

Investigating High-Order Behaviors in Multivariate Cardiovascular Interactions via Nonlinear Prediction and Information-Theoretic Tools

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Abstract—Objective: Assessing the synergistic high-order behaviors (HOBs) that emerge from underlying structural mechanisms is crucial to characterize complex systems. This work leverages the combined use of predictability and information-theoretic measures to detect and quantify HOBs in synthetic and physiological network systems. **Methods:** After providing formal definitions of mechanisms and behaviors in a complex system, measures of statistical synergy are defined as the whole-minus-sum (WMS) excess of mutual predictability (Δ_{MP}) or mutual information (Δ_{MI}) observed when considering the system as a whole rather than as a combination of its units. The two measures are computed using model-free methods based on nonlinear prediction and entropy estimation. **Results:** The application to simulated linear Gaussian systems and nonlinear deterministic and stochastic dynamic systems shows that Δ_{MP} tends to vanish for target variables influenced by additive effects of single independent source variables and is positive in the presence of group interactions between sources, while Δ_{MI} exhibits a higher propensity to display positive

values. Then, the analysis of physiological variables shows significant values of Δ_{MI} when investigating the additive effect of systolic and diastolic arterial pressure on mean arterial pressure, and of both Δ_{MP} and Δ_{MI} when assessing how diastolic pressure is modulated by pre-ejection period and left-ventricular ejection time. **Conclusion:** HOBs can be more clearly identified by information-theoretic WMS measures, while prediction WMS measures appear more sensitive to synergy arising from the governing rules of the system analyzed rather than from pure statistical dependencies. **Significance:** Quantifying HOBs through WMS measures sensitive to complex structural mechanisms can provide new biomarkers to assess physio-pathological alterations of cardiovascular networks.

Index Terms—High-order interactions, information theory, network systems, predictability, synergy.

I. INTRODUCTION

PHYSIOLOGICAL dynamics arise from complex interactions among parts of the human body at different scales, ranging from small cells to entire organ systems [1]. In this scenario, networks have become a paradigmatic tool to describe interconnected physiological systems, with representations spanning from structural links within each physiological system to functional connectivity between different systems [2]. The field of Network Physiology [2] commonly relies on tools developed in the broader field of Network Science [1], [3] to assess links between central and peripheral organ systems, e.g., for the analysis of brain-heart interactions [4], or within the same physiological system, e.g., to characterize cardiovascular interactions [5]. Nevertheless, it is nowadays widely acknowledged that a comprehensive understanding of real-world network systems necessitates a shift from simplistic representations merely depicting single nodes and their pairwise links to more sophisticated descriptions incorporating interactions among more than two nodes. These interactions, commonly denoted as *high-order interactions* (HOIs), have become the focus of several recent investigations within the field of Network Physiology [6], [7], [8].

Despite groupwise interactions in network systems have long been recognized [9], [10], [11], systematic analyses of HOIs have only recently gained popularity in the study of complex

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systems [12]. Particularly, this interest is driven by two distinct lines of inquiry: the study of structural rules of group interactions governing the causal evolution of the system, typically referred to as *high-order mechanisms* (HOMs) [13], and the statistical assessment of collective activity patterns irreducible to individual components, denoted as *high-order behaviors* (HOBs) [6], [14]. Crucially, mechanisms and behaviors provide complementary but closely related perspectives on the description of high-order phenomena. Although HOMs and HOBs are interrelated, their relationship is far from trivial [15], [16]: simple structures can generate complex HOBs, and complex structures may produce different types of HOBs [16], [17]. Consequently, identifying behavioral signatures can help constrain possible underlying mechanisms, but it does not ensure their full characterization [17].

Assessing the interplay between the two forms of HOIs described above is difficult because, while HOMs can be clearly formulated through mathematical laws involving beyond-pairwise interactions, the definition of HOBs is less unequivocal. In general, HOBs are related to the concept of statistical synergy, whereby the system behavior can be better predicted from considering all its units jointly rather than in isolation [14], [17], [18]. Several approaches exist to operationalize this concept based on nonlinear prediction [19] or information theory [20]. Here, we formalize two different approaches to quantify HOBs from network systems and compare them in simulated systems with known underlying mechanisms and in physiological networks whose underlying interactions are established or well-acknowledged in the literature.

By modelling the behavior of a network system in terms of random variables, given one target and two source variables we quantify synergy as the excess of predictive power or mutual information obtained when the sources are taken jointly to predict the target rather than individually. The resulting “whole-minus-sum” (WMS) measures are implemented in practice employing nearest-neighbor techniques for nonlinear prediction or entropy estimation. These measures are validated in simulated settings, first analytically in Gaussian systems and then empirically in nonlinear deterministic and stochastic dynamic systems with and without HOMs. Then, we applied the method to cardiovascular interactions to assess HOBs in the description of the variability of mean arterial pressure (MAP) from systolic (SAP) and diastolic arterial pressure (DAP), and of the variability of DAP from cardiac pre-ejection period (PEP) and left-ventricular ejection time (LVET). These physiological variables were measured in a resting state and during a postural stress task responsible to evoke changes in their neuro-autonomic modulation.

A preliminary version of this work has been reported in [21]. Matlab codes and functions useful for applying the proposed measures are accessible in the HOBs toolbox.

II. METHODS

A. Definitions of High-Order Mechanisms and Behaviors

Let us consider a network system $\mathcal{S} = \{\mathcal{Y}, \mathcal{X}_1, \dots, \mathcal{X}_{N_s}\}$ in which the activities of the single nodes are described by the target random variable Y and the vector of source

variables $\mathbf{X} = [X_1 \cdots X_{N_s}]$. HOMs are denoted by the presence of group interactions between the sources and the target that cannot be modeled simply using laws involving their pairwise relations [15], [16]. Accordingly, in a system *without* HOMs the target is a noisy function that can be written as a sum of functions each depending on only one source, i.e., $Y = f(\mathbf{X}) = f_1(X_1) + \cdots + f_{N_s}(X_{N_s}) + U$, where f_i are general nonlinear functions and the variable $U \perp \mathbf{X}$ captures the portion of Y unrelated to X_i , $i = 1, \dots, N_s$. When this generalized additive model cannot fully represent the relation between Y and $\mathbf{X}$, e.g., when cross-terms $X_i \cdot X_j$ appear in $f(\cdot)$, the system is said to possess HOMs w.r.t. the target Y .

