Comparison of Linear Model-Based and Nonlinear Model-Free Directional Coupling Measures: Analysis of Cardiovascular and Cardiorespiratory Interactions at Rest and During Physiological Stress

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Abstract. In this work, we present an investigation of the cardiovascular and cardiorespiratory regulatory mechanisms involved during stress responses using the information-theoretic measure of transfer entropy (TE). The analysis was carried out on the series of heart period, systolic arterial pressure and respiration measured from 61 young healthy subjects, at rest and during orthostatic and mental stress states, by using both a linear model-based and a nonlinear model-free approaches to compute TE. The results reveal mostly significant correlations for the measures of TE estimated with the two approaches, particularly when assessing the influence of respiration on cardiovascular activity during mental stress and the influence of vascular dynamics on cardiac activity during tilt. Therefore, our findings suggest that the simpler linear parametric approach is suitable in conditions predominantly regulated by sympathetic nervous system or by the withdrawal of the parasympathetic system.

Keywords: stress, time series analysis, transfer entropy (TE), short term cardiovascular variability

1 Introduction

The human body is a complex network of interdependent systems and control mechanisms that work together to maintain homeostasis [9]. However, currently there is not well-established analytical methodologies, computational tools, and theoretical frameworks that can effectively extract and quantify the interactions between physiological systems from continuous streams of data. The dynamics of these interactions are complex and occur across multiple scales, which presents significant challenges in identifying and measuring these networks. While traditional methods such as cross-correlation and coherence have been proposed to investigate the relationships between two systems [21], there is growing interest in the use of the framework of information-theory to better understand the complex interplay between organ systems [12].

Turing's theory suggests that any type of information carried by a system can be broken down into three distinct components: information storage, information transfer, and information modification [24]. The measurement of information transfer is commonly achieved through the use of transfer entropy (TE), which calculates the directional effects between two processes by analyzing the information provided by a putative driver system above and beyond the predictability given by the target itself. Related to the concept of Granger causality [25], the TE measure has been shown to be a valuable tool for assessing information transfer between interconnected systems in various contexts [4, 20, 1, 25, 10].

A main challenge regards the practical estimation of the TE from short realizations of physiological processes [6]. Over the years, various methodologies have been proposed in the literature for estimating transfer entropy, which can be classified as either model-based or model-free. Both approaches rely on the assumption of stationarity, but in the former case, the probability density function used to calculate TE can be fully described by a specific model, while in the latter case, it is directly estimated from the data [17]. When dealing with a linear model, the model-based approach requires less data and computational resources and should be chosen when only short datasets are available. However, the model-free method is crucial for revealing the intricate structure of physiological connections supported by nonlinear feedback interactions [5, 7].

In this context, the present study proposes an analysis of the information transfer assessed from short term series reflecting the spontaneous variability of heart period, systolic arterial pressure and respiration in healthy subjects undergoing a protocol including orthostatic and mental stress. In particular, the main goal is to compare two different estimation approaches, i.e., a simpler linear parametric and a more sophisticated non linear k-nearest neighbors method.

2 Material and methods

2.1 Subjects, experimental protocol and time series extraction

In this study, an historical database previously employed to study cardiovascular variability was used [13, 10]. In detail, electrocardiographic (ECG; CardioFax ECG-9620, NihonKohden, Japan), arterial blood pressure (ABP; Finometer Pro, FMS, Netherlands) and respiratory volume (RespiTrace, NIMS, USA) signals acquired at a sampling rate of 1 kHz on a group of sixty-one healthy young subjects (37 females, 17.5±2.4 years old) were analysed [10]. The experimental protocol was approved by the Ethical Committee of the Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia, and consisted of (i) a supine resting state

(REST, 15 minutes), (ii) an orthostatic stress phase (HUT, 8 minutes) during which an head-up tilt test was performed tilting a motorized table to 45 degrees, and (iii) a mental arithmetic stress phase (MA, 6 minutes) during which subjects were instructed to perform a series of additions with three-digit numbers until a one-digit number was reached, and to indicate whether the result was odd or even. Both HUT and MA phases were followed by 10 minutes of supine recovery, which were not considered in our analysis.

