Comparing Model-Free and Model-Based Transfer Entropy Estimators in Cardiovascular Variability

Alessandro Montalto[1], Daniele Marinazzo[1], Dimitris Kugiumtzis[2], Giandomenico Nollo[3], Luca Faes[3]

[1] Gent University, Gent, Belgium
[2] University of Trento, Trento, Italy
[3] Aristotle University of Thessaloniki, Thessaloniki, Greece

Abstract

Information flow between heart period (T), systolic pressure (S) and respiration (R) variability in a head-up tilt (HUT) protocol is assessed by transfer entropy (TE). Two estimates of TE are compared: the model-based (MB) approach using linear regression under the Gaussian assumption, and the model-free (MF) approach combining binning estimates of entropy and non-uniform delay embedding. The approaches were applied to 300-beats series of T, S, R measured in the supine (su) and upright (up) positions during HUT. Both MB and MF approaches detected a unidirectional information transfer from R to T and from R to S, and a significant decrease of the TE from R to T, as well as a significant increase of the TE from S to T, moving from su to up. For the MF approach, these trends were supported by the statistical test for TE significance. These results suggest that TE estimated from T, S and R variability can successfully describe the physiological mechanisms involved in the short term cardiovascular and cardiorespiratory regulation during HUT.

1. Introduction

In the last years, a variety of time series analysis methods have been proposed to quantify cardiovascular, cardiopulmonary and vasculo-pulmonary interactions through the study of simultaneously measured heart period (HP), systolic arterial pressure (SAP), and respiratory flow (RF) spontaneous variability [1]. Recent developments aimed to infer the causal direction between HP, SAP and RF that would give some insight onto the interaction mechanism of the three systems. In this context, one of the most promising tools for causality analysis is the transfer entropy (TE) [2], an increasingly used measure of information flow between physiological time series. The TE has a solid foundation in information theory and, in principle, is sensitive to both linear and nonlinear interactions between time series. In practical applications where only time series of finite length are available, the TE is commonly estimated through a linear model-based (MB) approach exploiting the close relation with Granger causality that holds under the assumption of Gaussianity [3]. Only recently, nonlinear model-free (MF) estimation approaches that favor the empirical estimation of information-theoretic measures of causality related to the TE have been proposed [4, 5]. In this study, we compare MB and MF approaches as regards the detection of information transfer in short-term cardiovascular and cardiorespiratory variability. To this end, we considered HP, SAP and RF series measured from healthy subjects during a head-up tilt test protocol, and assessed in the supine and upright positions the interactions between the series resulting from MB and MF computation of TE. MB and MF approaches were compared as to their capability to characterize, in terms of TE values and statistical significance, the response of known regulation mechanisms to the orthostatic stimulus provided by tilt.

2. Methods

Let us consider a physical system composed of 3 interacting dynamical subsystems, and suppose that we are interested in evaluating the information flow from the driving system X to the response system Y, in the presence of the remaining system Z. The systems can be seen as stochastic processes and let x_n, y_n, z_n denote the observations of the stochastic variables of the respective processes at time n. Moreover, let $X_n^- = [x_{n-1}, x_{n-2}, \ldots]$, $Y_n^- = [y_{n-1}, y_{n-2}, \ldots]$, $Z_n^- = [z_{n-1}, z_{n-2}, \ldots]$, be the vector variables describing the past states of the systems up to time $n-1$. Then, the TE from X to Y conditioned to Z can be defined as the difference between two conditional entropy (CE) terms, specifically the entropy of the present state of the response conditioned to the past states of all systems except the driver, and the entropy of the present state of the response conditioned to the past states of all systems including the driver [6]:

$$\mathrm{TE}_{X\to Y|Z} = H(y_n|Y_n^-, Z_n^-) - H(y_n|X_n^-, Y_n^-, Z_n^-) \quad (1)$$

Each CE term in (1) is in turn defined as the difference between two Shannon entropies, i.e.,

$$H(y_n|Y_n^-, Z_n^-) = H(y_n, Y_n^-, Z_n^-) - H(Y_n^-, Z_n^-)$$

and the same for $H(y_n|X_n^-, Y_n^-, Z_n^-)$, where the entropy of any vector variable **a** is defined as $H(\mathbf{a}) = -\sum p(\mathbf{a}) \ln p(\mathbf{a})$. Estimation of the TE relies essentially on determining a suitable estimator for the probability functions $p(\cdot)$ involved in the entropy computations, and on devising approaches for setting an appropriate number of past components to be used in place of the infinite-dimensional vectors X_n^-, Y_n^-, and Z_n^-. Two alternative estimation approaches are described in the following.