Differently, a system is said to display HOBs when the statistical dependence of the target on the sources cannot be attributed to any source on its own, but emerges only from the way the sources interact together [15], [20]. Accordingly, given a measure $C(\cdot; \cdot)$ quantifying the statistical coupling between pairs of (possibly vector) variables, the system is said to possess HOBs w.r.t. the target Y when the following synergistic relation holds: $C(Y; \mathbf{X}) > \sum_{i=1}^{N_s} C(Y; X_i)$. This definition formalizes the rationale of WMS measures, which quantify the concept of synergy when the system results more coupled if it is considered as a whole rather than as the sum of its parts.

In the following we will consider only three-node systems ($N_s = 2$); theoretical and computational issues arising for large systems are discussed in Section V.

B. Quantifying High-Order Behaviors Through Predictability and Information-Theoretic Measures

In this section, two WMS measures are defined which quantify the concept of synergy by measuring how much the activity at a target node in a network system is explained better considering the combined influences of some predetermined source nodes than examining their effect in isolation. Specifically, the concept of synergy is operationalized exploiting both nonlinear prediction and information theory.

1) Predictability Measure of HOBs: Within the framework of predictability [22], the synergistic interaction of the sources in influencing the target can be investigated by evaluating how the prediction of the target variable is improved when considering the source variables together rather than separately. In the two-sources case, this is achieved by decomposing the variance of the target into terms related to the residual uncertainty that remains when one or both sources are known. This concept is quantified by the measure of *mutual predictability* (MP), which is defined, when prediction is performed using only one source variable X_i ($i = 1, 2$), as the difference between the variance of the target, σ_Y^2 , and its residual variance, $\sigma_{Y|X_i}^2$, i.e., $\lambda^2(Y; X_i) = \sigma_Y^2 - \sigma_{Y|X_i}^2$. Considering the MP terms between the target and the sources taken both jointly, $\lambda^2(Y; \mathbf{X})$, and separately, $\lambda^2(Y; X_1)$ and $\lambda^2(Y; X_2)$, the WMS measure of synergy is defined as

$$\begin{aligned} \Delta_{\text{MP}}(Y; \mathbf{X}) &= \lambda^2(Y; \mathbf{X}) - \lambda^2(Y; X_1) - \lambda^2(Y; X_2) \\ &= \sigma_{Y|X_1}^2 + \sigma_{Y|X_2}^2 - \sigma_Y^2 - \sigma_{Y|\mathbf{X}}^2. \end{aligned} \quad (1)$$

The measure (1) is related to interaction predictability [19], and it takes positive values when, thanks to the synergistic interplay

between the two sources, the target is better predicted using both sources together rather than in isolation.

2) Information Measure of HOBs: An information-theoretic quantification of the synergistic interactions between two sources and a target variable can be obtained by evaluating the amount of information that the target shares with the sources considered jointly, beyond the information it shares with each source considered individually. This concept is implemented by combining terms representative of the mutual information (MI) shared between the target and the sources. MI is defined, when considering only one source variable X_i , as the difference between the entropy of the target, $H(Y)$, and its entropy conditioned on the source, $H(Y|X_i)$, i.e., $I(Y; X_i) = H(Y) - H(Y|X_i)$. Considering the MI terms between the target variable and the sources together, $I(Y; \mathbf{X})$, and separately, $I(Y; X_1)$ and $I(Y; X_2)$, the WMS measure of synergy is defined as

$$\begin{aligned}\Delta_{\text{MI}}(Y; \mathbf{X}) &= I(Y; \mathbf{X}) - I(Y; X_1) - I(Y; X_2) \\ &= H(Y|X_1) + H(Y|X_2) - H(Y) - H(Y|\mathbf{X}).\end{aligned}\quad (2)$$

This measure corresponds with the known interaction information [20], and takes positive values denoting synergy when the information shared by the target and the two sources is bigger than the sum of the information shared by the target and each source.

C. Practical Computation

Let us consider a realization of length N of the target variable Y , i.e., $y = \{y_1, \dots, y_N\}$, and of the source variables X_1 and X_2 , i.e., $x_1 = \{x_{1,1}, \dots, x_{1,N}\}$ and $x_2 = \{x_{2,1}, \dots, x_{2,N}\}$. We remark that considering each observed data point y_i as a realization of the same random variable Y presupposes the implicit assumption of stationarity for the data-generation process (the same holds for the variables X_1 and X_2). In the following, we describe the methods used to estimate the WMS measures based on predictability and information. Specifically, the MP terms are quantified through nonlinear prediction based on k -nearest neighbor local linear approximation (Section II-C1) [23], while the MI terms are evaluated by nearest-neighbor entropy estimation (Section II-C2) [24]. We stress that predictability and information measures are estimated using model-free approaches, which facilitate the characterization of nonlinearities potentially involved in the analyzed interactions: this aspect is crucial for our analysis, as such approaches enable the identification of nonlinear interactions in systems where HOBs arise from non-additive mechanisms. As an alternative to model-free estimators, nonlinear parametric methods can be adopted to compute the WMS measures; the use of nonlinear regression models showing highly similar performances is reported in the Supplementary Material (Section S1).

