Quantifying High-Order Interactions in Cardiovascular and Cerebrovascular Networks

Luca Faes, Gorana Mijatovic, Laura Sparacino, Riccardo Pernice, Yuri Antonacci, Alberto Porta, and Sebastiano Stramaglia

***Abstract*— We present a method to analyze the dynamics of physiological networks beyond the framework of pairwise interactions. Our method defines the so-called O-information rate (OIR) as a measure of the higher-order interaction among several physiological variables. The OIR measure is computed from the vector autoregressive representation of multiple time series, and is applied to the network formed by heart period, systolic and diastolic arterial pressure, respiration and cerebral blood flow variability series measured in healthy subjects at rest and after head-up tilt. Our results document that cardiovascular, cerebrovascular and respiratory interactions are highly redundant, and that redundancy is enhanced by the entrainment of cardiovascular and cerebrovascular oscillations and by sympathetic activation.**

I. Introduction

Data-driven methods for the analysis of physiological networks typically describe the interactions between different physiological systems (e.g., cardiovascular, cardiorespiratory or cerebrovascular interactions) using pairwise measures of coupling or causality [1]. However, there is increasing evidence that pairwise measures cannot capture emergent dynamics in complex systems [2], and that higher-order interactions (HOIs) play a key role in governing the overall behavior of physiological networks [3]. HOIs are interactions involving more than two network nodes, and have been analyzed in physiological networks using information decomposition methods evidencing the synergistic or redundant nature of the interplay among triplets of variability series [4]. Nevertheless, HOI measures able to capture interactions for arbitrarily large groups of nodes are desired in networks where multiple physiological mechanism drive global biological oscillations. One of such measures is the O-information, a metric capable to reveal synergy- and redundancy-dominated circuits in multi-variable systems [5]. This measure has been recently generalized to stochastic processes defining the so-called *O-information rate* (OIR), within a framework providing its causal decomposition and spectral expansion [6]. In this work, we complete the framework introducing a method to assess the statistical significance of the redundant or synergistic contributions brought by the processes of a multiplet, and apply the approach to the network formed by heart period, systolic and diastolic arterial pressure, respiration and cerebral blood flow variability. Our focus is on assessing the nature of cardiovascular, cerebrovascular and respiratory interactions when they are evaluated jointly during a resting state and in a condition of postural stress.

L.F., L.S., R.P. and Y.A. are with the Department of Engineering, University of Palermo, Italy. G. M. is with the Faculty of Technical Sciences, University of Novi Sad, Serbia. A.P. is with the Dept. of Biomedical Sciences for Health, University of Milano, Italy, and with the Dept. of Cardiothoracic, Vascular Anesthesia and Intensive Care, IRCCS Policlinico San Donato, Italy. S.S. is with the Dept. of Physics, University of Bari Aldo Moro, and INFN Sezione di Bari, Italy.

II. Framework to Measure O-Information Rate

Considering M stationary discrete-time stochastic processes $X^M = \{X_1, ..., X_M\}$ which map the states visited by a network of dynamic systems, their *organizational structure* is assessed in the information-theoretic domain using the so-called O-information rate (OIR) [5], [6]. The OIR of a subset of N processes taken from X^M is defined recursively as [7]

$$\begin{aligned} &\Omega_{X^2} = 0, \\ &\Omega_{X^N} = \Omega_{X^N_{-j}} + \Delta_{X^N_{-j};X_j}, N \geq 3 \end{aligned} \tag{1}$$

where $X^N_{-j} = X^N \backslash X_j$ is the subset without the process X_j and where the OIR increment obtained adding X_j to X^N_{-j} is

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

with $X^N_{-mj} = X^N \backslash \{X_m, X_j\}$ and with $I_{\cdot;\cdot}$ denoting the mutual information rate (MIR) between two vector stochastic processes. The MIR and the OIR quantify respectively the information shared by two processes and by multiplets (i.e., groups of $N > 2$ processes) per unit of time. The OIR is null for a pair of processes, while it can be either positive or negative for multiplets of order $N \geq 3$: $\Omega_{X^N} > 0$ and $\Omega_{X^N} < 0$ denote respectively the prevalence of redundant or synergistic interactions within the multiplet, i.e. interactions which can or cannot be retrieved from sub-groups of processes considered separately.