2.1. Linear model-based approach

The model-based (MB) approach works under the assumption that the multivariate process $\{x, y, z\}$ has a joint Gaussian distribution. This assumption allows to work with well-known expressions for the probability density functions. Under this assumption, the CE terms defining the TE in (1) are expressed by means of linear regressions involving the p past states of the systems collected in the vector variables, i.e. $X_n^p = [x_{n-1}, \ldots, x_{n-p}]$ for X, $Y_n^p = [y_{n-1}, \ldots, y_{n-p}]$ for Y and $Z_n^p = [Z_{n-1}, \ldots, Z_{n-p}]$ for Z [7]. Specifically, an unrestricted regression of y_n on the $Mp \times 1$ vector $V^{(u)} = [X_n^p \, Y_n^p \, Z_n^p]^T$, and a restricted regression of y_n on the $(M-1)p \times 1$ vector $V^{(r)} = [Y_n^p \, Z_n^p]^T$, are defined as follows:

$$y_n = A^{(u)} V^{(u)} + \varepsilon_n^{(u)} \tag{2}$$

$$y_n = A^{(r)} V^{(r)} + \varepsilon_n^{(r)} \tag{3}$$

where $A^{(u)}$ and $A^{(r)}$ are vectors of linear regression coefficients with dimension $1 \times Mp$ and $1 \times (M-1)p$, respectively. The terms $\varepsilon_n^{(u)}$ and $\varepsilon_n^{(r)}$ are scalar white noise residuals with variance $\sigma^{(u)}$ and $\sigma^{(r)}$. Under the Gaussian assumption, it has been demonstrated [3] that the entropy of y_n conditioned to the unrestricted or restricted regression vectors is, respectively, $H(y_n|V^{(u)}) = 0.5(\log \sigma^{(u)} + 2\pi e)$ and $H(y_n|V^{(r)}) = 0.5(\log \sigma^{(r)} + 2\pi e)$, from which it follows immediately the TE estimate:

$$\mathrm{TE}_{X \to Y|Z} = \frac{1}{2} \log \frac{\sigma^{(r)}}{\sigma^{(u)}} \tag{4}$$

In this study, the unrestricted and restricted regression models in (2) and (3) were estimated by the least-squares method, and the order p was selected by the Bayesian information criterion [8]. The statistical significance of the TE computed through the MB approach was assessed by the parametric F-test for the null hypothesis that the p coefficients of $A^{(u)}$ which weigh the driving variable X_n^p are all zero [9]. In our case, the test statistic is $F = ((RSS_r - RSS_u)/p)/(RSS_u/(N-Mp))$, where RSS_r and RSS_u are the residual sum of squares of the restricted and the unrestricted model, and N is the time series length. The TE is considered statistical significant if F is larger than the critical value of the Fisher distribution with $(p, N-p)$ degrees of freedom at the significance level $\alpha = 0.05$.

