Decomposition of the Dynamic Information Shared in Complex Networks of Physiological Variables

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Abstract

Complex networks of physiological variables have been extensively investigated through classical time series analysis approaches, often inherently limited by their pairwise nature and thus overlooking high-order interactions. In this context, the partial information rate decomposition (PIRD) framework has been formalized recently to dissect information flow in multivariate systems of stationary random processes rich of oscillatory content. In this study, we employ the PIRD to unravel the physiological mechanisms governing the joint beat-to-beat regulation of heart period, arterial pressure, respiration and arterial compliance, during the resting state and in response to postural stress. Our findings highlight the importance of the beat-to-beat interplay between cardiac/vascular variables and arterial compliance occurring within spectral bands with physiological meaning, and advocates the non-negligible involvement of this parameter into the intricate autonomic cardiac regulation.

1. Introduction

In the field of Network Physiology, the human organism is described as an integrated network constituted by multiple organ systems continuously interacting to coordinate their functions [1]. For instance, the spontaneous oscillations and interactions between cardiac and vascular or respiratory variables have been abundantly studied through noninvasive data-driven methods for network inference based on time series analysis [2–5], whilst recent studies have been focused on characterizing the short-term-variability of arterial compliance, expected to be mostly affected by sympathetic activity, as well as by heart rate, blood pressure and respiration [6, 7].

Classical approaches defined in the time, frequency and information-theoretic domains have been used to describe the dynamic interplay between the heart and vascular or respiratory systems (see, e.g., [4,5]). However, these methods are limited by their intrinsic pairwise formulation and neglect the effects due to unobserved confounders. Recent efforts have been oriented to capture the complex dynamics involving three or more processes. In this context, the spectral partial information rate decomposition (PIRD) framework has been recently designed to understand how information is distributed in multivariate systems of stationary random processes with oscillatory components [8], with the goal to decompose the information rate that a *target* process shares with a set of *source* processes into components highlighting the *unique* information rate exclusively available from each source, the *redundant* information rate obtained from at least two different sources, and the *synergistic* information rate revealed only when multiple sources are considered simultaneously.

In this study, we exploit the PIRD framework to elicit the physiological mechanisms underlying complex cardiovascular regulation from the joint analysis of the spontaneous beat-to-beat variability of heart period, arterial pressure, respiration and arterial compliance, in the supine resting state and in response to postural stress. The physiological relevance and meaning of the observed behaviors in different spectral bands is discussed in terms of novel insights on the complex mechanisms governing the cardiovascular, cardiorespiratory and vascular-respiratory interplays.

2. Materials and Methods

Experimental Protocol and Data Preprocessing. The study included 39 young healthy subjects (22 women; median age: 18.7 yr), and was approved by the ethical committee of Comenius University of Bratislava [6]. The protocol consisted of two consecutive phases, with subjects in the resting supine (RS, 15 min), and 45° head-up tilt (T, 8 min) body positions. Electrocardiogram (ECG), arterial pressure (AP) curve from finger, impedance cardiography (ICG) and respiration signal from thoracic and abdominal impedance belts were simultaneously and noninvasively recorded, and then digitized at a sampling rate of 1 kHz.
Beat-to-beat variability series were measured as follows.

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Heart period (HP) intervals were approximated as the time distance between the n^{th} and the $(n+1)^{th}$ R peaks of the ECG (HP_n), with n the temporal counter; the n^{th} systolic AP (SAP) value (SAP_n) was measured as the maximum of the AP signal inside HP_n. The n^{th} diastolic AP (DAP) value (DAP_n) was taken as the minimum of AP between the occurrences of SAP_n and SAP_{n+1}. Mean AP (MAP) was calculated averaging the AP curve between the occurrences of DAP_{n-1} and DAP_n. The n^{th} respiration amplitude (RESP) value ($RESP_n$) was computed sampling the respiration signal on the n^{th} R peak of the ECG. Beat-to-beat cardiac output (CO_n) was estimated from the stroke volume derived from ICG signal, while peripheral vascular resistance (PVR) was calculated as $PVR_n = MAP_n/CO_n$. Finally, the value of arterial compliance (AC) was quantified on a beat-to-beat basis as $AC_n = \tau_n/PVR_n$, with τ the rate of the peripheral AP decay during the diastolic phase. Stationary segments of 300 consecutive beats were extracted from the original HP, MAP, AC, and RESP time series (referred to as *H*, *M*, *C*, and *R*, respectively), in RS starting 8 min after the beginning of the measurement, and in T 3 min after the position change from supine to tilt. We refer the reader to [6] for further details about the study protocol, data acquisition and time series extraction. Time series were then preprocessed to remove the slow trends with an AR high-pass filter (zero phase, cut-off frequency 0.0156 Hz) and normalized to zero mean.