In this work, the OIR is computed following a linear parametric approach based on vector autoregressive (VAR) models [6]. Specifically, X^M is represented as a VAR process in the framework of state-space models, and the N submodels describing the joint dynamics of $Z_1 = X_j$ and $Z_2 = X^N_{-mj}$ are derived (m varying as in (2)). Then, the MIR between Z_1 and Z_2 is computed as $I_{Z_1;Z_2} = T_{Z_1 \to Z_2} + T_{Z_2 \to Z_1} + I_{Z_1 \bullet Z_2}$, where $T_{Z_1 \to Z_2}$ and $T_{Z_2 \to Z_1}$ are measures of Granger causality (GC) and $I_{Z_1 \bullet Z_2}$ quantifies the instantaneous interaction; the three terms are computed from the error covariance matrices of the sub-model fitting Z_1 and Z_2.

In addition, the genuine redundant or synergistic contribution of each individual process to a given multiplet is

assessed testing the significance of the OIR increments in (2). Specifically, the significance of $\Delta_{X^N_{-j};X_j}$ is tested by generating a bootstrap distribution of $\Omega_{X^N_{-j}}$ via the equation $\Omega^{(j)}_{X^N_{-j}} = \Omega_{X^N_{-mj}} + \Delta^{(j)}_{X^N_{-m};X_m}$, where $\Delta^{(j)}_{X^N_{-m};X_m}$ denotes the distribution of the OIR increment obtained adding X_m to the set X^N_{-m} in which the process X_j is randomized ($X_j, X_m \in X^N; j \neq m$). Randomization is performed using the iterative amplitude-adjusted procedure for the generation of surrogate time series preserving amplitude distribution and autocorrelation [8]. Finally, $\Delta_{X^N_{-j};X_j}$ is deemed as significantly positive (negative), reflecting significant redundant (synergistic) contribution to OIR, when Ω_{X^N} is higher than the 97.5^{th} (lower than the 2.5^{th}) percentile of $\Omega^{(j)}_{X^N_{-j}}$.

III. Application to Cardiovascular Oscillations

The framework was applied to a database of physiological time series collected to study the effect of postural stress on cardiovascular, cerebrovascular and respiratory variability [9]. The analyzed series are stationary sequences of 250 beat-to-beat values of heart period (tachogram, series T) systolic and diastolic arterial pressure (S, D), respiratory movements (R) and mean cerebral blood flow velocity (F), measured from 13 young healthy subjects during supine resting (REST) and passive standing in the 60° upright position (TILT). Considering the $M = 5$ series measured for each subject and condition as realizations of the vector process $X^M = \{T, S, D, R, F\}$, a VAR model was identified using the least squares method and setting the order according to the Akaike Criterion. Then, the OIR measure was computed for each multiplet of order $N = 3, 4, 5$, and the statistical significance of each OIR increment was assessed using the surrogate test.

The results in Fig. 1 show that the OIR measure was positive in the large majority of subjects in both the analyzed conditions, and increased with the order of the analyzed multiplets. The dominance of redundant interactions was confirmed by the statistically significant values of $\Delta_{X^N_{-j};X_j}$ revealed in at least 11 subjects out of 13 for all multiplets; this result indicates that each time series contributes to the OIR increment in a way such that the redundancy showed by a group of network nodes is not inherited by its lower-order components. The highest redundancy was displayed by multiplets including the series S, D and F, and redundancy decreased significantly in multiplets including the series R. These findings likely reflect the strength of cerebrovascular interactions driven by pressure-to-flow effects, and the fact that respiration-related mechanisms occur at different time scales than pure cardiovascular and cerebrovascular interactions. The OIR showed a tendency to increase also with tilt, documenting an effect of sympathetic activation on the redundant interactions among cardiovascular and cerebrovascular oscillations.