2.2. Nonlinear model-free approach

The model-free (MF) approach does not make any prior assumption about the probability distributions of the observed multivariate process, and is based on a sequential conditioning procedure for selecting the past system components to be used in CE estimation which are more relevant to the description of the response variable [4, 5]. Specifically, a conditioning vector V_n is built progressively from the past L observations of the systems forming the set $\Omega = \{x_{n-1}, \ldots, x_{n-L}, y_{n-1}, \ldots, y_{n-L}, z_{n-1}, \ldots, z_{n-L}\}$ ($L = 10$ in this study). Starting with an empty conditioning vector $V_n^{(0)} = \emptyset$, at each step $k \geq 1$ the conditioning vector is $V_n^{(k)} = [w_n^{(k)} V_n^{(k-1)}]$ where $w_n^{(k)}$ minimizes the CE $H(y_n|w_n, V_n^{(k-1)})$ for $w_n \in \Omega - V_n^{(k-1)}$. The selection of components is terminated when an irrelevant component is selected, i.e., when the decrease in the CE brought by the component is not statistically significant. To assess its statistical significance, the CE decrease $I(y_n, w_n^{(k)}|V_n^{(k-1)}) = H(y_n|V_n^{(k-1)}) - H(y_n|w_n^{(k)}, V_n^{(k-1)})$ is tested against its null distribution formed by the values of CE decrease computed on replications of $w_n^{(k)}$, where at each replication the time ordered samples of $w_n^{(k)}$ are time-shifted by a randomly selected lag (larger than 20, set to exclude autocorrelation effects). If the original CE decrease is above the $100(1-\alpha)^{\mathrm{th}}$ percentile of its null distribution (where $\alpha = 0.05$), $w_n^{(k)}$ is included in the conditioning vector, otherwise it is discarded and the procedure terminates including $k-1$ components in the final vector $V_n = V_n^{(k-1)}$. After termination of the sequential conditioning procedure, the conditioning vector is composed as $V_n = [V_n^X, V_n^Y, V_n^Z]$, where V_n^X, V_n^Y, and V_n^Z denote the components of V_n belonging respectively to X, Y, and Z. Then the TE is estimated as:

$$\mathrm{TE}_{X \to Y|Z} = H(y_n|V_n^Y, V_n^Z) - H(y_n|V_n) \tag{5}$$

In this study, practical estimation of the CE from time series data was performed using the classical histogram-based method, that consists in coarse-graining the observed dynamics using Q quantization levels ($Q = 6$ in this study), and computing entropies by approximating probability distributions with the frequencies of occurrence of the quantized values [4]. The statistical significance of the TE computed through the MF approach resulted implicitly from the randomization test used to test the significance of each added component. In particular, if at least one component from X was selected during the procedure (i.e., when $V_n^X \neq \emptyset$) the TE was strictly positive and was taken as statistically significant; if, on the contrary, no components from X were selected, $V_n^X = \emptyset$, $\mathrm{TE}_{X \to Y|Z} = 0$ and the TE was taken as non significant.

3. Protocol and data analysis

We considered 15 young healthy subjects (25.7 ± 2.7 years old) undergoing a standard head-up tilt testing protocol [4]. The acquired signals were the surface ECG, the finger arterial blood pressure, and the respiratory nasal flow, measured at 1 kHz sampling rate for 15 min in the resting supine position, and 15 further min in the 60° position after passive head-up tilting of the bed table.

The beat-to-beat variability series of HP, $T(n)$, SAP, $S(n)$, and RF, $R(n)$, were offline measured respectively as the temporal interval occurring between the n-th and the $(n+1)$-th R waves of the ECG, as the local maximum of the pressure signal inside the n-th cardiac interval, and as the sample of the respiratory tracing taken at the onset of the n-th cardiac interval. This measurement convention allows instantaneous (i.e., non-delayed) effects from $S(n)$ to $T(n)$, as well as from $R(n)$ to $S(n)$ and to $T(n)$. The subsequent data analysis was performed on stationary windows of 300 beats taken in supine (*su*) and upright (*up*) body positions; inside these windows, the series were normalized to zero mean and unit variance, obtaining the dimensionless series $r(n)$, $s(n)$, $t(n)$. For each subject, the TE between each pair of series was estimated in the two body positions using MB and MF approaches.

Statistical analysis was performed comparing the distributions over subjects of each measure obtained in the *su* and *up* conditions by means of the Wilcoxon signed rank test for paired data; the same test was used to assess the statistical significance of the TE estimated along the two directions of each possible pairwise interaction. The number of subjects for which the null hypothesis of zero TE was rejected was also counted for each causal direction in the two conditions.

