Quantifying High-Order Interactions in Complex Physiological Networks: A Frequency-Specific Approach

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Abstract. Recent advances in information theory have provided several tools to characterize high-order interactions (HOIs) in complex systems. Among them, the so-called O-information is emerging as particularly useful in practical analysis thanks to its ability to capture the overall balance between redundant and synergistic HOIs. While the O-information is computed for random variables, its extension to random processes studied in the frequency domain is very important to widen the applicability of this tool to networks whose node exhibit rich oscillatory content, such as brain and physiological networks. This work presents the O-information rate (OIR), a measure based on the vector autoregressive and state space modelling of multivariate time series devised to assess the synergistic and redundant HOIs among groups of series in specific bands of biological interest. The new measure is illustrated in two paradigmatic examples of physiological networks characterized by coupled oscillations across a wide range of temporal scales, i.e. the network of cardiovascular and cerebrovascular interactions where redundant synchronized activity emerges around the frequencies of vasomotor and respiratory rhythms, and the network of scalp electroencephalographic signals where synergetic HOIs are detected among the alpha and beta waves recorded over the primary sensorimotor cortex.

Keywords: Brain connectivity · Cardiovascular oscillations · Information dynamics · Multivariate time series · Spectral analysis · Vector autoregressive models

1 Introduction

The increasing availability of recordings of biomedical signals is nowadays boosting the development of new methods for the data-driven modelling of complex biological systems. These methods typically describe the interactions between different systems (e.g.,

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cardiovascular, cardiorespiratory, cerebrovascular or brain interactions) using pairwise measures of coupling or causality [19]. However, in spite of the widespread utilization of pairwise measures to describe interactions in a network, there is evidence that such measures cannot full capture the interplay among the multiple nodes of a complex system [5]. In fact, brain and physiological networks exhibit collective behaviors which are integrated at different hierarchical levels, thus displaying interactions that involve more than two network nodes. These so-called high-order interactions (HOIs) occur for instance when cardiovascular interactions are influenced by the effects of the respiratory activity [9], and identify brain sub-networks with distinct neurocognitive profiles [15]. HOIs have been analyzed in physiological and brain networks using information decomposition methods that evidence the synergistic or redundant nature of the interplay among multiplets of variability series [9]. One of such measures is the O-information [20], a metric capable of revealing synergy- and redundancy-dominated circuits in multivariate systems mapped by vector random variables. The concept underlying the definition of the O-information was applied to random processes quantifying, in a network of N processes, the synergistic or redundant causal contribution brought to the target by the remaining $N-1$ processes [22]. While the dynamic O-information [22] is an asymmetric (target-specific) measure of HOIs, a recent work defined a symmetric measure which generalizes the O-information to dynamic random processes [7]; this measure, denoted as O-information rate (OIR), was defined from the linear parametric representation of vector autoregressive (VAR) processes and was expanded in the frequency domain exploiting the framework of state-space (SS) models [3].

The possibility to assess HOIs in the frequency domain offered by the spectral expansion of the OIR [7] opens the way to the evaluation of redundant and/or synergistic interactions within specific frequency bands with physiological meaning. In this context, the present work applies the spectral OIR measures to networks of physiological time series and brain signals, with the aim of investigating the nature of multivariate interactions underlying the communication among different physiological systems, or among spatially distributed units of the same physiological systems. To this end, we focus first on multivariate physiological time series reflecting the dynamics of heart period, arterial pressure, breathing volume and cerebral blood flow to investigate the joint cardiovascular, cerebrovascular and respiratory regulation during postural stress [8], and then on multichannel EEG recordings measured in different scalp locations to assess brain connectivity during motor execution [1]. The two applications feature physiological time series rich of oscillatory content, which thus lend themselves to the spectral analysis of HOIs performed by the proposed tools.