1) MP Estimation: The nonlinear approach used here to estimate predictability measures is based on the idea that the interdependencies among target and sources can be locally approximated as linear even if their global relation is assumed to be nonlinear [23]. The approach is used to compute the three MP terms appearing in (1) to quantify Δ_{MP} , i.e., $\lambda^2(Y; \mathbf{X})$,

$\lambda^2(Y; X_1)$, and $\lambda^2(Y; X_2)$. Therefore, this is presented in the following for a generic source variable $X \in \{X_1, X_2, \mathbf{X}\}$.

For each sample of the target variable y_n , a neighbor search is performed in the d -dimensional source space $\{X\}$ by identifying the k nearest neighbors with lowest Chebyshev distance from the source sample x_n , i.e., $z_n = [z_{n_1}, \dots, z_{n_k}]$ being z_{n_i} , $i = 1, \dots, k$, the i^{th} neighbor of x_n . These neighbors are used to write a system of k equations which linearly approximate the dependence of the target variable on the source, i.e., $y_{n_i} = a_i z_{n_i} + u_{n_i}$, where u_{n_i} is the prediction error. The least squares approach is used to solve the linear system and the estimated vector coefficient $\hat{A} = [\hat{a}_1, \dots, \hat{a}_d]$ is then used to predict the target sample, i.e., $\hat{y}_n = \hat{A} z_n$. Moreover, the current sample of the prediction error is obtained as $\hat{u}_n = y_n - \hat{y}_n$ [23]. In this way, the prediction error is estimated for each sample of Y and X , and its variance is taken as the partial variance of Y that cannot be explained by X , i.e., $\sigma_U^2 = \sigma_{Y|X}^2$. The partial variance is finally subtracted from the variance of the target variable to compute the MP term $\lambda^2(Y; X) = \sigma_Y^2 - \sigma_U^2$.

In this work, the optimization procedure introduced in [25] was used to set the number of neighbors k to be used for each of the samples and based on the maximization of the predictability of the target variable given the source. Specifically, the variance of the prediction error σ_U^2 was evaluated for values of k ranging from very local prediction ($k = 2$) to global prediction ($k = N$) and then the value of k corresponding to the lowest σ_U^2 is considered optimal and used to find the MP term.

2) MI Estimation: The model-free nearest-neighbor estimation approach was adopted for the computation of the MI terms needed to obtain Δ_{MI} (see (2)) [26]. Specifically, accounting for the estimation bias deriving from the combination of information terms computed on variables of different dimensions, the formulation introduced in [24] was employed.

Being the joint space of the target variable and both sources, i.e., $\{Y, \mathbf{X}\}$, the highest-dimensional observed space, k neighbors are searched for each sample of the joint variable to compute $I(Y; \mathbf{X})$, and the projected range search used in the lower dimensional spaces to compute $I(Y; X_1)$ and $I(Y; X_2)$. Specifically, the formulas $I(Y; \mathbf{X}) = \psi(k) + \psi(N) - \langle \psi(N_Y + 1) + \psi(N_{\mathbf{X}} + 1) \rangle$ and $I(Y; X_i) = \psi(N) + \langle \psi(N_{Y X_i} + 1) - \psi(N_Y + 1) - \psi(N_{X_i} + 1) \rangle$, for $i = \{1, 2\}$, are employed, where $\langle \cdot \rangle$ represents the average across the N realizations of the variables and, being $\epsilon_{n,k}$ the maximum distance from the generic observation of $[Y, \mathbf{X}]$ to its k^{th} neighbor, with N_Y , $N_{\mathbf{X}}$, $N_{Y X_i}$ and N_{X_i} representing the number of samples in the spaces $\{Y\}$, $\{\mathbf{X}\}$, $\{Y X_i\}$, and $\{X_i\}$ with distance lower than $\epsilon_{n,k}$ from their generic observation, respectively. The number of neighbors k was fixed to 5 according to common choice in literature, which enables a trade-off between the bias and variance of the estimated quantities [27].

D. Statistical Significance

A surrogate data analysis approach was used to assess the significance of the HOI measures evaluated through the predictability and information approaches, i.e., Δ_{MP} and Δ_{MI} . To preserve the statistical structure of each individual variable while

disrupting the correlations between the two sources and the target we applied a circular-shift surrogate strategy. Specifically, each source was shifted by a different number of samples, while the target remained unchanged [19], [28]. The shift magnitude was randomly selected, excluding very small values that would be insufficient to break target-sources correlations. The samples shifted beyond the end of the original source data were wrapped around to the beginning of the surrogate series. The procedure was repeated N_{sur} times, and the considered measure was computed at each iteration, resulting in a distribution. To test for the presence of synergistic interactions (i.e., $\Delta > 0$), the $100(1 - \alpha)^{\text{th}}$ percentile of this distribution was extracted and compared with the original value. Statistical significance was established when the measure exceeded the extracted threshold. For the computation of the Δ_{MP} terms on surrogate data, the optimal values of k found on the original ones for the computation of $\lambda^2(Y; \mathbf{X})$, $\lambda^2(Y; X_1)$, and $\lambda^2(Y; X_2)$ were employed.

III. VALIDATION ON SIMULATIONS

This section investigates the performance of the WMS measures introduced in Section II-B in five simulated scenarios, reproducing a linear Gaussian system (Section III-A) and four nonlinear systems (Section III-B) including coupled logistic maps, coupled Hénon maps, nonlinear autoregressive process and a nonlinear mix of linear autoregressive processes. As these deterministic and stochastic processes are mathematically well-defined, their characterization in terms of HOMs can be established according to the definitions given in Section II-A. Specifically, since in linear Gaussian, coupled logistic and nonlinear stochastic processes the target variable depends on each source separately via additive functions, these systems do not present HOMs. The analyzed coupled Hénon maps and nonlinearly mixed stochastic processes, on the other hand, display a target variable related to the source variables through cross-terms, and thus present HOMs.

