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Assessing Transfer Entropy in cardiovascular and respiratory time series under long-range correlations*

Hélder Pinto[1], Riccardo Pernice[2], Celestino Amado[1], Maria Eduarda Silva[3]
Michal Javorka[4], Luca Faes[2], *Senior Member*, *IEEE* and Ana Paula Rocha[1], *Member*, *IEEE*

***Abstract*— Heart Period (H) results from the activity of several coexisting control mechanisms, involving Systolic Arterial Pressure (S) and Respiration (R), which operate across multiple time scales encompassing not only short-term dynamics but also long-range correlations. In this work, multiscale representation of Transfer Entropy (TE) and of its decomposition in the network of these three interacting processes is obtained by extending the multivariate approach based on linear parametric VAR models to the Vector AutoRegressive Fractionally Integrated (VARFI) framework for Gaussian processes. This approach allows to dissect the different contributions to cardiac dynamics accounting for the simultaneous presence of short and long term dynamics. The proposed method is first tested on simulations of a benchmark VARFI model and then applied to experimental data consisting of H, S and R time series measured in healthy subjects monitored at rest and during mental and postural stress. The results reveal that the proposed method can highlight the dependence of the information transfer on the balance between short-term and long-range correlations in coupled dynamical systems.**

I. INTRODUCTION

In the study of complex biomedical systems represented by multivariate stochastic processes, such as the cardiovascular and respiratory systems, an issue of great relevance is the description of the system dynamics spanning multiple temporal scales [1]. Recently, the quantification of multiscale complexity based on linear parametric models, incorporating autoregressive coefficients and fractional integration, encompassing short-term dynamics and long-range correlations, was extended to multivariate time series [2]. Reliable estimation of Transfer Entropy (TE) can be achieved at longer time scales only when long range correlations are properly modeled and, moreover, the latter have been demonstrated to influence the complexity of cardiovascular time series [3]. Within the Vector AutoRegressive Fractionally Integrated (VARFI) framework formalized for Gaussian processes, in this work we propose to estimate the TE, or equivalently Granger Causality, in the cardiovascular and respiratory systems. This allows to assess the information flow and the directed interactions accounting for the simultaneous presence of short-term dynamics (corresponding to high frequency oscillations) and long-range correlations (reflecting slower oscillations with lower frequencies).

The proposed approach, described in sections II, III, is firstly tested on simulations of a benchmark VARFI in section IV. Then, in section V, it is applied to experimental data consisting of heart period (H), systolic arterial pressure (S) and respiration (R) time series measured in healthy subjects monitored at rest and during mental and postural stress.

II. INFORMATION TRANSFER DECOMPOSITION

In the information-theoretic framework, the directed transfer of information between components of a network of interacting processes is assessed by the TE. Here, we consider H as the target process and S and R as the sources. The information transferred individually from S to H and from R to H is quantified by the individual TEs:

$$T_{S\to H} = I\left(H_n; S_n^- \mid H_n^-\right), \tag{1}$$

$$T_{R\to H} = I\left(H_n; R_n^- \mid H_n^-\right), \tag{2}$$

where $I(\because;\cdot|\cdot)$ denotes conditional mutual information, H_n denotes the present state of H, and H_n^-, S_n^- and R_n^- represent the past states of H, S and R, respectively. Moreover, the joint TE (JTE) quantifies the information transferred towards H from the sources R and S when they are taken together and is thus defined as [4]

$$T_{RS\to H} = I\left(H_n; S_n^-, R_n^- \mid H_n^-\right). \tag{3}$$

Generally, the JTE differs from the sum of the two individual TEs, since R and S typically interact with each other while they transfer information to H (as reflected by Interaction Transfer Entropy (ITE), $I_{RS\to H}$). Such an interaction is synergistic ($I_{RS\to H} > 0$) if the two sources transfer more information to the target when they are considered together than when they are considered individually, and is redundant ($I_{RS\to H} < 0$) in the opposite case. The Interaction Information Decomposition (IID) of the JTE is given by [4]:

$$T_{RS\to H} = T_{S\to H} + T_{R\to H} + I_{RS\to H}. \tag{4}$$

III. MULTISCALE IID OF VARFI PROCESSES

To describe both short-term dynamics and long-range correlations we represent the multivariate process $\mathbf{X} = [X_R, X_S, X_H]$ with a VARFI model [5]:

