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Model-based assessment of baroreflex and cardiopulmonary couplings during graded head-up tilt

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ABSTRACT

We propose a multivariate dynamical adjustment (MDA) modeling approach to assess the strength of baroreflex and cardiopulmonary couplings from spontaneous cardiovascular variabilities. Open loop MDA (OLMDA) and closed loop MDA (CLMDA) models were compared. The coupling strength was assessed during progressive sympathetic activation induced by graded head-up tilt. Both OLMDA and CLMDA models suggested that baroreflex coupling progressively increased with tilt table inclination. Only CLMDA model indicated that cardiopulmonary coupling due to the direct link from respiration to heart period gradually decreased with tilt table angles, while that due to the indirect link mediated by systolic arterial pressure progressively increased.

1. Introduction

Heart period, usually automatically measured as the temporal distance between two consecutive QRS complexes on the ECG (RR), exhibits spontaneous beat-by-beat variations around its mean value. These fluctuations, referred to as RR variability, are clearly visible in recordings of few minutes and its characterization in time and/or frequency domains provided indirect measures of the state of the autonomic nervous system [1]. Several models [2–5] have been proposed in the attempt to link beat-to-beat RR variability to specific physiological mechanisms and estimate indexes more closely related to particular aspects of cardiovascular regulation (e.g. baroreflex and/or cardiopulmonary interactions) directly from spontaneous cardiovascular variability derived from noninvasive recordings. These models, mainly belonging to the class of trivariate open [5] and closed [2] loop causal linear parametric models, describe RR variability as driven by systolic arterial pressure (SAP) changes, by respiration (R) producing RR fluctuations independent of SAP changes at the respiratory frequency, and by undetermined slow periodical inputs adjusting RR independently of SAP and R. These different sources of RR variability can explain about 80% of the total RR variance in humans [2] and model the action of baroreflex (i.e. the RR–SAP dependence) [5] and of influences independent of it due to, for example, Bainbridge reflex [6], respiratory modulations of the autonomic motoneurone firing [7] and central sympathetic rhythm at frequency slower than respiration not mediated by arterial pressure changes [8]. Open loop models hypothesize that both SAP and R are exogenous to RR [5], while closed loop models account for RR–SAP closed loop interactions and hypothesize that R is exogenous to RR and SAP [2].

The aim of this study is to propose a method for the evaluation of the strength of the baroreflex and cardiopulmonary couplings through a model-based approach exploiting causal structures and to compare trivariate open and closed loop models. The proposed method was applied to an experimental protocol capable to produce a progressive increase of sympathetic activity and modulation (i.e. graded head-up tilt) [9–12].

2. Methods

2.1. Multivariate dynamic adjustment (MDA) class

The class of MDA models [13,14] describes the interactions among a set of M zero mean signals as

$$y(i) = A(z)y(i) + u(i) \quad (1)$$

where $y = |y_1, \ldots, y_M|'$ is the $M \times 1$ column vector of the signals ($1 \le m \le M$), $u = |u_1, \ldots, u_M|'$ is the $M \times 1$ column vector of the autoregressive (AR) noises ($1 \le m \le M$) and $A(z)$ is the $M \times M$ matrix of causal finite impulse response filters of order p describing the

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interactions among signals and z^{-1} represents the one-delay operator in the z-domain.

The elements of $A(z)$ along the main diagonal

$$A_{kk}(z)=\sum_{j=1}^{p} a_{kk}(j)z^{-j} \tag{2}$$

describe the dependence of y_k on its own past values, while the elements outside the main diagonal

$$A_{kl}(z)=\sum_{j=0}^{p} a_{kl}(j)z^{-j} \tag{3}$$

with $l\neq k$ describe the dependence of y_k on past values of y_l. While Eq. (2) suggests that immediate effects of y_k on itself (i.e. autoloop without delay) are not allowed (i.e. $a_{kk}(0)=0$), Eq. (3) suggests that immediate effects of y_l on y_k might be allowed and set according to the structure given to $A(z)|_{z=\infty}$ [13] (i.e. to the specific canonical form chosen for the application).

Any element of u is an AR process of order p modeled as

$$u_m(i)=D_m(z)u_m(i)+w_m(i) \tag{4}$$

where w_m is a white noise with zero mean and variance λ_m^2, uncorrelated to any other w_k with $k\neq m$ and $1\leq k$, $m\leq M$ even at zero lag, and $D_m(z)$ has the same structure as in Eq. (2). We define as open loop MDA (OLMDA) model of y_k a MDA model, where $A_{kl}(z)\neq 0$ but $A_{lk}(z)=0$ with $l\neq k$ (i.e. y_l acts on y_k but the reversal is prevented). Conversely, we define closed loop MDA (CLMDA) model of y_k a MDA model where y_l can influence y_k and vice versa (i.e. $A_{kl}(z)\neq 0$ and $A_{lk}(z)\neq 0$ with $l\neq k$).