A. Linear Gaussian System

The first analyzed system is a linear Gaussian system for which a theoretical analysis is performed providing the exact mathematical derivation of the WMS measures based on MP and MI. Specifically, we consider three variables, Y , X_1 and X_2 with joint Gaussian distribution; without loss of generality, we set zero mean and unit variance for all the variables. Since Gaussian systems are fully described by linear regression models [29], the MP and MI terms needed to compute the WMS measures (1) and (2) can be derived from the models relating the target variable to each individual source, $Y = aX_1 + U_1$ and $Y = bX_2 + U_2$, and to both sources, $Y = \bar{a}X_1 + \bar{b}X_2 + U$, where U_1 , U_2 and U are the Gaussian residual variables unrelated to the predictors. From these models, it is possible to show that the variance of the residuals can be written, in this case with $\sigma_Y^2 = \sigma_{X_1}^2 = \sigma_{X_2}^2 = 1$, as a function of the elements of the covariance matrix of the joint vector variable $[Y X_1 X_2]$ [30]:

$$\sigma_{U_i}^2 = \sigma_{Y|X_i}^2 = 1 - r_i^2, i = 1, 2 \quad (3a)$$

$$\sigma_U^2 = \sigma_{Y|\mathbf{X}}^2 = \frac{1 - (r_1^2 + r_2^2 + r_{12}^2) + 2r_1r_2r_{12}}{1 - r_{12}^2}, \quad (3b)$$

where $r_1 = \mathbb{E}[YX_1]$, $r_2 = \mathbb{E}[YX_2]$, and $r_{12} = \mathbb{E}[X_1X_2]$ are the pairwise correlations between the variables. Then, the WMS predictability measure is obtained substituting (3) in (1):

$$\Delta_{\text{MP}}(Y; \mathbf{X}) = \frac{(r_1^2 + r_2^2)r_{12}^2 - 2r_1r_2r_{12}}{1 - r_{12}^2}. \quad (4)$$

The WMS information measure is obtained considering that the MI between target and source variables become, for jointly Gaussian variables, $I(Y; X_i) = \frac{1}{2} \log \frac{\sigma_Y^2}{\sigma_{U_i}^2}$ and $I(Y; \mathbf{X}) = \frac{1}{2} \log \frac{\sigma_Y^2}{\sigma_U^2}$, and substituting these MI terms in (2):

$$\Delta_{\text{MI}}(Y; \mathbf{X}) = \frac{1}{2} \log \frac{(1 - r_1^2)(1 - r_2^2)(1 - r_{12}^2)}{1 - (r_1^2 + r_2^2 + r_{12}^2) + 2r_1r_2r_{12}}. \quad (5)$$

The above reported analytical formulations allow us to determine the exact values of the WMS measures of synergy based on predictability and entropy as a function of the correlations between pairs of Gaussian variables composing the observed triplet. A first important observation is that, when $r_{12} = 0$, we have $\Delta_{\text{MP}} = 0$ and $\Delta_{\text{MI}} > 0$; thus, if the sources are uncorrelated the WMS entropy measure detects synergistic HOBs, while the WMS predictability measure does not. This is a consequence of the fact that, for independent predictors, the predictive power is additive and thus $\Delta_{\text{MP}} = 0$ by (1); on the other hand, as depicted in Fig. 1(a), the concave property of the logarithm makes $\Delta_{\text{MI}} > 0$.

To investigate how HOBs emerge from the correlation structure of the system, we performed a systematic analysis of the measures Δ_{MP} and Δ_{MI} at varying the pairwise links between variables. Fig. 1(b) shows that, in the presence of equal-strength links between the target and each source ($r_1 = r_2$), only the entropy-based measure can take positive values when the sources are positively correlated ($r_{12} > 0$), while both measures can be positive when the sources are anti-correlated ($r_{12} < 0$). When the target-source correlations are unbalanced (Fig. 1(c)), both measures can be positive for anti-correlated sources but also for positively correlated sources if the target tends to be uncorrelated with one of them; the entropy-based measure displays positive values for a wider range of parameter combinations (Fig. 1(c.2)).

Overall, this simulation evidences that HOBs can emerge even for simple linear systems where the generating equations exclude the presence of HOMs, and that the entropy-based WMS measure shows a higher propensity to display HOBs.

B. Nonlinear Systems

This section reports the comparison of the predictability- and information-based WMS measures computed for nonlinear systems. Given the dynamic nature of all the simulated nonlinear systems, the target and source variables need to be chosen sampling the dynamic processes at a given time step. Here, analyses were performed taking Y_n as the target and $X_{1,n-1}$, $X_{2,n-1}$ as the sources (see (6c), (7c), (8c), (9c)).

In the simulations of nonlinear systems where exact values for the WMS measures cannot be provided, an empirical analysis