From these signals, the heart periods (RR) time series was measured as the time differences between two consecutive ECG R peaks, the systolic arterial pressure (SAP) time series was obtained by identifying the maximum values of the ABP signal within each detected heart period, while the respiratory (RESP) one by sampling the respiratory volume signal at each detected ECG R peak. Time series windows of 300 samples were extracted for each subject and protocol phase discarding any transient periods, as detailed in [10] to which we refer the reader for further information about data acquisition and experimental protocol.

Before computing the directional coupling measures, all time series were pre-processed applying a zero phase high-pass autoregressive filter, by removing and interpolating samples differing more than three times standard deviation from the mean value, and normalizing the series to zero mean and unit variance.

2.2 Directional coupling measure

Given a bivariate system $\mathcal{S} = \{\mathcal{X}, \mathcal{Y}\}$, its joint and dynamical evolution can be described looking at the stochastic processes X and Y. Let us indicate as X_n, Y_n the scalar random variables describing the current state of X and Y, as $\boldsymbol{X}_n^k = [X_{n-1} \cdots X_{n-k}]^\top \in \mathcal{R}^{k\times 1}$, $\boldsymbol{Y}_n^k = [Y_{n-1} \cdots Y_{n-k}]^\top \in \mathcal{R}^{k\times 1}$ the vector variables sampling the two processes over the past k lags, and as $\boldsymbol{X}_n^- = \lim_{k\to\infty} \boldsymbol{X}_n^k$, $\boldsymbol{Y}_n^- = \lim_{k\to\infty} \boldsymbol{Y}_n^k$ the infinite-dimensional variables sampling X and Y over their whole past history. Considering X and Y respectively as driver and target processes, the information transferred from X to Y is defined as [20]

$$TE_{X\to Y} = I(Y_n; \boldsymbol{X}_n^- | \boldsymbol{Y}_n^-) = H(Y_n|\boldsymbol{Y}_n^-) - H(Y_n|\boldsymbol{X}_n^-, \boldsymbol{Y}_n^-), \tag{1}$$

where $I(\cdot;\cdot|\cdot)$ and $H(\cdot|\cdot)$ denote conditional mutual information and conditional entropy, respectively. The TE measure reflects the directional influence of the driver process X on the target one Y; in absence of any interaction between the dynamical systems $\mathcal{X}$ and $\mathcal{Y}$, the whole predictive information about the target is stored in its own past history and the information transferred from X to Y is equal to zero.

Given a pair of time series $\{x, y\}$ representing a realization of the driver and target processes, TE estimates can be obtained either from the parametric representation of the bivariate system dynamics, using a model-based (MB) approach, or directly from the probability density distribution of data, using a model-free (MF) approach. In the follow, the two approaches are described considering two joint Markov processes of order p, whose past processes can be approximated to p lags, i.e., $\boldsymbol{X}_n^- \approx \boldsymbol{X}_n^p \in \mathcal{R}^{p\times 1}$ and $\boldsymbol{Y}_n^- \approx \boldsymbol{Y}_n^p \in \mathcal{R}^{p\times 1}$.

Linear parametric method. Under the hypothesis of gaussianity of the investigated stochastic processes, the current state of the target process Y_n can be described in terms of the past history of the driver process $\boldsymbol{X}_n^p$ by using the autoregressive (AR) model, i.e., $Y_n = \boldsymbol{A}\boldsymbol{Y}_n^p + U_n$, and of both the driver and the target processes $[\boldsymbol{X}_n^p, \boldsymbol{Y}_n^p]$ via the cross-AR (ARX) model, i.e., $Y_n = \boldsymbol{A}\boldsymbol{Y}_n^p + \boldsymbol{B}\boldsymbol{X}_n^p + W_n$, where $\boldsymbol{A}$ and $\boldsymbol{B}$ are the vectors of the models coefficients belonging to the space $\mathcal{R}^{1\times p}$, while U_n and W_n are two zero-mean white Gaussian noises of variance σ_U^2 and σ_W^2, respectively. In this framework, the linear estimate (lin) of the information transferred from the X process to Y one is expressed as:

$$TE_{lin} = \frac{1}{2} \ln \frac{\sigma_U^2}{\sigma_W^2}, \tag{2}$$

where the variance of the prediction error of the AR and ARX models, i.e., σ_U^2 and σ_W^2, can be obtained through the identification of the two models via the Ordinary Least Square (OLS) method.