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[1]H. P., A. P. R., C.A. are with Faculdade de Ciências, Universidade do Porto & CMUP, Portugal aprocha@fc.up.pt

[2]R. P. and L. F. are with Department of Engineering, University of Palermo, Italy

[3]M. E. S. is with Faculdade de Economia, Universidade do Porto & CIDMA, Portugal

[4]M. J. is with Department of Physiology, Comenius University in Bratislava, Jessenius Faculty of Medicine & Biomedical Center Martin, Slovakia

$$\mathbf{A}(L)\,\mathrm{diag}\left(\nabla^{\mathbf{d}}\right)\mathbf{X}_n = \mathbf{E}_n \tag{5}$$

where L is the back-shift operator $\left(L^i\mathbf{X}_n = \mathbf{X}_{n-i}\right), \mathbf{A}(L) = \mathbf{I_3} - \sum_{i=1}^{p}\mathbf{A}_i L^i$ ($\mathbf{I}_3$ is the identity matrix), $\mathbf{A}(L)$ is a vector autoregressive (VAR) polynomial of order p, and $\mathrm{diag}\left(\nabla^{\mathbf{d}}\right) = \mathrm{diag}\left[(1-L)^{d_i}\right], i = R,S,H$, and $(1-L)^{d_i}$ is the fractional differencing operator. The parameter $\mathbf{d} = (d_R, d_S, d_H)$ determines the long-term behavior of the process X_i, while the coefficients of $\mathbf{A}(L)$ allow the description of the short-term dynamics. A $VARFI(p,d)$ is approximated by a finite order $VAR(p+q)$ process, p is chosen by Bayesian Information Criterion (BIC) and $q = 50$ [2].

The multiscale representation is obtained through filtering the time series after standardization (mean 0 and variance 1) using a lowpass filter with cutoff frequency $1/2\tau$ and then downsampling the series using a decimation factor τ [4]. Exact expressions of the information transfer are obtained using innovations state space (ISS) representation for coupled Gaussian processes at multiple temporal scales [4]. The individual and joint TE, (1)-(2) are obtained from the prediction error variances as

$$T_{i\to j} = \frac{1}{2}\ln\frac{\lambda_{j|j}}{\lambda_{j|ij}}, \tag{6}$$

$$T_{ik\to j} = \frac{1}{2}\ln\frac{\lambda_{j|j}}{\lambda_{j|ijk}}, \tag{7}$$

with $\lambda_{j|j}$ variance of the prediction error on $X_{j,n}^-$, $\lambda_{j|ij}$ variance of the prediction error of X_j on $\left[X_{j,n}^-, X_{i,n}^-\right]$ and $\lambda_{j|ijk}$ variance of the prediction of error of X_j on $\left[X_{j,n}^-, X_{i,n}^-, X_{k,n}^-\right]$ $(i,k,j = R,S,H)$.

IV. Simulation Study

To investigate the theoretical properties of the TE measures in presence of long memory we incorporate long range correlations [3] in a benchmark trivariate VAR model [6], where S and H interact in a closed loop, both driven by R:

$$\begin{aligned}
R_n &= 2\rho_r \cdot \cos 2\pi f_r \cdot R_{n-1} - \rho_r^2 \cdot R_{n-2} + U_{r,n}, \qquad (8)\\
S_n &= 2\rho_s \cdot \cos 2\pi f_s \cdot S_{n-1} - \rho_s^2 \cdot S_{n-2} + a\cdot H_{n-2} + e\cdot R_{n-1} + U_{s,n},\\
H_n &= 2\rho_h \cdot \cos 2\pi f_h \cdot H_{n-1} - \rho_h^2 \cdot H_{n-2} + b\cdot S_{n-1} + c\cdot R_{n-1} + U_{h,n}.
\end{aligned}$$