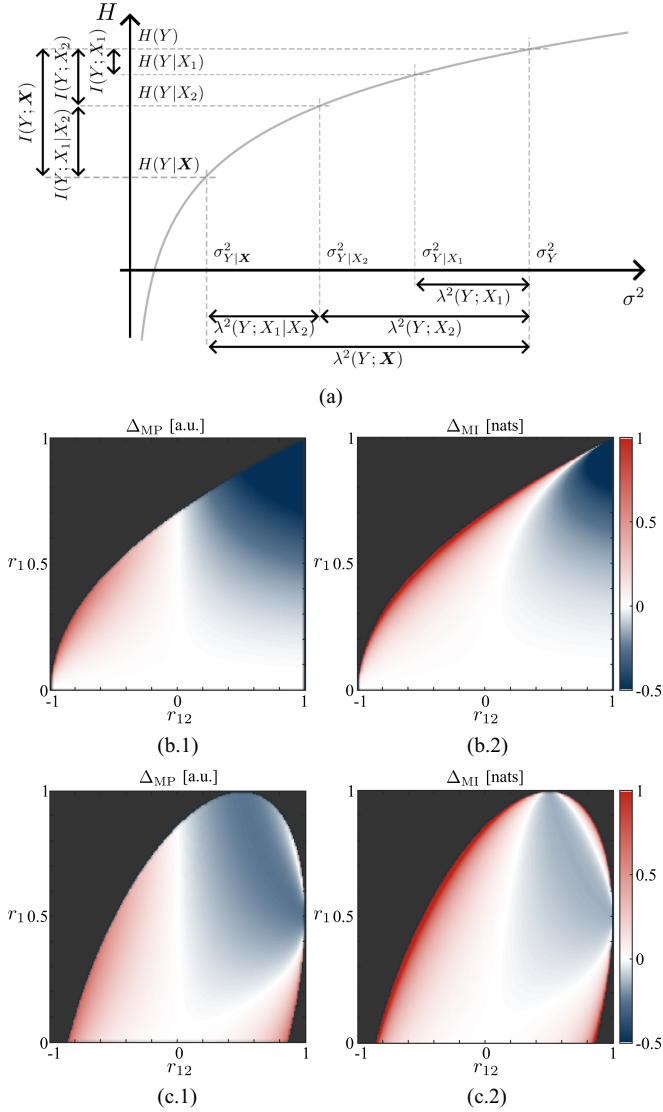


Fig. 1. Detection of HOBs in linear Gaussian systems. (a) Graphical representation of the derivation for Gaussian variables (target Y , sources X_1, X_2) of the predictability and information-theoretic WMS measures defined in (1) and (2); note that, if $X_1 \perp X_2$, $\lambda_{Y;X_1|X_2}^2 = \lambda_{Y;X_1}^2$ and thus $\Delta_{MP}(Y; X) = 0$, but $I(Y; X_1|X_2) > I(Y; X_1)$ and thus $\Delta_{MI}(Y; X) > 0$. (b), (c) Color-coded values of $\Delta_{MP}(Y; X)$ and $\Delta_{MI}(Y; X)$ at varying the strength of the link between the sources (r_{12}) and between the target and each source, either balanced ($r_1 = r_2$, (b)) or unbalanced (r_1 , with fixed $r_2 = 0.5$, (c)).

was conducted by generating fifty realizations of length $N = 1000$. For each realization, the measures Δ_{MP} and Δ_{MI} were estimated and their statistical significance was assessed by using one-hundred surrogate data, generated by randomly shifting the source variables of at least 50 samples, and fixing a significance threshold of $\alpha = 0.05$. The results of the analysis are reported in Fig. 2, showing the values and the statistical significance of the two WMS measures computed for each simulation. Moreover, simulations were repeated to investigate scenarios reproducing conditions of practical relevance in which the measures can be affected by factors such as data length, measurement noise, and confounding latent variables; these scenarios are described in

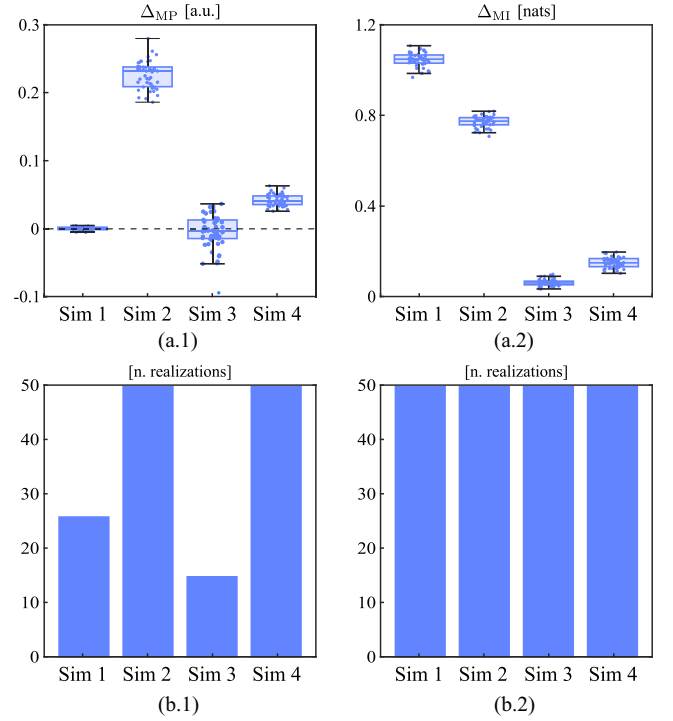


Fig. 2. Detection of HOBs in nonlinear deterministic and stochastic systems with and without HOMs. Panels depict boxplots with individual values of the predictability (a.1) and information-theoretic (a.2) WMS measures, and number of realizations for which the measures were detected as statistically significant (b.1), (b.2), for the simulations of coupled logistic maps (Sim 1), coupled Hénon maps (Sim 2), nonlinear autoregressive processes (Sim 3), and nonlinearly coupled linear autoregressive processes (Sim 4).

detail the supplementary material (Sections S2, S3; Figs. S2, S3, S4).

1) Nonlinear Deterministic System Without HOMs: In the first empirical simulation (Sim 1), two logistic maps in the chaotic regime are coupled linearly to generate a discrete-time deterministic nonlinear system defined by the equations [31], [32]:

$$X_{1,n} = 3.9X_{1,n-1}(1 - X_{1,n-1}), \quad (6a)$$

$$X_{2,n} = 3.7X_{2,n-1}(1 - X_{2,n-1}), \quad (6b)$$

$$Y_n = c_1X_{1,n-1} + c_2X_{2,n-1} + 0.1Y_{n-1}, \quad (6c)$$

where $c_1 = 0.9$ and $c_2 = 0.7$ are the parameters controlling the linear influence of the processes X_1 and X_2 on Y , respectively. Initial random conditions were selected from uniform distribution in the range $[0, 1]$ and a transient period of 500 samples discarded for each realization.