Nonlinear model-free method. The model-free estimation of the information transferred from X to Y was performed using the Kraskov-Stögbauer-Grassberger formulation of the k-nearest neighbors (knn) approach [11]. Based on a neighbour search of samples in the highest dimensional space and then on range searches in the projected lower dimensional spaces for estimating the probability data distribution, TE is computed as [4]:

$$TE_{knn} = \psi(k) + \langle \psi(N_{\boldsymbol{Y}_n^p} + 1) - \psi(N_{Y_n \boldsymbol{Y}_n^p} + 1) - \psi(N_{\boldsymbol{X}_n^p \boldsymbol{Y}_n^p} + 1) \rangle, \tag{3}$$

where $\psi(\cdot)$ is the digamma function, k is the number of neighbors, $\epsilon_{n,k}$ is twice the distance from each point to its k-th neighbor in the higher dimensional space (i.e., $[Y_n \boldsymbol{Y}_n^p \boldsymbol{X}_n^p]$), and $N_{\boldsymbol{Z}}$ is the number of neighbors whose distance in the $\boldsymbol{Z}$ space is lower than $\epsilon_{n,k}/2$.

2.3 Data and statistical analysis

The two formulations of transfer entropy described in Sect. 2.2 were used to compute the information transferred from X to Y, being $X = RESP$ and $Y = RR$ when considering the cardiorespiratory system, $X = RESP$ and $Y = SAP$ when considering vascular and respiratory systems, and $X = SAP$ and $Y = RR$ when considering the cardiovascular system.

The MB approach was implemented using the Bayesian Information Criterion (BIC) to set the optimal orders p for AR and ARX models (with the maximum order was fixed to 10) [22], while the MF approach was implemented through a non-uniform embedding technique which minimises the conditional mutual information [4]. According to previous works [4, 15], the number of neighbors k was fixed to 10, while a maximum lag of 10 and 100 random shuffling surrogates have been used to establish the exit criterion.

Non-parametric statistical tests were used for each estimator to identify differences in the TE among physiological states, since the assumption of gaussianity of the transfer entropy distributions was rejected using the Anderson-Darling test. Specifically, the Kruskal-Wallis analysis of variance followed by the Wilcoxon post-hoc signed rank test with Bonferroni correction (n=3) was applied. Moreover, the statistical significance of the estimated TE value was assessed for each subject, condition and estimator using 100 surrogates generated randomly shifting the target series over time (minimum shift of 20 lags). The McNemar test for paired proportions was then carried out to determine significant variations between conditions of the number of subjects showing significant TE.

The Pearson product-moment correlation coefficient r was computed between the TE measures computed through MB and MF approaches for each direction and protocol phase, testing the null hypothesis of absence of linear relation between the two estimates of information transfer.

For all statistical tests, the significance level was set at 0.05.

Data processing and analysis were performed using MATLAB 2020a (The Mathworks, Inc.); the functions used to estimate transfer entropy measures are collected in the ITS toolbox (http://www.lucafaes.net/its.html).

3 Results and discussion

Figure 1 reports the distributions across subjects of the information transfer from RESP to RR and SAP, and from SAP to RR, during the three physiological states (i.e., rest, orthostatic and mental stress). A decrease of the influence of the ventilation activity on both cardiac (Fig. 1a) and vascular (Fig. 1b) dynamics is reported during both physical (in pink) and mental stress (in green) states in compared with resting (in light blue). This decrease is associated with a reduction in the activity of the parasympathetic nervous system (PNS) [2, 19] evoked by stress, which leads to a weakened respiratory sinus arrhythmia (RSA) mechanism [8, 10], as well as a decrease in the mechanical effect of ventilation during mental arithmetic [23]. Moreover, the causal influence of SAP on RR increased significantly during head-up tilt, but not during mental arithmetics, compared to the resting condition (Fig. 1c). This results is related to the fact that tilting activates the feedback mechanism in the closed-loop cardiovascular regulatory system [2]. Previous studies have demonstrated that ventilation activity is a primary source of cardiovascular variability related to stress [10, 21], as here evidenced by the results of both the surrogate data analysis (Figs. 1d-f), with the significance of $TE_{SAP \rightarrow RR}$ being lower than the other two measures, and the McNemar test.