The parameters of the model were set to reproduce oscillations and interactions commonly observed in cardiovascular and cardiorespiratory variability [6], i.e, the self-sustained dynamics typical of R ($\rho_r = 0.9$, $f_r = 0.25$) and the slower oscillatory activity commonly observed in the so-called low-frequency (LF) band in the variability of S ($\rho_s = 0.8$, $f_s = 0.1$) and H ($\rho_h = 0.8$, $f_h = 0.1$).

Illustrative theoretical profiles of the multiscale TEs and of the interaction for a VARFI process, varying the long memory parameter d of the target H, are presented in Fig.1. Generally, the individual and joint information transfer at longer time scales increase with d of the target. On the other hand, ITE decreases suggesting an increased redundancy (lower right panel of Fig.1). The theoretical profiles of multiscale TE (Fig.2) varying d of the sources suggest opposite trends: TE decreasing with d and increased synergy regarding ITE.

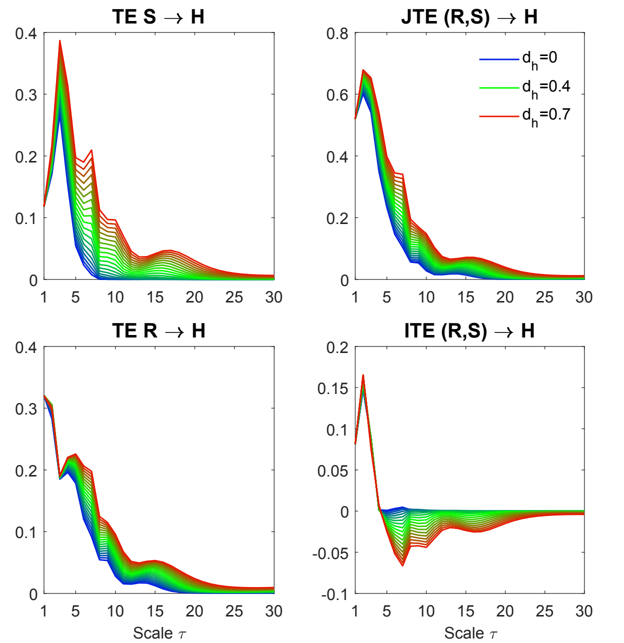

Fig. 1. Theoretical profiles of $T_{S\to H}$, $T_{R\to H}$, $T_{R,S\to H}$ and of the interaction $I_{R,S\to H}$ for a VARFI process with fixed long memory parameters $d_r = 0.1$, $d_s = 0.25$ (sources) and varying d_h, 0 (blue) - 0.7 (red).