As shown in Fig. 2, this setting results in high and always significant Δ_{MI} values and in values of Δ_{MP} very close to zero (about half of the realizations detect significant synergy). These results reproduce empirically the results of the theoretical simulation in Section II-A showing that, in this nonlinear system with independent non-Gaussian sources and in the absence of HOMs, HOBs are clearly detected by entropy-based WMS measure but not by the prediction-based one.

2) Nonlinear Deterministic System With HOMs: In the second empirical simulation (Sim 2), we study a nonlinear deterministic system composed by three coupled Hénon maps, defined by the equations [33], [34]:

$$X_{1,n} = 1.4 - X_{1,n-1}^2 + 0.3X_{1,n-2}, \quad (7a)$$

$$X_{2,n} = 1.4 - X_{2,n-1}^2 + 0.3X_{2,n-2}, \quad (7b)$$

$$Y_n = 1.4 - c(X_{1,n-1} + X_{2,n-1})^2 + 0.3Y_{n-1}, \quad (7c)$$

with $c = 0.5$ the coupling parameter. Again, for each realization, initial random conditions were fixed by considering uniformly distributed values in the range $[0 \ 1]$ and the initial transient period of 500 samples discarded.

Fig. 2 shows how both Δ_{MP} and Δ_{MI} take high positive values which are statistically significant in all realizations of the simulation. These results indicate that, in this nonlinear system with independent non-Gaussian sources and in the presence of HOMs, both the prediction-based and the entropy-based WMS measures clearly detect the presence of HOBs.

3) Nonlinear Stochastic System Without HOMs: The third simulation (Sim 3) realizes the nonlinear first-order vector autoregressive process defined by the stochastic equations [33], [35]:

$$X_{1,n} = 3.4X_{1,n-1}(1 - X_{1,n-1}^2)e^{-X_{1,n-1}^2} + 0.1e_{1,n}, \quad (8a)$$

$$X_{2,n} = 3.4X_{2,n-1}(1 - X_{2,n-1}^2)e^{-X_{2,n-1}^2} \quad (8b)$$

$$+ 0.5X_{1,n-1}X_{2,n-1} + 0.1e_{2,n},$$

$$Y_n = 3.4Y_{n-1}(1 - Y_{n-1}^2)e^{-Y_{n-1}^2} + c_1X_{1,n-1}^2 + c_2X_{2,n-1} + 0.1e_{3,n}, \quad (8c)$$

where the coefficients $c_1 = 0.5$ and $c_2 = 0.3$ set the strength of the additive effect of the sources X_1 and X_2 on the target Y , respectively, and e_i , $i = 1, \dots, 3$, are uncorrelated white Gaussian noises with zero mean and unit variance. Here, realizations of the simulations were obtained drawing random samples for the noise inputs.

The results depicted in Fig. 2 highlight a similar situation than that described in Section III-B1, with high and statistically significant values of Δ_{MI} and low and barely significant values of Δ_{MP} . The larger dispersion of Δ_{MP} might be due to the correlation between the sources which could possibly induce a detection of HOBs also with the prediction-based method.

4) Nonlinear Stochastic System With HOMs: The last simulation (Sim 4) considers a system with two autoregressive processes X_1 and X_2 that interact nonlinearly to determine a third process Y , according to [36], [37]:

$$X_{1,n} = 0.8X_{1,n-1} + 0.2e_{1,n}, \quad (9a)$$

$$X_{2,n} = 0.6X_{2,n-1} + 0.2e_{2,n}, \quad (9b)$$

$$Y_n = 0.5Y_{n-1} + c(X_{1,n-1}X_{2,n-1}) + 0.2e_{3,n}, \quad (9c)$$

being $c = 2$ the coupling parameter, and e_i , $i = 1, \dots, 3$, uncorrelated Gaussian noises with zero mean and unit variance. Again, different realizations of the processes were obtained drawing random samples for the inputs and iterating the system equations.

Fig. 2 shows that, similarly to the system described in Section III-B2, both Δ_{MP} and Δ_{MI} measures are positive and statistically significant in all realizations, documenting the existence of HOBs according to both prediction and entropy approaches.

5) Dependence on Noise, Data Length and Latent Variables: The four nonlinear systems described in this Section were analyzed to study the effects of factors which are expected to have an impact on the entropy- and predictability-based WMS measures. The analysis of the dependence on additive noise and reduction in the length of the data sequences analyzed (Section S2) revealed that both these factors tend to decrease the magnitude of the WMS measures and impair their statistical significance. In particular, we found that even a small amount of additive noise (with variance equal to 10 % of that of the original data) can often impair the detection of HOBs (Fig. S2). The dependence on data length was less critical, with a preserved capability to detect statistically significant HOBs also starting from data sequences as short as 200 points (Fig. S3). The impact of these two factors is stronger on Δ_{MI} than on Δ_{MP} , and is less evident when HOBs emerge from HOMs, thus suggesting that the presence of structural synergy confers robustness to the detection of synergistic behaviors.

The analysis of the effects of latent variables (Section S3) revealed that the common driver effect of such unmeasured variables generally tends to introduce redundant information within the investigated systems, which is manifested by a bias of both Δ_{MI} and Δ_{MP} towards lower values, often negative and not statistically significant values (Fig. S4). While these detrimental effects were always detected if the confounder was set to affect both the target and the source variables, the behavior was more heterogeneous when the confounder was set to act only on the sources or on the target and only one source; interestingly, we observed instances in which HOBs were enhanced by the presence of confounders acting on the sources but not on the target, suggesting such cases as potential amplifiers of statistical synergy.

IV. APPLICATION TO PHYSIOLOGICAL DATA

The proposed frameworks of analysis were applied to investigate the presence of synergistic HOBs in two representative small-size networks underlying the short-term regulation of cardiovascular system. Specifically, the two proposed WMS measures were computed to investigate arterial pressure interactions, exploring the well-known linear relationship explaining how MAP is determined by SAP and DAP [38], as well as cardiovascular interactions, exploring the less studied nonlinear dependence between mechanical heart timing parameters of PEP and LVET in influencing DAP values [39].