IV. Conclusions

The proposed framework for the evaluation of HOIs revealed a dominance of redundant interactions within the network of cardiovascular, cerebrovascular and respiratory

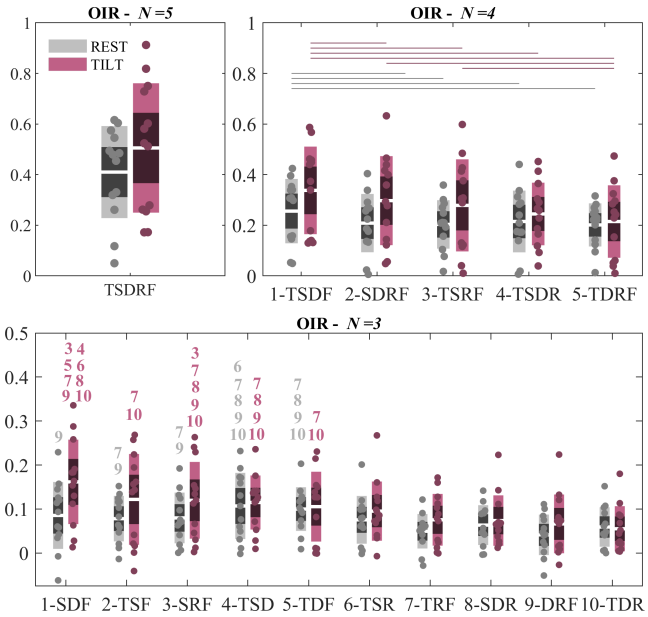

Fig. 1. Distribution across subjects and individual values of the OIR computed at rest (gray) and during tilt (violet) for multiplets of order 3,4,5 obtained grouping the time series of heart period (T), systolic pressure (S), diastolic pressure (D), respiration (R) and mean cerebral blood flow velocity (F). Lines in the OIR(4) panel and numbers in the OIR(3) panel indicate pairs of distributions for which the mean OIR differed significantly in a given condition (Student t-test for paired data, $p < 0.05$).

dynamics tested at rest and during postural stress. Future frequency-domain extensions will be helpful to clarify the role played sympathetic activation in driving the synchronization of cardiovascular and cerebrovascular oscillations in different physio-pathological conditions.

References

[1] A. Porta and L. Faes, "Wiener–granger causality in network physiology with applications to cardiovascular control and neuroscience," *Proc. IEEE*, vol. 104, no. 2, pp. 282–309, 2015.

[2] F. Battiston, G. Cencetti, I. Iacopini, V. Latora, M. Lucas, A. Patania, J.-G. Young, and G. Petri, "Networks beyond pairwise interactions: structure and dynamics," *Physics Reports*, vol. 874, pp. 1–92, 2020.

[3] Y. Antonacci, L. Minati, D. Nuzzi, G. Mijatovic, R. Pernice, D. Marinazzo, S. Stramaglia, and L. Faes, "Measuring high-order interactions in rhythmic processes through multivariate spectral information decomposition," *IEEE Access*, 2021.

[4] L. Faes, A. Porta, G. Nollo, and M. Javorka, "Information decomposition in multivariate systems: definitions, implementation and application to cardiovascular networks," *Entropy*, vol. 19, no. 1, p. 5, 2017.

[5] F. E. Rosas, P. A. Mediano, M. Gastpar, and H. J. Jensen, "Quantifying high-order interdependencies via multivariate extensions of the mutual information," *Phys. Rev. E*, vol. 100, no. 3, p. 032305, 2019.

[6] L. Faes, G. Mijatovic, Y. Antonacci, R. Pernice, C. Barà, L. Sparacino, M. Sammartino, A. Porta, D. Marinazzo, and S. Stramaglia, "A framework for the time-and frequency-domain assessment of high-order interactions in brain and physiological networks," *arXiv preprint:2202.04179*, 2022.

[7] S. Stramaglia, T. Scagliarini, B. C. Daniels, and D. Marinazzo, "Quantifying dynamical high-order interdependencies from the o-information: an application to neural spiking dynamics," *Front. Physiol.*, vol. 11, p. 1784, 2021.

[8] T. Schreiber and A. Schmitz, "Improved surrogate data for nonlinearity tests," *Phys. Rev. Lett.*, vol. 77, no. 4, p. 635, 1996.

[9] V. Bari, A. Marchi, B. De Maria, G. Rossato, G. Nollo, L. Faes, and A. Porta, "Nonlinear effects of respiration on the crosstalk between cardiovascular and cerebrovascular control systems," *Phil. Trans. Royal Soc. A*, vol. 374, no. 2067, p. 20150179, 2016.