2 O-Information Rate

The organizational structure of M stationary discrete-time stochastic processes $X^M = \{X_1, ..., X_M\}$, which map the states visited by a network of dynamic systems, is assessed in the information-theoretic domain using the so-called O-information rate (OIR). The OIR quantifies the net synergistic or redundant information shared per unit of time by a subset of N processes taken from X^M. The OIR is null for pairs of processes ($\Omega_{X^2} = 0$),

while for multiplets (i.e., groups of $N > 2$ processes) it is defined recursively as [7]:

$$\Omega_{X^N} = \Omega_{X^N_{-j}} + \Delta_{X^N_{-j};X_j}, \tag{1}$$

where X^N_{-j} is the subset without the process X_j, and where the OIR increment obtained adding X_j to X^N_{-j} is:

$$\Delta_{X^N_{-j};X_j} = (2-N) I_{X^N_{-j};X_j} + \sum_{\substack{m=1 \\ m\neq j}}^{N} I_{X^N_{-mj};X_j}, \tag{2}$$

with $X^N_{-mj} = X^N \backslash \{X_m, X_j\}$. In (2), $I_{A;B}$ denotes the mutual information rate (MIR) between the vector stochastic processes A and B; the MIR quantifies the information shared by two processes per unit of time. The OIR can be either positive or negative for multiplets of order $N \geq 3$, with $\Omega_{X^N} > 0$ and $\Omega_{X^N} < 0$ denoting respectively redundant or synergistic interactions, i.e. interactions which can or cannot be retrieved from sub-groups of processes considered separately.

In this work, the OIR is computed in time and frequency domains following a linear parametric approach. The original vector X^M is represented by the vector autoregressive (VAR) model:

$$\mathbf{X}_n = \sum_{k=1}^{p} \mathbf{A}_k \mathbf{X}_{n-k} + \mathbf{U}_n, \tag{3}$$

where p is the model order, defining the maximum lag used to quantify interactions, $\mathbf{X}_n = [X_{1,n} \ldots X_{M,n}]^T$ is an M-dimensional vector collecting the present states of all processes, $\mathbf{A}_k$ is the $M \times M$ coefficient matrix describing the interaction from $\mathbf{X}_{n-k}$ to $\mathbf{X}_n$ at lag k, and $\mathbf{U}_n$ is a vector of zero-mean uncorrelated white noise processes with $M \times M$ positive definite covariance matrix Σ_U. While the VAR model (3) provides a global representation of the overall multivariate process, to describe the linear interactions relevant to the subset of processes $Z = \{Z_1, Z_2\}$, with $Z_1 = X_j$ and $Z_2 = X^N_{-mj}$ (m varying as in (2)), there is the need to define reduced VAR models involving only those processes. Hence, X^M is represented as a VAR process in the framework of state-space (SS) models, and the N submodels describing the joint dynamics of Z_1 and Z_2 are derived [3]. Their frequency domain representation allows to obtain the power spectral density (PSD) matrices describing the autonomous oscillatory content of Z_1 and Z_2 and their cross-spectra. A logarithmic spectral measure of the total coupling between Z_1 and Z_2 is then defined as [11]:

$$f_{Z_1;Z_2}(\omega) = \log \frac{|\mathbf{S}_{Z_1}(\omega)||\mathbf{S}_{Z_2}(\omega)|}{|\mathbf{S}_Z(\omega)|}, \tag{4}$$

where $\omega = 2\pi \frac{f}{f_s}$, with frequency $f \in [0, f_s/2]$ and f_s the sampling frequency, $\mathbf{S}_{Z_1}(\omega)$ and $\mathbf{S}_{Z_2}(\omega)$ are the autospectra of the two processes Z_1 and Z_2 while $\mathbf{S}_Z(\omega)$ is the PSD matrix of the joint process $\mathbf{Z} = [Z_1 Z_2]$, and $|\cdot|$ is the matrix determinant. Given that the integration over the whole frequency axis of the spectral measure (4) yields the corresponding time-domain measure $I_{Z_1;Z_2}$ in (2), the frequency-specific OIR increment

can be then defined in analogy to (2) as [7]:

$$\delta_{X^N_{-j};X_j}(\omega) = (2-N) f_{X_j;X^N_{-j}}(\omega) + \sum_{\substack{m=1 \\ m\neq j}}^{N} f_{X^N_{-mj};X_j}(\omega), \tag{5}$$

and can be used to compute recursively a frequency-domain version of the OIR, in analogy to (1), i.e. [7]:

$$\nu_{X^N}(\omega) = \nu_{X^N_{-j}}(\omega) + \delta_{X^N_{-j};X_j}(\omega). \tag{6}$$

It is easy to show that the spectral OIR increment in (5) and the spectral OIR in (6) satisfy the spectral integration property, i.e. the average over all frequencies of each of these spectral functions yields the corresponding information-theoretic function (respectively, (2) and (1)).