A. Experimental Protocol and Data Acquisition

Part of a big dataset comprising cardiovascular and cardiorespiratory signals for investigating physiological response to stressors was employed [40], [41], [42]. Specifically, data acquired from a cohort of 84 young healthy subjects (50 females, age

range 18.65 ± 3.20 years) performing the head-up tilt maneuver were analyzed.

Subjects underwent a two phases protocol consisting of a resting state period of 15 minutes (REST), during which they lied in a supine position, and of an orthostatic stress condition of 8 minutes (HUT), during which they were passively tilted to 45 degrees by means of a motorized bed. All subjects were asked to spontaneously breathe during the execution of the protocol. No signs of presyncope were evidenced for the whole cohort during HUT.

The recorded signals were the electrocardiogram (ECG), finger photoplethysmographic arterial blood pressure (BP, volume-clamp method) and impedance cardiography (ICG) signal. The latter signal evaluates changes in the trans-thoracic impedance ΔZ as proportional to volume and blood flow velocity variations in the aorta, as well as changes in blood volume in the transthoracic region over time as the first mathematical derivative of ΔZ , i.e., dZ/dt . All signals were synchronously acquired with a sampling frequency of 1 kHz.

The experimental protocol was approved by the ethical committee of the Jessenius Faculty of Medicine, Comenius University, Slovakia. All subjects or their legal representatives, in participants under 18 years of age, signed a written informed consent before the examination. Detailed information on experimental protocol and signal acquisition is provided in [40], [41].

B. Time Series Extraction and Pre-Processing

Starting from the acquired signals, the following physiological beat-to-beat time series representative of the variability of different cardiovascular parameters were extracted. The n^{th} systolic and diastolic arterial pressure, S_n and D_n , were obtained as the first maximum of the BP waveform measured after the n^{th} heartbeat detected from the ECG, and as the first minimum measured after the $(n + 1)^{\text{th}}$ heartbeat, respectively. The mean arterial pressure, M_n , was calculated as the average of the BP waveform considered between D_{n-1} and D_n . Moreover, starting from the dZ/dt waveform, PEP and LVET time series were obtained as follows. After the identification of the points B (first notch after n^{th} ECG R peak) and X (first significant minimum after n^{th} ECG R peak) corresponding to the opening and closure of the aortic valve, respectively, P_n is obtained as the time difference between the n^{th} B point in the ICG derivative and the onset of n^{th} Q wave in the ECG signal, and L_n as the time difference between the n^{th} X and B points in dZ/dt .

For each subject and condition, visually stationary 300-samples time series were extracted after the stabilization of the physiological parameters, i.e., around 8 minutes after the beginning of the REST phase, and to avoid the transient period due to the tilting procedure, i.e., around 3 minutes after the beginning of the HUT phase. The considered time series were preprocessed through a zero-phase highpass autoregressive filter with a cutoff frequency of 0.0156 Hz to remove slow trends. Moreover, outliers detected as samples falling above the 75th percentile or below the 25th percentile of the distribution representing the whole series were removed and replaced via the cubic spline interpolation approach.

C. Data and Statistical Analysis

High-order interactions within the two systems composed of the variables $\{M, S, D\}$ and $\{D, P, L\}$ were evaluated by using the WMS measures Δ_{MP} and Δ_{MI} considering the variables M and D as target, respectively, and the other two variables as sources. MP and MI measures were computed as detailed in Section II-C, and the statistical significance of the two WMS measures evaluated for each subject, condition, and physiological system through the surrogate data analysis approach described in Section II-D generating one-hundred testing data by randomly shifting the two source variables of at least 20 samples.

Statistical differences between the two acquisition phases were assessed for both Δ_{MP} and Δ_{MI} in the two physiological systems via the paired nonparametric Wilcoxon signed rank test. Moreover, the Fisher's test of proportion was applied to statistically evaluate the variation in the proportion of significant synergistic interactions occurred in the two conditions for both measures and settings, as well as in the two setting for both measures during the same condition. A significant threshold of $\alpha = 0.05$ was employed for all statistical tests.

D. Results

Fig. 3 shows the distributions across subjects of Δ_{MP} (panel a.1) and Δ_{MI} (panel a.2) measures considering the contribution of SAP and DAP to MAP (left) and of PEP and LVET to DAP (right), as well as the number of subjects for which the two WMS measures are significant (panels b).

Overall, Δ_{MP} takes negative values when considering the $\{M, S, D\}$ system, with a significant decrease from REST to HUT and almost zero significance in both conditions. On the contrary, Δ_{MP} is mostly positive for the $\{D, P, L\}$ system, with values that are low but statistically significant for approximately half of the subjects during both REST and HUT. The Fisher's test confirms the significance of this modulation across the two investigated systems.

As regards Δ_{MI} , it reveals a slightly positive average value at REST in the system $\{M, S, D\}$ which significantly decreases during HUT leading to a prevalence of negative values; this decrease is confirmed statistically by comparing the number of subjects for which the WMS measure is assessed as significant. On the other hand, the values of Δ_{MI} obtained for the system $\{D, P, L\}$ are mainly unvaried between conditions, with average close to zero and a number of statistically significant positive values close to half of the subjects in both conditions. The Fisher's test reveals a significantly higher number of subjects demonstrating synergistic interactions in the system $\{D, P, L\}$ compared to the system $\{M, S, D\}$ during HUT.