The reported differences are detected statistically significant using both estimators, except for the decrease in directional coupling from RESP to RR during tilt, which is only detected by the nonlinear estimator (Fig. 1a). The agreement between linear and knn estimates of the TE is corroborated by the correlation analysis results presented in Figure 2.

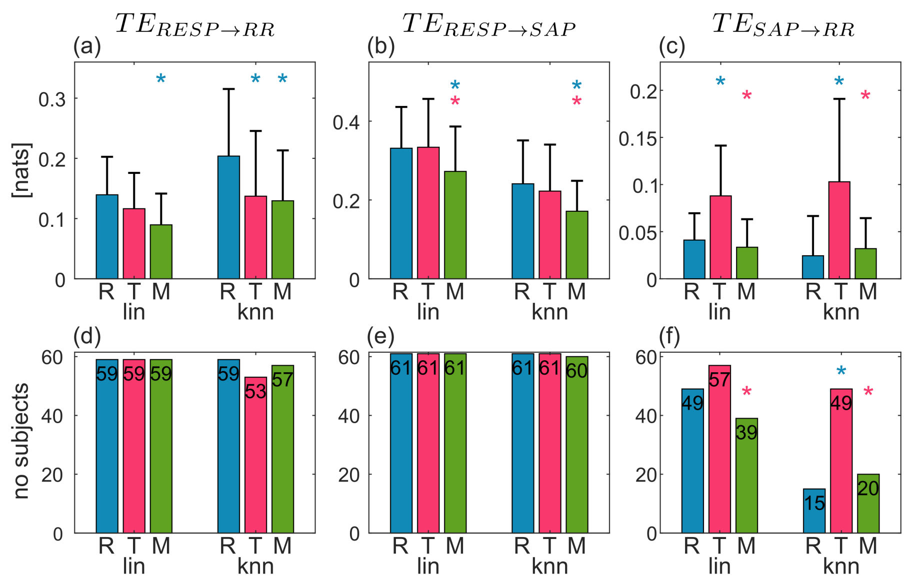

Fig. 1. Error bar graphs of TE computed (**a**) from RESP to RR, (**b**) from RESP to SAP and (**c**) from SAP to RR for all subjects during resting (R, light blue), orthostatic stress (T, pink) and mental stress (M, green) states with both linear (lin) and nonlinear (knn) estimators. In panels **a-b-c**, the asterisks indicate a statistically significant difference comparing the given phase to the one corresponding to the asterisk colour according to Wilcoxon test with Bonferroni correction (n=3). The Kruskal-Wallis analysis results are not reported in the figure, being always statistically significant. The number of subjects with statistically significant TE according to surrogate analysis are reported in the bar plots in panels (**d**), (**e**) and (**f**) and the asterisks indicate a statistically significant difference comparing conditions according to McNemar test.

The correlation between the parametric and the model-free estimates of $TE_{RESP \to RR}$ is low during REST (Fig. 2a) and increases with stress, with the maximum value reported during MA with the highest significance as well (Fig. 2g). This finding can be explained by the linearization of cardiorespiratory dynamics during stress, as nonlinearities are known to be common in healthy individuals in situations with a dominant vagal modulation [17, 7, 3]. When looking at the influence of the respiratory activity to the vascular system, we may infer that nonlinear dynamics are predominant during HUT, as evidenced by a lower correlation of the measure $TE_{RESP \to SAP}$ during tilting (Fig. 2e) compared to the other two conditions (Figs. 2b,h). As reported in literature, this can be related to the nonlinear influence of breathing activity on cardiac baroreflex and venous return mechanisms [18]. On the other hand, when investigating the cardiovascular regulatory mechanism, a nearly constant correlation between parametric and model-free estimates is observed throughout the various phases of the protocol (Figs. 2c,f,i). Indeed, previous studies have provided evidences that sympathetic activity predominantly regulates SAP dynamics and that such activity is not reflected in nonlinear dynamics [16].