Partial Information Rate Decomposition. The *H*, *M*, *C* and *R* time series were taken as realizations of random processes representing the activities at the nodes of a dynamic network system, with each series assumed as the *target* (Y) process and the rest of the system as the vector of *sources* ($\mathbf{X} = \{X_1, X_2, X_3\}$). The PIRD framework [8] was exploited to decompose the rate of information shared between the target and the sources, i.e., the mutual information rate (MIR) $I_{Y;\mathbf{X}}$, by making explicit the *unique information rate* (UIR) $\mathcal{U}$ that each source holds about the target, the *redundant information rate* $\mathcal{R}$ that the sources hold about the target, and the *synergistic information rate* $\mathcal{S}$ about the target that only arises from knowing all the sources:

$$I_{Y;\mathbf{X}} = \sum_{m=1}^{3} \mathcal{U}_{Y;X_m} + \mathcal{R}_{Y;\mathbf{X}} + \mathcal{S}_{Y;\mathbf{X}}, \qquad (1)$$

where $\mathcal{U}_{Y;X_m} = I_{Y;X_m} - \mathcal{R}_{Y;\mathbf{X}}$.

To solve the PIRD (1), we defined the *redundancy rate* function through a *pointwise* representation of the MIR in the frequency domain, as described in [8]. The entire PIRD was thus performed for a particular frequency ω ($\omega = 2\pi\frac{f}{f_s} \in [-\pi, \pi]$ is the normalized circular frequency, with $f \in [-\frac{f_s}{2}, \frac{f_s}{2}]$, f_s the sampling frequency), i.e., we decomposed the spectral MIR $i_{Y;\mathbf{X}}(\omega)$ through a coarse-grained representation similar to (1). Then, we assessed spectral redundancy following the minimum mutual information (MMI) principle [9] applied to the spectral MIR computed between the target and each source process at the frequency of interest [8]. Moving from the spectral PIRD to that defined in the time domain (1) is straightforward exploiting spectral integration applied to the unique, redundant and synergistic atoms of the coarse-grained spectral PIRD to their corresponding time-domain atoms of the PIRD [8]. Under the assumption of joint Gaussianity, the analyzed set of stochastic processes was described in terms of its power spectral density matrix $\mathbf{P}(\omega)$, whose elements were exploited to retrieve the spectral MIR as $i_{Y;\mathbf{X}}(\omega) = \frac{1}{2}\log\frac{|\mathbf{P}_X(\omega)|P_Y(\omega)}{|\mathbf{P}(\omega)|}$ [8], where $P_Y(\omega)$ and $\mathbf{P}_X(\omega)$ are the autospectra of Y and $\mathbf{X}$ on the main diagonal of $\mathbf{P}(\omega)$, $|\cdot|$ denotes matrix determinant and $I_{Y;\mathbf{X}} = \frac{1}{2\pi}\int_{-\pi}^{\pi} i_{Y;\mathbf{X}}(\omega)\mathrm{d}\omega$.

A vector autoregressive (VAR) model was fitted to the four time series; model identification was performed via the ordinary least-squares approach, setting the model order according to the Akaike Information Criterion for each subject (maximum scanned model order: 14). Time ($[0 - f_s/2]$), low frequency (LF, $[0.04 - 0.15]$ Hz) and high frequency (HF, $[0.15 - 0.4]$ Hz) measures of mutual, unique, redundant and synergistic information rates were computed from the estimated model parameters and spectra of the processes, assuming the series as uniformly sampled with $f_s = 1/\langle HP\rangle$, with $\langle\cdot\rangle$ the temporal average. To test the null hypothesis of absence of UIRs shared between the sources and the target, 100 sets of surrogate time series were generated by building time-shifted versions of the original sources according to a delay larger than the maximal order of the VAR model (i.e., > 20 cardiac beats), thus destroying the short-term temporal correspondence between the sources and the target, while preserving static and dynamical properties of all the series (the target was left unchanged). If the values of the UIRs derived from the original data were significantly higher than the 95^{th} percentiles computed over the surrogate sets, the null hypothesis was rejected at the 5% significance level.

