RR interval and the systolic arterial pressure (SAP) were measured on a beat-by-beat basis, and stationary series lasting 300-points were constructed by considering the ith SAP value inside the ith RR interval [10].

3. Results

Figure 3 shows the phase spectra obtained by 2AR and ARXAR models applied to the simulated bivariate process for values of the parameter γ moving from zero to one ($\delta=1$). The 2AR model returns correct estimates of the imposed phase lag (i.e., a straight line with slope 4π, corresponding to a constant delay of 2s) only when the relationships from r to s is deterministic (i.e., $\gamma=0$), while
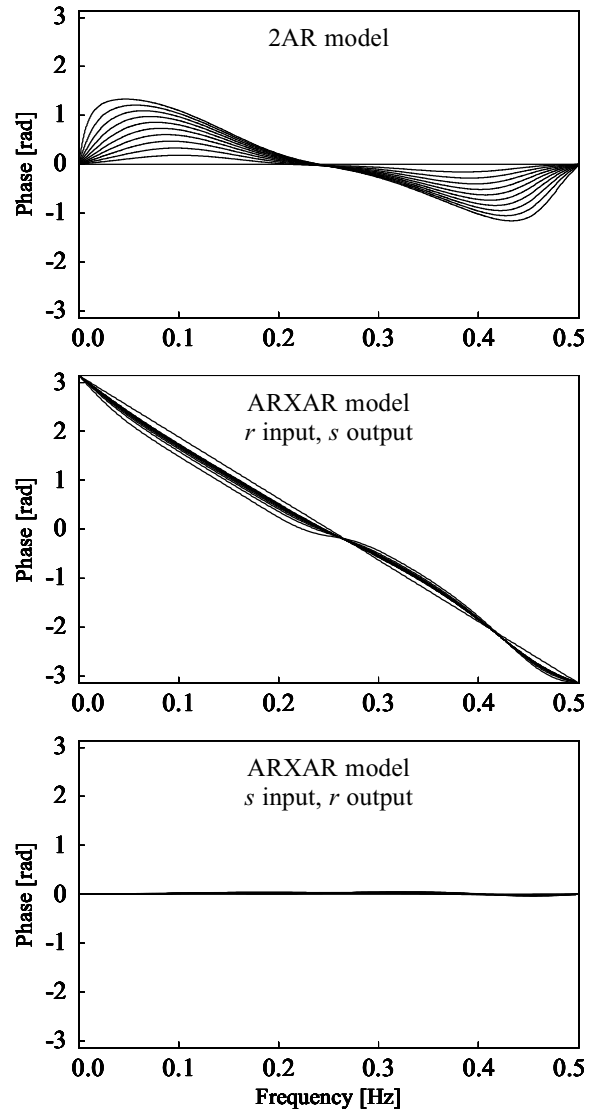
the estimated phase resulted as a mix of the delays of the two interacting pathways when the coupling became significant in both causal directions.

When $\delta=\gamma=1$, the phase plot exhibited a slope of about 2π, indicating an estimated delay of 1 s. On the contrary, the ARXAR model returned the expected slopes of the phase plot, namely 4π with r as input and 0 with s as input, for all values of γ.

A similar behavior was observed by varying the parameter δ while keeping γ equal to 1 (Figure 4). With $\delta=0$, both 2AR and ARXAR models were able to detect the imposed phase lags, while the rise of δ caused an increasing unreliability of 2AR phase estimates and an unchanged response of the ARXAR estimate.
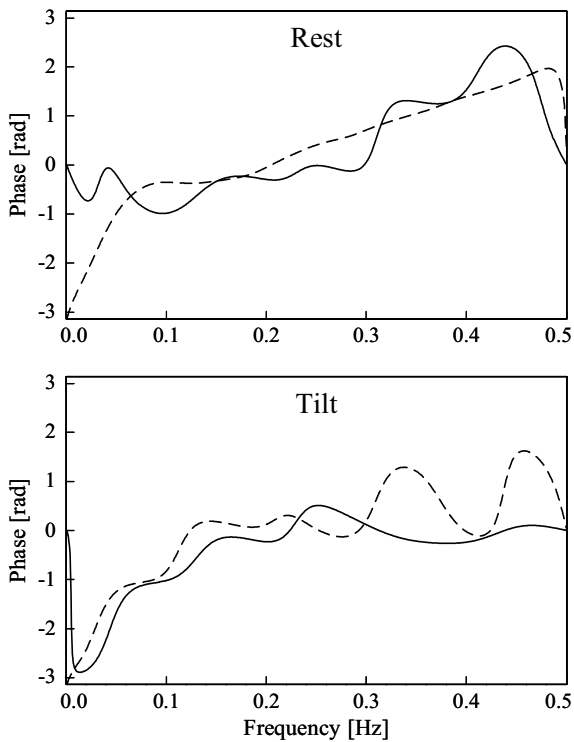
Figure 5. Example of phase estimation in a young healthy subject in rest and tilt by 2AR model (continuous line) and ARXAR model from s to r (dashed line).