In this work, the VAR model fitting the M series was identified through the ordinary least squares method. Starting from the estimated VAR parameters (i.e., the VAR coefficients $\mathbf{A}_k$ and the innovation covariance Σ_U) and exploting the SS representation, the spectral functions in (5) and (6) were computed for all multiplets of orders 3 to N. Each spectral distribution obtained as in (6) was then integrated within specific frequency bands of the spectrum to retrieve information about high-order interactions within those bands. This procedure allowed us to evaluate redundant and/or synergistic interactions specific of band-limited stochastic oscillations with physiological meaning.

3 Application to Physiological Networks

3.1 Cardiovascular and Cerebrovascular Variability Series

We applied the framework to a database of physiological time series collected from 13 young healthy subjects during supine resting (REST) and passive standing in the 60° upright position reached after head-up tilt (TILT) [2]. For each subject and condition, $M = 5$ stationary sequences of 250 beat-to-beat values of heart period (tachogram, series T), systolic and diastolic arterial pressure (S, D), respiration (R), and mean cerebral blood flow velocity (F), were considered for the analysis. A VAR model was fitted on the time series measured for each subject and condition, with model order set according to the Akaike Criterion. Then, the spectral OIR was computed for each multiplet of order $N = 3, 4, 5$ and integrated within the low frequency (LF, 0.04–0.15 Hz) and high frequency (HF, 0.15–0.4 Hz) bands of the spectrum.

The results collected in Fig. 1 show that the OIR integrated in both LF and HF bands was positive in the large majority of subjects in both the analyzed conditions, and showed a tendency to increase with the number of series in the analyzed multiplets. This finding suggests that physiological networks probed by beat-to-beat variability series are dominated by redundancy. The result confirms similar findings observed in cardiovascular and cardiorespiratory networks [8, 18], and extends them to cerebrovascular and integrated physiological networks.

Multivariate interactions were found to be stronger for HF oscillations than in the LF band, suggesting a main role of respiration, whose oscillations are typically mostly

confined within the HF band [9], in driving redundant interactions in the cardiovascular and cerebrovascular networks. This result is confirmed by the observation that in the LF band the highest redundancy was displayed by multiplets including the series T, S, D and F, while significantly lower values were found in multiplets including the series R, in both experimental conditions. For these multiplets, a tendency towards an increase in the redundancy (though not statistically significant) was observed moving from REST to TILT, suggesting a possible role of sympathetic activation in driving the redundancy of LF oscillations in cardiovascular and cerebral blood flow variables [18]. Conversely, results in the HF band showed some statistically significant differences between multiplets only during TILT; specifically, the multiplets containing the series R, S and F displayed the highest redundancy.

Overall, these results confirm for HOIs the redundant nature of cardiovascular and cerebrovascular interactions previously reported for triplets of physiological processes [7,9,18], and document the relevance of separating LF and HF contributions to elicit the role of respiration on cardiovascular and cerebrovascular interactions. Moreover, the tendency of the OIR to increase with tilt was not statistically significant, suggesting that these redundant effects are preserved during postural stress.

The understanding of the different and complex ways of dynamic integration of organ systems as a complex network remains one of the biggest problems in field of Network Physiology. Physiological systems exhibit complex dynamics, operate at different time scales and are regulated by multi-component mechanisms, which has been known to challenge the study of physiologic coupling and causality [4,13]. These aspects, together with the evidence that cardiovascular and cerebrovascular interactions occur through the coupling of rhythms in different frequency bands with different physiological meaning [19], make our spectral approach eligible to probe HOIs in these networks. [8]. Our results document that respiration acts as a major driver of multivariate redundant interactions in physiological networks, confirming that HOIs can have different nature for different rhythms because synergistic and redundant behaviors generally alternate in different bands of the frequency spectrum [1,8].