3. Results and Discussion

Results are displayed in Fig. 1 in the form of four-node networks depicting the average UIRs shared between the target (head of the arrows) and the sources (tails) in the RS (left) and T (middle) conditions, as well as their significant differences (right); the balance $\mathcal{R} - \mathcal{S}$ is shown as node-specific information.

We detected strong and significant *cardiorespiratory interactions* in the TIME and HF bands of the spectrum (panels a,c, left), decreasing with tilt (panels a,c, right); the latter is indicative of respiratory sinus arrhythmia and/or car-

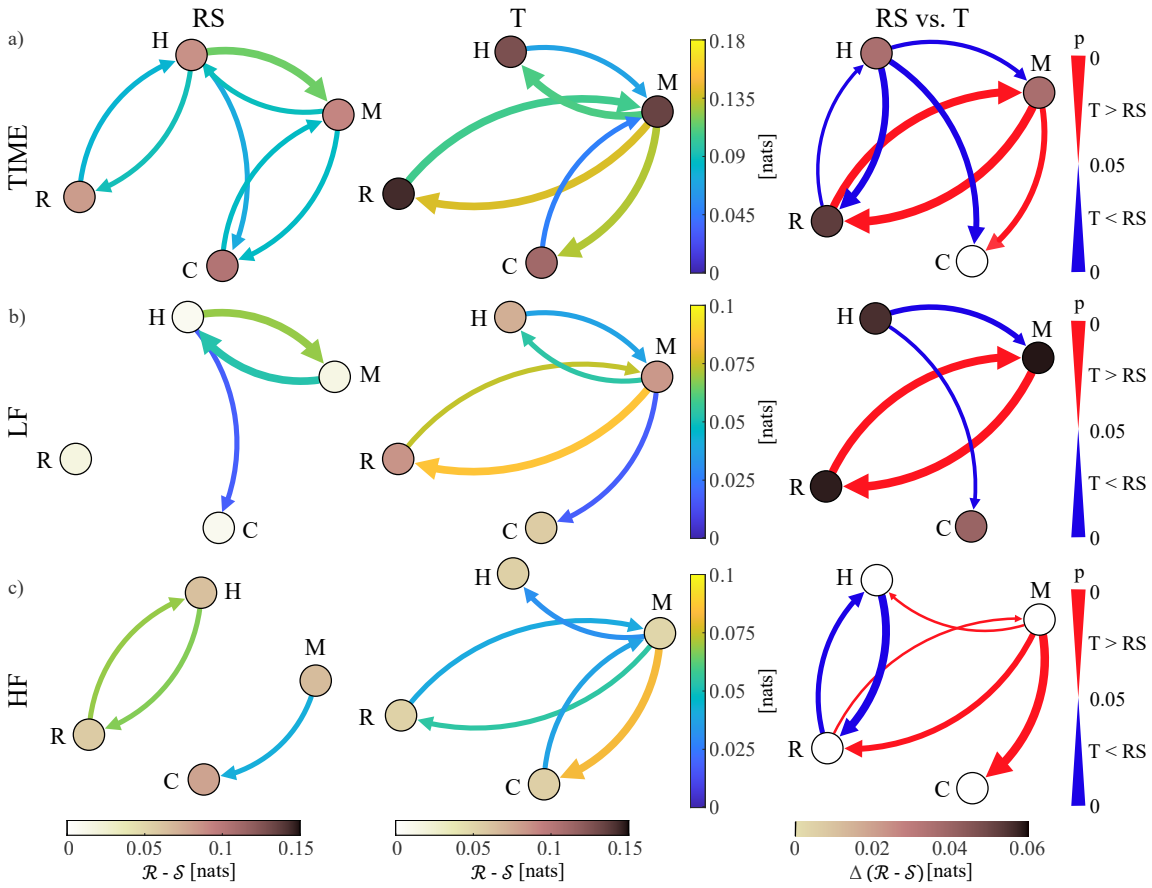

Figure 1. Networks depicting the average unique information rates shared between each target node (head of the arrows) and the corresponding source (tail) and the balance $\mathcal{R} - \mathcal{S}$ (color-coded inside each node) computed in the RS (left) and T (middle) conditions, as well as their significant differences (right), in the (a) time domain (TIME), (b) low-frequency (LF) and (c) high-frequency (HF) bands. Arrows are shown only if the corresponding percentage of significance is above 50% for the selected condition (RS/T) or for at least one of the conditions (RS vs. T); the different widths reflect two levels of significance (thinner: $[50\% - 75\%]$, thicker: $[75\% - 100\%]$, left/middle), or the p-value (right). Wilcoxon signed rank test for paired data, $p < 0.05$: red, T > RS and blue, T < RS (UIRs); the difference of the redundancy-synergy balance $\Delta(\mathcal{R} - \mathcal{S})$ is always positive (T > RS) except for white nodes, for which it is not significant (right).

dioventilatory coupling weakening with the postural stress [5, 10]. *Cardiovascular interactions* are highly significant in both conditions, as evidenced by time- and LF-domain analysis (panels a,b, left and middle columns). In these bands, we observe a significant decrease of the UIR shared between the target *M* and the source *H* in line with previous studies [4]; the fact that this decrease is evident only in the LF band may be related either to weakened Windkessel and/or Frank–Starling effects [4], or to a marked significant increase of redundant effects (panel b, right). On the other hand, we observed a significant increase of the UIR shared between the target *H* and the source *M* in the HF band of the spectrum (panel c, right) although the measure is significant only in the 25% of subjects in the resting state (panel c, left); this finding could be ascribed to respiratory-related fluctuations of both MAP and HP [2, 5]. *Respiratory-vascular* interactions were found to be strong and markedly enhanced during the postural stress in both LF and HF bands of the spectrum (middle and left columns), although with higher p-values in LF. The significance and increase of the information shared when MAP is the target can be ascribed to the mechanical effects of respiration on arterial pressure, as confirmed by previous studies (e.g., [3]); on