4. Results and discussion

Figures 1 and 2 report the distributions of TE computed respectively using the MB and the MF approach, and assessed for all the directions of interaction between RF, SAP and HP series in the supine and upright positions. Three main results were obtained using both the MB and the MF approaches: (i) the existence of almost unidirectional interactions from RF to SAP and to HP, documented by the markedly higher magnitude of $TE_{R \to S|T}$ and $TE_{R \to T|S}$, respectively compared with $TE_{S \to R|T}$ and $TE_{T \to R|S}$, in both *su* and *up* conditions; (ii) the weakening of the information transfer from RF to HP with the tilt transition, documented by the statistically significant decrease of $TE_{R \to T|S}$ moving from *su* to *up*; (iii) the enhancement of the information transfer from SAP to HP with the tilt transition, documented by the statistically significant increase of $TE_{S \to T|R}$ moving from *su* to *up*. These results document the capability of TE to reflect expected cardiovascular and cardiorespiratory physiological mechanisms. In particular, the existence of an unidirectional information flow from respiration to the two cardiovascular variables confirms previous studies suggesting that the respiratory activity acts as an exogenous disturbance over cardiovascular regulation, i.e., affecting arterial pressure and heart rate variability without being affected by them [10]. The weaker flow from RF to HP after tilt confirms that central effects of the respiratory drive on the cardiac vagal motor neurons, evident in the supine position, are blunted after tilt as a consequence of the vagal withdrawal that de-

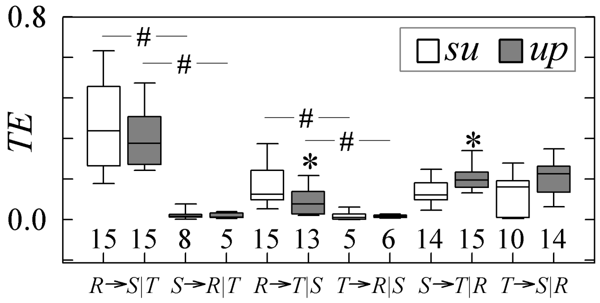

Figure 1. Distribution of TE estimated by the MB approach. Values are median, 25-75 percentile (box) and 5-95 percentile (whiskers) over 15 subjects considered for each causal direction in the *su* and *up* body positions. The number of subjects showing statistically significant TE is reported below each distribution. $*$ stands for $p < 0.05$ for su vs. up; # stands for $p < 0.05$ for $\mathrm{TE}_{X \to Y|Z}$ vs. $\mathrm{TE}_{Y \to X|Z}$, where X, Y, Z can be any of R, S, T.

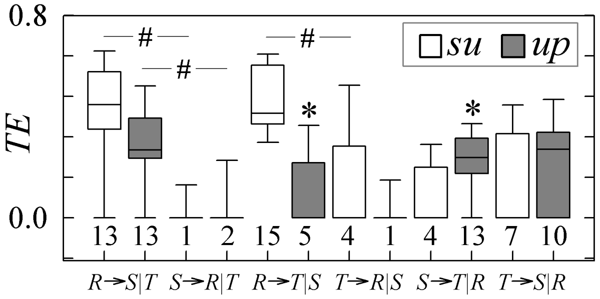

Figure 2. Distribution of TE estimated by the MF approach. Symbols are as in Fig. 1.

creases the amplitude of RF-related oscillations in the HP [11]; this effect was evidenced more clearly by the MF-based TE estimate $TE_{R \to T|S}$, which after tilt was no more significantly higher than $TE_{T \to R|S}$ (Fig. 2; this was not observed for the MB-based TE of Fig. 1). On the other hand, the stronger flow from SAP to HP reflects the well-studied involvement of the cardiac baroreflex in controlling the heart rate consequent to the tilt-induced activation of the sympathetic nervous system [11].