2.2. Partial process decomposition in the time domain

The joint process y can be seen as the output of the $M\times M$ transfer function matrix $N(z)$ fed by the $M\times 1$ column vector of the white noises, $w=|w_1,\ \ldots,\ w_M|'$, as

$$y(i)=N(z)w(i) \tag{5}$$

where $N(z)$ is

$$N(z)=(I-A(z))^{-1}D(z) \tag{6}$$

I is the identity matrix and $D(z)=\mathrm{diag}[(1-D_m(z))^{-1}]$ is the $M\times M$ matrix containing $(1-D_m(z))^{-1}$ along the main diagonal and 0 outside the main diagonal. The elements of $N(z)$ (i.e. $N_{kl}(z)$) are single-input single-output transfer functions with both zeroes and poles filtering w_l to produce the partial process y_{kl} as

$$y_{kl}(i)=N_{kl}(z)w_l(i). \tag{7}$$

According to Eq. (5) y_k is sum of partial processes due to all noises

$$y_k(i)=\sum_{l=1}^{M} N_{kl}(z)w_l(i). \tag{8}$$

Under the hypothesis of uncorrelation of w_l the variance of y_k, σ_k^2, can be decomposed as sum of the variances of partial processes y_{kl}, σ_{kl}^2

$$\sigma_k^2=\sum_{l=1}^{M}\sigma_{kl}^2. \tag{9}$$

2.3. Strength of causal coupling in the MDA class

The variance σ_{kl}^2 represents the contribution of the partial process y_{kl} to the total variance of y_k. It depends on the magnitude of the direct pathway linking y_l to y_k and on the magnitude of any indirect pathway linking y_l to y_k through the mediation of one (or more) different signals. Therefore, σ_{kl}^2 is an index of the importance of the causal (both direct and indirect) relationship from y_l to y_k in producing the overall variance of y_k. The larger this index, the more important the causal link from y_l to y_k. The variance σ_{kl}^2 depends on the magnitude of the variance of y_k, σ_k^2, according to Eq. (9), and on the variance of w_l, λ_l^2, according to Eq. (8). Therefore, we define

$$\chi_{kl}^2=\frac{\sigma_{kl}^2}{\sigma_k^2} \tag{10}$$

to normalize for the dependence of σ_{kl}^2 on σ_k^2 and

$$\eta_{kl}^2=\frac{\chi_{kl}^2}{\lambda_l^2} \tag{11}$$

to normalize for the dependence of χ_{kl}^2 on λ_l^2. This normalization can be helpful to compare results obtained from model structures characterized by significantly different goodness of fit.

The indexes χ_{kl}^2 and η_{kl}^2 can be customized by imposing $A_{il}(z)=0$ with $i=1,\ ..,\ M$ with $i\neq k$ to give an indication of the importance of the causal coupling from y_l to y_k due to the direct link from y_l to y_k and, conversely, by imposing only $A_{kl}(z)=0$ to give an indication of the importance of the causal coupling from y_l to y_k due to any connection linking y_l to y_k as a result of the mediation of one (or more) y_i with $i\neq k\neq l$.

2.4. Application to cardiovascular regulation

We exploited this approach to assess the relevance of the causal relationship from SAP to RR series along baroreflex and from R to RR series along the cardiopulmonary pathway. The series $RR=\{RR(i),\ i=1,\ldots,\ N\}$, $SAP=\{SAP(i),\ i=1,\ldots,\ N\}$ and $R=\{R(i),\ i=1,\ldots,\ N\}$ were first demeaned and, then, divided by the standard deviation, thus obtaining rr, sap and r series with zero mean and unit variance. The joint process $y=|y_1\ y_2\ y_3|'$ with $y_1=$rr, $y_2=$sap and $y_3=r$ was described according to OLMDA and CLMDA models originally proposed in Refs. [5] and [15], respectively. The OLMDA model [5] describes the interactions among rr, sap and r by setting $A_{21}(z)=0$, $A_{23}(z)=0$, $A_{31}(z)=0$, $A_{32}(z)=0$ in $A(z)$ and $D_2(z)=0$, $D_3(z)=0$ in $D(z)$. The CLMDA model [15] describes the interactions among rr, sap and r by setting $A_{31}(z)=0$ and $A_{32}(z)=0$ in $A(z)$ and $D_3(z)=0$ in $D(z)$. Accordingly, in the case of OLMDA model

$$y_{12}(i)=\frac{A_{12}}{(1-A_{11})(1-A_{22})}w_2(i) \tag{12}$$

and

$$y_{13}(i)=\frac{A_{13}}{(1-A_{11})(1-A_{33})}w_3(i). \tag{13}$$

Conversely, in the case of CLMDA model

$$y_{12}(i)=\frac{A_{12}}{\Delta_{loop}(1-D_2)}w_2(i) \tag{14}$$

and

$$y_{13}(i)=\frac{A_{12}A_{23}+A_{13}(1-A_{22})}{\Delta_{loop}(1-A_{33})}w_3(i) \tag{15}$$

with $\Delta_{loop}=(1-A_{11})(1-A_{22})-A_{12}A_{21}$.

3. Experimental protocol and data analysis

3.1. Data recordings

We studied 19 healthy humans (aged from 21 to 48, median=30; 11 females and 8 males). ECG (lead II), continuous arterial pressure (Finometer MIDI, Finapres Medical Systems,