As regard the comparison of the two estimation approaches in discriminating the two stress conditions, similar findings have been found on heart rate variability during tilt using the univariate measure of conditional entropy [17]. Furthermore, our results are supported by previous researches on the interaction between different physiological systems during physical or mental stress,

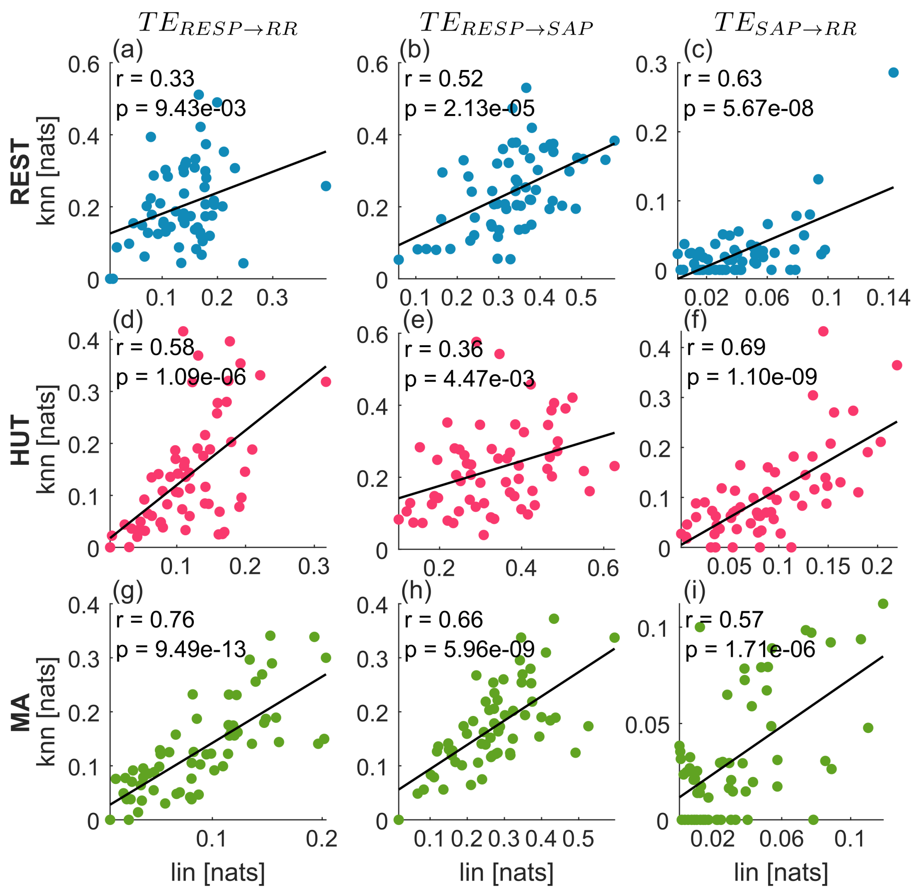

Fig. 2. Scatter plots of pair of linear (lin) and nonlinear (knn) estimates of TE measures computed for each subject in a given experimental condition (REST in light blue, HUT in pink and MA in green). The values of the information transferred from RESP to RR (left column: **a**,**d**,**g** panels), from RESP to SAP (middle column: **b**,**e**,**h** panels), and from SAP to RR (right column: **c**,**f**,**i**) are reported. In each subplot, the solid line depicts the regression line between the two estimators, and the correlation value r as well as its significance level p are reported at the top left of each subplot.

which reported comparable trends in the different directional measures using both linear [10] and nonlinear [4] approaches.

4 Conclusion

Our findings confirm that respiratory activity has a reduced influence on cardiovascular activity during stress, owing to the decrease in parasympathetic activity and the increase in the sympathetic one; the latter determines an increase in baroreflex activity during orthostatic stress. The robustness of these results is corroborated by the fact that both model-based and model-free approaches for TE estimation perform similarly in discriminating between stressful and resting conditions. This is further supported by the significant correlation between the TE values obtained using the two approaches. Therefore, our findings support the adoption of the parametric approach for the investigation of physiological control mechanisms in healthy subjects undergoing tasks leading to the activation of the sympathetic system, given its simplicity compared to model-free ones.

Future research should explore the use of simpler and computationally faster model-free estimation methods, e.g. binning or permutation-based approaches [1], and compare their discriminative capability with that of the linear approach also on other databases, including in pathological conditions where nonlinear interaction dynamics are dominant [14].

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