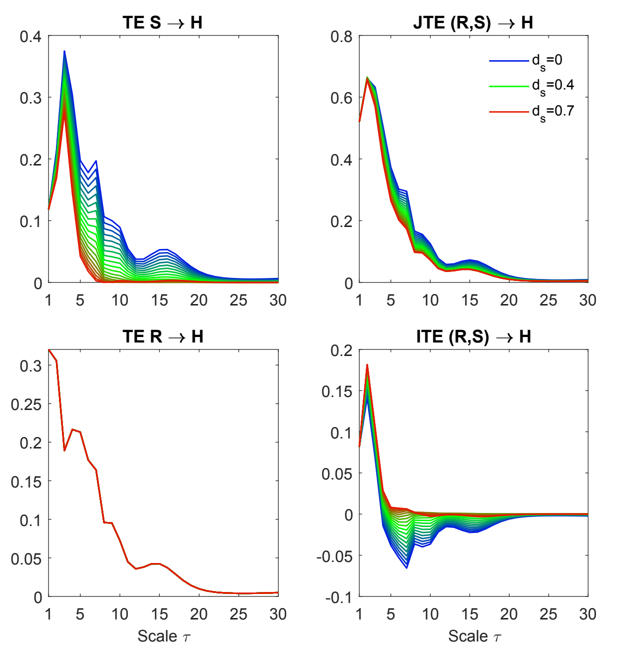

Fig. 2. Theoretical profiles of $T_{S\to H}$, $T_{R\to H}$, $T_{R,S\to H}$ and of the interaction $I_{R,S\to H}$ for a VARFI process with fixed long memory parameters $d_r = 0.1$, $d_h = 0.45$ (source and target) and varying d_s, 0 (blue) - 0.7 (red). Note that for $T_{R\to H}$ all the profiles coincide.

V. APPLICATION TO EXPERIMENTAL DATA

A. Experimental Protocol

The H, S and R time series (stationary windows of at least 400 beats) were measured in a group of 62 healthy subjects

(19.5 3.3 years old, 37 females) monitored in the resting supine position (SU_1), in the upright position (UP) reached through passive head-up tilt, during the recovery in supine position (SU_2) and during a mental arithmetic task (MA) in the supine position [2], [7]. The experimental procedure was approved by the local ethical committee.

B. Results and Discussion

The decomposition of the joint information transfer evidences different types of contributions with physiological meaning. The analysis of the data in the resting supine (SU_1) and the upright position (UP) for the VARFI modeling approach is summarized in Figs.3-4. For SU_1 at $\tau = 1$, $T_{R\to H} > T_{S\to H}$ (left column of Fig.3), indicating prevalence of Respiratory Sinus Arrhythmia (RSA), i.e. the heart rate oscillations related to the respiration [7]. At $\tau = 1$, $T_{R\to H}$ in SU_1 is higher than in UP, while at $\tau > 1$ $T_{R\to H}$ in UP is higher than in SU_1 (lower left panel of Fig.3). The multiscale representation allows to highlight that RSA for slow oscillations is enhanced by tilt; this may be an effect of long-range correlations, as suggested by the simulation of $T_{R\to H}$ (Fig.1) where the information transfer at long time scales increases with d of target.

The postural stress induced by UP is associated with a markedly higher $T_{S\to H}$ (upper left panel of Fig.3) at low time scales (up to ≈ 5). This finding is in agreement with previous works reporting baroreflex activation with UP [7]–[10]. For the UP position, at $\tau = 1$ the information transfer from R to H is lower. This finding is consistent with previous works reporting weakening of RSA with UP [7]–[10]. In particular, in [7] the drop of the $T_{RESP\to HP}$ has been ascribed to a dampening of the nonbaroreflex path of RSA. The two previous effects determine a higher joint information transfer $T_{R,S\to H}$ during UP for scales up to $\tau \approx 10$. The ITE decreases significantly with tilt (lower right panel of Fig.3), denoting stronger redundancy, as expected from previous works [7].

Fig.4 reports the mean and 95% confidence intervals of the paired differences between the values of TE measures computed in UP and SU_1 conditions for VAR and VARFI based approaches; the statistical variation from SU_1 to UP is detectable at a given timescale if the confidence intervals do not encompass the zero line. Comparing VARFI with VAR model, higher values of $T_{S\to H}$ are reported using VARFI during UP for all time scales, while for $T_{R,S\to H}$ this occurs only for $\tau > 3$. These trends suggest that long-range correlations affect the changes of cardiovascular information transfer during UP, especially with regard to slower oscillations.

The results obtained comparing the SU_2 and MA phases for VARFI are presented in Fig.5-6. The transfer entropy $T_{S\to H}$ at longer time scales ($\tau > 1$) is higher during MA if compared to SU_2, while this does not occur for $\tau = 1$. The transfer entropy $T_{R\to H}$ at scale $\tau = 1,2$ is lower during MA than during SU_2, while the opposite occurs at longer time scales ($\tau > 2$).