While MB and MF estimation of information transfer produced similar results in terms of the TE magnitude, some differences were evidenced when the statistical significance of the estimates was considered. First, the null hypothesis of zero TE was rejected in more subjects using the F-test associated with the MB analysis than when using the randomization test associated with the MF analysis. Moreover, the trends in the TE magnitude leading to the results discussed above were supported by similar trends of the statistical significance only when the TE was estimated through the MF approach. For instance, the tilt-induced decrease of $TE_{R \to T|S}$ and increase of $TE_{S \to T|R}$ were not accompanied by substantial variations of the number of subjects showing significant TE when the MB approach was used (see Fig. 1). On the contrary, using the MF approach this number was significantly decreased (from 15 to 5) along the $R \to T$ direction, and significantly increased (from 4 to 13) along the $S \to T$ direction (Fig. 2). Also the unidirectional nature of the coupling between RF and SAP was evidenced more clearly, in terms of statistical significance of TE, by the MF than the MB approach. Indeed, the MB approach detected a non-negligible number of subjects with significant coupling from SAP to HP (8 and 5 during *su* and *up*), while this number was reduced to 1 and 2 during *su* and *up* using the MF approach.

5. Conclusion

The present study showed that the main mechanisms of cardiovascular and cardiorespiratory regulation operating in the resting supine position and in the upright position after head-up tilt can be characterized from the structure of interactions between RF, SAP and HP variability, assessed in terms of TE magnitude, both using a novel MF approach and a more standard MB approach. Moreover, these mechanisms can be better elicited, when looking at the statistical significance of the estimated TE, by means of the sequential conditioning procedure adopted by the MF approach, than with the linear regression statistics adopted by the MB approach.

The partial overlap in the results obtained from the application of linear MB and nonlinear MF approaches could suggest that the information flow among RF, SAP and HP variability series is governed, at least in the considered head-up tilt test protocol, mainly by linear interaction mechanisms. Future studies will explore further this issue by extending the comparison presented here to experimental protocols and/or pathological conditions which are able to evoke nonlinear interactions between cardiovascular and cardiorespiratory variables.

Acknowledgements

This work is supported by: the Belgian Science Policy (IUAP VII project CEREBNET P7 11); the University of Gent (Special Research Funds for visiting researchers)

References

[1] Schulz S, Adochiei FC, Edu IR, Schroeder R, Costin H, Bär KJ, Voss A. Cardiovascular and cardiorespiratory coupling analyses: a review. Philosophical Transactions of the Royal Society A Mathematical Physical and Engineering Sciences 2013;371(1997).

[2] Schreiber T. Measuring information transfer. Physical review letters 2000;85(2):461.

[3] Barnett L, Barrett A, Seth A. Granger causality and transfer entropy are equivalent for gaussian variables. Physical review letters 2009;103(23):238701.

[4] Faes L, Nollo G, Porta A. Information domain approach to the investigation of cardio-vascular, cardio-pulmonary and vasculo-pulmonary causal couplings. Frontiers in Physiology 2011;2(80).

[5] Kugiumtzis D. Direct-coupling information measure from nonuniform embedding. Phys Rev E Jun 2013;87:062918.

[6] Faes L, Nollo G, Porta A. Compensated transfer entropy as a tool for reliably estimating information transfer in physiological time series. Entropy 2013;15(1):198–219.

[7] Barrett AB, Barnett L, Seth AK. Multivariate granger causality and generalized variance. Physical Review E 2010;81(4):041907.

[8] Schwarz G. Estimating the dimension of a model. The annals of statistics 1978;6(2):461–464.

[9] Brandt PT. Multiple time series models. Number 148. Sage, 2007.

[10] Cohen MA, Taylor JA. Short-term cardiovascular oscillations in man: measuring and modelling the physiologies. The Journal of physiology 2002;542(3):669–683.

[11] Cooke WH, Hoag JB, Crossman AA, Kuusela TA, Tahvanainen KU, Eckberg DL. Human responses to upright tilt: a window on central autonomic integration. The Journal of Physiology 1999;517(2):617–628.

Address for correspondence:

Alessandro Montalto
Data Analysis Department, Henri Dunantlaan 1, Gent 9000 Belgium
alessandro.montalto@ugent.be