3.2 EEG Recordings

The analyzed dataset refers to EEG signals relevant to 20 healthy subjects randomly chosen from a database of 109 participants (https://physionet.org/content/eegmmidb), recorded for each subject from 64 electrodes referenced to both mastoids (international 10–20 system, $f_s = 160$ Hz) [12,21]. We analyzed a resting state condition in which the participants were relaxed (REST) and a condition in which they were asked to open and close the right fist cyclically (RIGHT). The raw signals were firstly detrended, then filtered (band-pass, 2–35 Hz; notch, 59–61 Hz) and finally epoched to extract 15 trials of 4 s each for each participant and condition. We performed the analysis on the signals recorded by the four electrodes depicted in Fig.2(a), i.e. $X_1 = C_3, X_2 = C_z, X_3 = C_4, X_4 = F_z$. For each subject and trial, a VAR model was identified from the four selected time series setting the model order according to the Bayesian Information criterion. Then, the estimated VAR parameters were used to compute the spectral OIR for each multiplet of order $N = 3, 4$. Finally, values indicative of HOIs occurring for the α and β brain

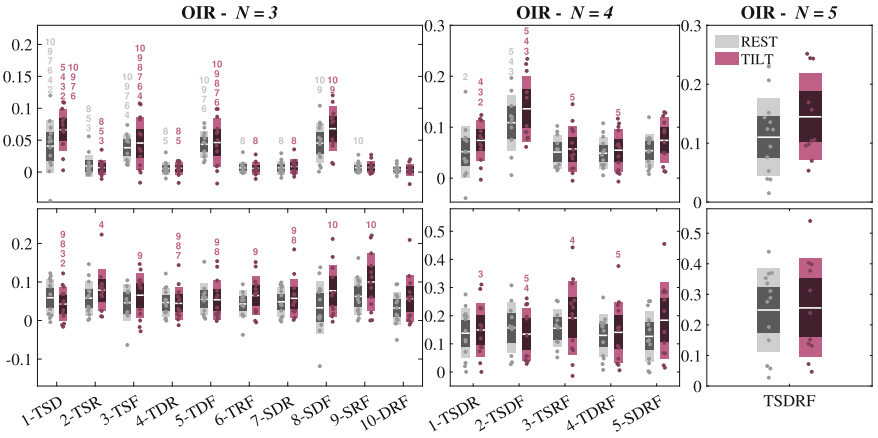

Fig. 1. Distribution across subjects and individual values of the OIR (top panels: spectral OIR integrated in the LF band, 0.04–0.15 Hz; bottom panels: spectral OIR integrated in the HF band, 0.15–0.4 Hz) computed at REST (gray) and during TILT (violet) for all possible multiplets of order 3,4,5 obtained grouping the time series of heart period (T), systolic pressure (S), diastolic pressure (D), respiration (R) and mean cerebral blood flow velocity (F). Numbers in the OIR(3) and OIR(4) panels indicate pairs of distributions for which the mean OIR differed significantly in a given condition (Student t-test for paired data, $p < 0.05$). No statistically significant differences between REST and TILT were detected.

rhythms were obtained by integrating the measures over the relevant frequency ranges (i.e., $\alpha = [8-12]$ Hz, $\beta = [16-26]$ Hz).

Figure 2(b,c,d,e,f) reports the grand-average over participants and trials of the frequency profiles obtained for each multiplet separately for the REST and RIGHT conditions in the frequency range 2–35 Hz. The trends reveal the prevalence of positive values of the OIR, denoting redundant interactions, for the triplets including the signal recorded at the electrode F_z (panels b,c,d), while the triplet $[C_3 - C_z - C_4]$ displays negative OIR values related to synergy within the α and β bands (panel e); synergistic interactions are detected, although weaker, also for the multiplet of order 4 including all the analyzed electrodes.

Fig. 2(g,h) depicts the distributions across participants and trials of the spectral OIR integrated over the α and β frequency bands, computed for each multiplet separately for the REST and RIGHT conditions. The execution of the motor task is generally associated with an increase of the OIR denoting higher redundancy for multiplets including the EEGs recorded at the central electrodes F_z and C_z, together with C_3, C_4, or both C_3 and C_4; the increase is observed particularly in the β band, and is statistically significant, according to a Wilcoxon paired test performed with 5% significance, for the multiplet of order 4 including the central electrodes F_z and C_z and both the lateral electrodes C_3 and C_4 (panel h). On the contrary, the OIR profiles exhibit a decrease in the α band when computed for the triplet $[C_3 - C_z - C_4]$ (panel g); such a decrease, though not statistically significant, denoties a tendency to higher synergy during task execution.