Overall, the reported trends suggest that, at lower time scales, MA produces an increase of the information transfer from S to H and a simultaneous decrease of the information

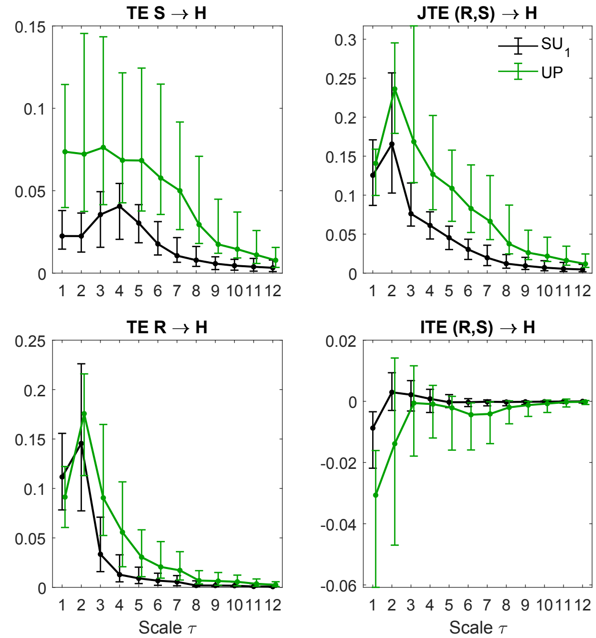

Fig. 3. Median and quartiles of TE measures across subjects during the resting supine (SU_1) and postural stress (UP) using the VARFI approach.

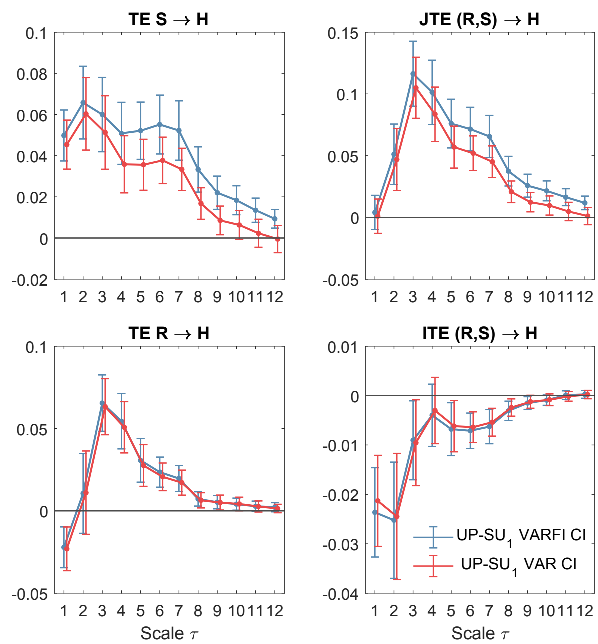

Fig. 4. 95% C.I. of the paired difference between tilt and rest $UP - SU1$ of each measure computed for the VARFI (blue) and VAR (red) models.

transfer from R to H similar to what observed during UP (Fig.3). Such results are in agreement with those reported in [7] suggesting an overall weakening of RSA due to vagal inhibition provoked by stress challenges [7]–[9] and the non-activation of the baroreflex-mediated RSA ($R \to S \to H$), conversely to what happens with UP. The different trends found for longer time scales support the usefulness to employ a multiscale approach in the analysis of cardiovascular and cardiorespiratory interactions [2], [7]. The increase of $T_{S\to H}$ for scales $\tau > 1$ and of $T_{R\to H}$ for scales $\tau > 2$ suggests