An example of phase spectra estimations with 2AR and ARXAR models on real data is showed in Figure 5. Low frequency phase values were markedly different when the subject was supine. Differently, the two estimators identified comparable low frequency phase when the sympathetically-mediated regulatory mechanism was activated by head-up tilt.

4. Discussion

At rest in, in human both feedforward and feedback pathways of the regulatory loop are important and a different balance between these two mechanisms often characterizes physiological and pathological conditions [5,6]. Thus, the approach to transfer function assessment thorough the traditional bivariate cross spectral analysis can be inappropriate to shed light on the real working condition of cardiovascular regulatory mechanism.

In this study the performance of causal and non-causal phase estimators were compared on a set of simulated signals generated by a bivariate process mimicking different levels of causal coupling. Simulations demonstrated that only when open loop condition were reproduced, 2AR and ARXAR phases were comparable and in agreement with the imposed delay, otherwise only the causal model was able to estimate the right delay between oscillations in the two simulate signals. Similar results were found when the two models were applied on real data with known closed or open loop conditions.

In conclusion, in the presence of closed loop relationship the phase estimated by bivariate model (2AR) is unreliable since mix the effect of the feedforward and feedback arms. The use of cross spectrum for calculating the delay of RR oscillations from SAP ones seems adequate only in particular condition of open-loop interactions.

References

[1] DeBoer R, Karemaker JM, Strackee J. Hemodynamic fluctuations and baroreflex sensitivity in humans: a beat-to-beat model. Am J Physiol 1987;253: H680-9.
[2] Saul JP, Berger RD, Albrecht P, Stein SP, Chen MH, Cohen RJ. Transfer function analysis of the circulation: unique insights into cardiovascular regulation. Am J Physiol 1991;261:H1231-45
[3] La Rovere MT, Bigger JTJ, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. Lancet 1998;351:478-84.
[4] Porta A, Furlan R, Rimoldi O, Pagani M, Malliani A, van de Borne P. Quantifying the strength of the linear causal coupling in closed loop interacting cardiovascular variability signals. Biol Cybern 2002;86:241-51.
[5] Nollo G, Faes L, Porta A, Pellegrini B, Ravelli F, Del Greco M et al. Evidence of unbalanced regulatory mechanism of heart rate and systolic pressure after acute myocardial infarction. Am J Physiol Heart Circ Physiol 2002;283:H1200-7.
[6] Legramante JM, Raimondi G, Massaro M, Iellamo F. Positive and negative feedback mechanisms in the neural regulation of cardiovascular function in healthy and spinal cord-injured humans. Circulation 2001;103:1250-5.
[7] Nollo G, Porta A, Faes L, Del Greco M, Disertori M, Ravelli F. Causal linear parametric model for baroreflex gain assessment in patients with recent myocardial infarction. Am J Physiol Heart Circ Physiol 2001;280:H1830-39.
[8] Baselli G, Cerutti S, Civardi S, Liberati D, Lombardi F, Malliani A et al. Spectral and cross-spectral analysis of heart rate and arterial blood pressure variability signals. Comput Biomed Res 1986;19:520-34.
[9] Porta A, Baselli G, Caiani E, Malliani A, Lombardi F, Cerutti S. Quantifying electrocardiogram RT-RR variability interaction. Med Biol Eng Comput 1998;36:27-34.
[10] Nollo G, Faes L, Pellegrini B, Porta A, Antolini R. Synchronization index for quantifying nonlinear causal coupling between RR interval and systolic arterial pressare after acute myocardial infarction. Computers in Cardiology 2000;27:143-6.

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