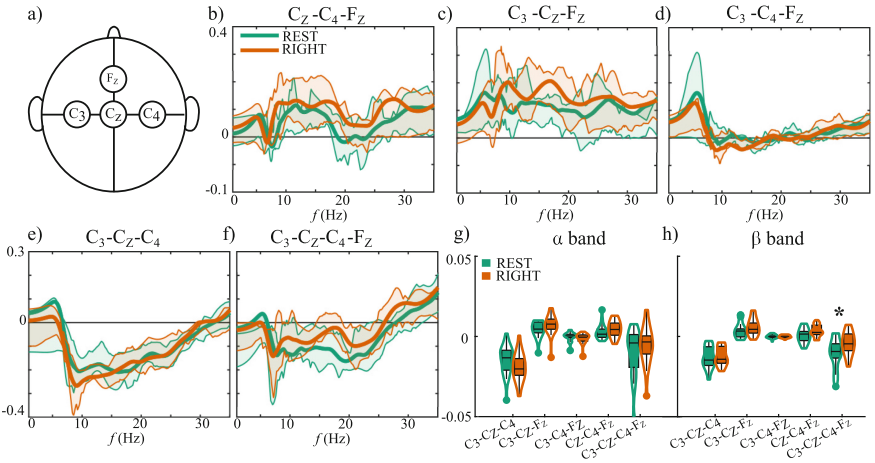

Fig. 2. (a) EEG electrodes montage highlighting the positions of the four selected electrodes. (b–f) Spectral profiles (mean (bold line) and 25th–75th percentiles (shades) over 20 subjects and 15 trials per subject) of the OIR computed for each multiplet during relaxation (REST, green lines) and while opening and closing the right fist (RIGHT, orange lines). (g–h) Violin plots of the distribution across participants and trials of the OIR values computed by integrating the spectral OIR within the α band (8−12 Hz (g)) and within the β band (16−26 Hz) during relaxation (REST) and opening/closure of the right fist (RIGHT). *, $p < 0.05$ Wilcoxon test.

The study of human brain activity during motor execution is very important in clinical contexts and in neuroscience. In fact, motor actions commonly derive from the involvement of several areas in the brain causing excitatory and inhibitory coupling among different regions in the two hemispheres [10]. To investigate the joint EEG activity of specific brain areas designated to the planning and execution of hand motor task [16], we selected four EEG signals recorded from channels located on the central line (F_z,C_Z) and on scalp areas contralateral and ipsilateral to the right-hand motor execution task (respectively, C_3 and C_4). In agreement with our previous work showing a widespread redundant behavior for this network of EEG interactions [1], we document the prevalence of redundancy for HOIs. However, we also show that combinations of signals measured from both central electrodes and electrodes located in ipsi- and contralateral locations give rise to synergistic HOIs that reflect the emergence of interaction mechanisms not retrievable from a pairwise analysis. From a physiological point of view, these functional mechanisms involve spatial locations (C_3 and C_4) and emerge in frequency bands (α and especially β) which are linked to the well-known phenomenon of event-related desynchronisation occurring during motor execution and imagery [17].

Nevertheless, we stress the preliminary nature of our results, which need confirmation on larger datasets [12], also after adopting methodological improvements (e.g., the consideration of the statistical significant of the detected OIR values and increments [22]) and addressing common issues of brain connectivity analyses (e.g., those related to the effects of volume conduction on pairwise and higher-order connectivity measures [14,23]).

4 Conclusions

Brain and physiological networks are not only composed by several functionally interconnected nodes, but are also endowed with oscillatory dynamics deployed across a wide range of temporal scales, which vary from the 20 s period of slow sympathetic and vasomotor rhythms up to a frequency of almost 100 Hz for the faster EEG waves. The spectral expansion of the O-information presented in this work allows to deal at the same time with the multivariate and multiscale nature of physiological dynamics, characterizing them by means of HOIs measures assessed within specific frequency bands.

Our results indicate that different networks whose collective dynamics are studied in different frequency bands display distinct peculiar patterns of HOIs. The physiological network probed by heart rate, arterial pressure and cerebral blood flow variability displays slower oscillations entrained by mechanical and autonomic influences, as well as faster rhythms driven by respiration [6], which give rise to mostly redundant interactions at different orders. On the other hand, a growing body of work is documenting how brain networks can display synergy as an emergent behavior, suggesting that synergistic interactions may serve to integrate and complement redundant sub-networks [15,24]. The results here obtained, albeit in a preliminary fashion, support this hypothesis, thus opening the way to the use of the frequency-specific O-information measures as a tool to uncover higher-order effects which otherwise, with current pairwise and time-domain approaches, would remain hidden.

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