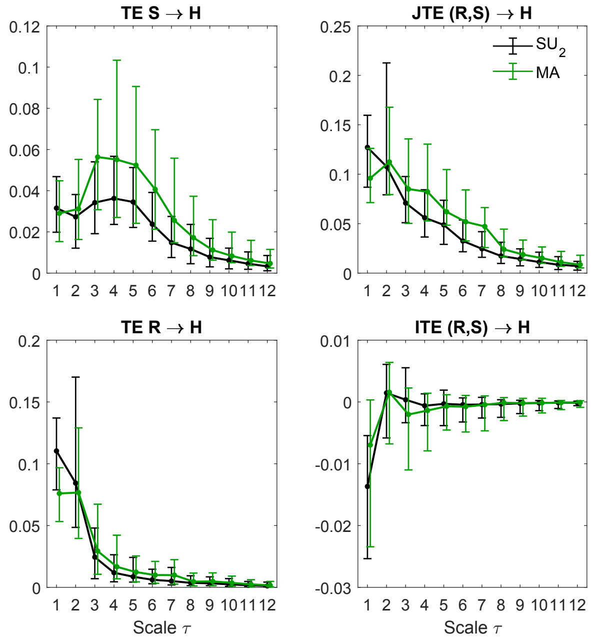

Fig. 5. Median and quartiles of TE measures across subjects during the recovery supine (SU_2) and mental stress (MA) using the VARFI approach.

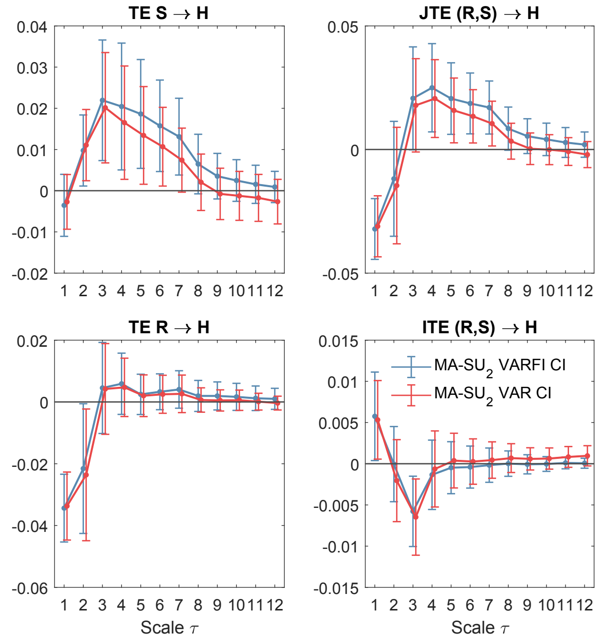

Fig. 6. 95% C.I. of the paired difference between MA and SU_2 ($MA-SU_2$) of each measure computed for the VARFI (blue) and VAR (red) models.

complex multiscale patterns adaptably responding to stress challenges and highlight that both lower baroreflex-mediated transfer of S oscillations and of slowly varying respiration influences to H occur during mental stress (due to changes of breathing patterns) [10].

The JTE $T_{R,S\to H}$ at scale $\tau=1$ is higher at SU_2 than during MA, while the opposite occurs at longer time scales ($\tau>1$). Mental stress produces increased ITE only at $\tau=1$, which means decreased redundancy and reduced joint information transfer, but only for $\tau=1$. Conversely, the significantly higher redundancy found for $\tau=3$ may be due to an involvement of respiration also in the LF band (caused by changes in the respiration pattern).

The mean and 95% confidence intervals of the paired differences between the values of TE measures computed in SU_2 and MA conditions for VAR and VARFI based approaches are presented in Fig.6, and indicate that higher values of $T_{S\to H}$ and $T_{R,S\to H}$ are reported using VARFI during MA for longer time scales ($\tau>3$). This suggests that long-range correlations can detect changes due to mental stress, but only regarding slower oscillations. Similar trends are reported in terms of the information transfer from R to H and the interaction transfer entropy, which are almost identical, suggesting that long-range correlations do not influence these information measures.

VI. Final Remarks

The VARFI approach to multiscale TE allows to assess the overall role of long range correlations in simulated and experimental data. We find that long range correlations in the target process enhance the information transfer, and this occurs particularly in response to postural stress.

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