the other hand, setting respiration as the target process also determines an increase of the UIR shared with MAP, probably due to the presence of a strong causal interaction $R \rightarrow M$ captured by the symmetric MIR. Interactions involving the beat-to-beat *arterial compliance* are poorly explored up to now. Here, we find a decrease of the UIR shared between the target *C* and the source *H* in the TIME and LF bands (panels a,b, right); this result could be related to pure mechanical visco-elastic

effect [11]. Moreover, we observed an increase in terms of both values and significance of the UIR shared between the target *C* and the source *M*, mainly visible in the HF band (panels a,c, right). To our knowledge, the latter finding has never been observed before and may be interpreted (i) methodologically, since the tilt-induced increased variability of MAP, though not shown here, may be partly responsible for the observed increase of the causal interactions $M \rightarrow C$ (here, we observe only an increase of the total interactions among MAP and AC), or (ii) physiologically, and thus related to modifications of the relation between MAP and AC during the orthostatic challenge as previously suggested [6]. Remarkably, our results suggest that redundant effects predominate in the HF with respect to the LF band during the resting state (left) and that they significantly increase with the postural stress in the LF band probably due to LF-driven common drive effects acting on the investigated variables, such as the sympathetic nervous system (panel b, $\Delta(\mathcal{R} - \mathcal{S}) > 0$ for all the nodes); the tendency towards synergistic interactions with tilt in the HF band ($\Delta(\mathcal{R} - \mathcal{S}) < 0$) is not significant (white nodes in panel c, right). Overall, the frequency-specific redundant interplay among the investigated cardiovascular variables is well evidenced by our spectral PIRD.

4. Conclusion

This study provides a comprehensive investigation of complex physiological interactions in a network of cardiac, vascular and respiratory variables in response to the orthostatic challenge. The use of the novel PIRD framework evidenced the importance of separating unique and redundant effects shared among the investigated processes to disentangle physiological mechanisms which cannot be observed through the utilization of either pairwise or conditional causality measures, such as those involving the beat-to-beat arterial compliance together with cardiac and vascular variables. Moreover, the expansion of the framework in the frequency domain is essential to retrieve spectral information related to oscillations with physiological meaning. Further studies should account for the possibility to develop a causal PIRD to identify driver–response relationships between the investigated physiological subsystems, which would allow a refined interpretation of physiological regulatory mechanisms.

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