V. DISCUSSION

This study presents a thorough analysis of HOBs in complex network systems using nonlinear prediction and information-theoretic frameworks, aimed at investigating how the detection of functional HOIs depends on the underlying structural HOMs. In particular, we examine how WMS measures of statistical

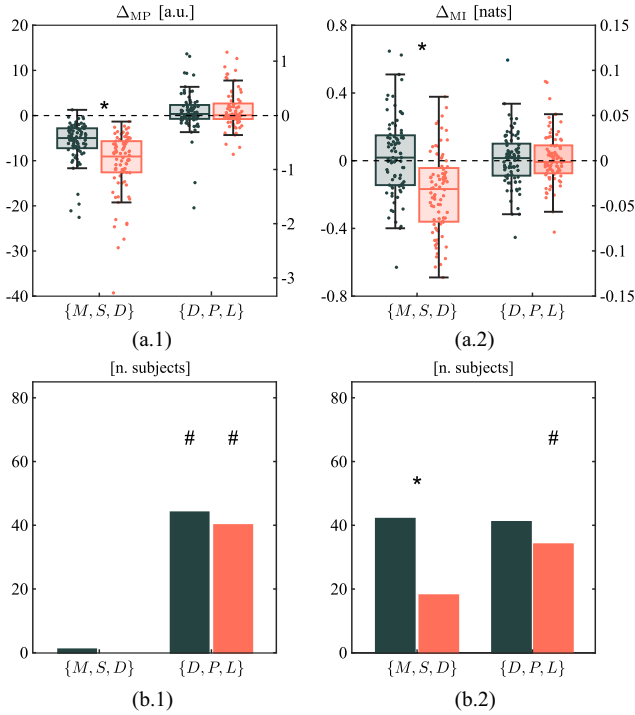


Fig. 3. Detection of HOBs in cardiovascular interactions. Panels depict boxplots with individual values of the predictability (a.1) and information-theoretic (a.2) WMS measures, and number of realizations for which the measures were detected as statistically significant (b.1), (b.2), for the two investigated physiological networks, i.e., $\{M, S, D\}$ obtained considering MAP (M) as target and SAP (S) and DAP as sources, and $\{D, P, L\}$ obtained considering DAP (D) as target and PEP (P) and LVET (L) as sources, at REST (bluish) and during HUT (pinkish). Statistical test in (a): Wilcoxon signed rank test, * $p < 0.05$, REST vs. HUT. Statistical tests in (b): Fisher's test, * $p < 0.05$, REST vs. HUT; # $p < 0.05$, $\{M, S, D\}$ vs. $\{D, P, L\}$.

high-order dependencies based on predictability or entropy functionals behave similarly or differently in the presence or absence of structural high-order effects in the generative equations. We first consider linear Gaussian systems, a benchmark case enabling the study of HOBs in absence of HOMs, and then extend the analysis to nonlinear deterministic and stochastic systems displaying either additive source–target relation or groupwise interactions, in accordance with the definition of HOMs as mechanisms arising from structural dependencies that cannot be decomposed into individual source effects. Lastly, we apply the framework of analysis to physiological variables descriptive of cardiovascular control systems, whose underlying relationship can be hypothesized based on previous literature.

Our analyses conducted in various simulation scenarios suggest that synergistic behavioral effects are quite commonly detected across different types of network systems, ranging from linear to nonlinear and from static to dynamic systems, as well as from deterministic to stochastic systems. Specifically, we observed how HOBs emerge in systems characterized by groupwise interactions, thus defined by HOMs, as in the case of nonlinearly coupled Hénon maps and autoregressive processes, but also in systems determined by a simple additive effect of their parts, thus in systems without HOMs as in the case of

linearly mixed logistic maps and nonlinear stochastic processes, and even in simple linear Gaussian systems. Moreover, the comparison of the results achieved by using the WMS concept operationalized through the MP and MI measures provides important insights about the detection of HOBs, both in general and in relation to the presence of HOMs. First, we found that the measure Δ_{MI} is more effective than the measure Δ_{MP} in displaying synergistic HOBs, as it took positive values for more parameter combinations in the theoretical analysis of Gaussian systems (Fig. 1), and assumed statistically significant values for all the settings simulated in the empirical analysis of nonlinear systems (Fig. 2). Furthermore, the full statistical significance of both Δ_{MP} and Δ_{MI} in the presence of HOMs (see Sim 2 and Sim 4 in Fig. 2) suggests the ability of the two WMS measures to detect HOBs evoked by HOMs. Nevertheless, we observed that the measure Δ_{MP} vanishes in the absence of HOMs when the sources are independent (e.g., for the linear Gaussian system when $r_{12} = 0$, as well as in Sim 1 and Sim 3); this results confirms recent theoretical works [30], [43]. However, Δ_{MP} turned out to be significantly positive even without HOMs when the sources are correlated (see Fig. 1(b.1), (c.1)). Therefore, we conclude that, compared to Δ_{MI} , Δ_{MP} is less sensitive to HOBs but more specific to HOMs, although its specificity is reduced by the correlation among the sources. Overall, in line with the many studies employing information-theoretic approaches to investigate functional HOIs [6], [7], [14], our observations suggest that Δ_{MI} should be preferred to assess HOBs, and that nonlinear prediction measures should be further investigated as a promising tool to dissect HOMs from empirical data [43], [44].

Similarly, the application of the two WMS measures on the considered cardiovascular systems revealed how HOIs investigated in terms of behaviors can be related to mechanisms. Importantly, the physiological behaviors investigated in the two analyzed cardiovascular systems are clinically relevant: deeper knowledge about the relations between arterial pressure components, as well as with heart timing parameters reflecting the mechanical functioning of heart, could be of interest in the treatment of patients with stroke, head injury and hypertension [38], [39] and the evaluation other hemodynamic parameters [39], [41]. When considering the system $\{D, P, L\}$ investigating the effects of PEP, reflecting the crucial time intervals between electrical depolarization and ejection of blood from the heart, and of LVET, reflecting the heart's phase of pumping blood in the aorta, on the diastolic arterial pressure, positive and quite significant values of both Δ_{MP} and Δ_{MI} are observed. This result, suggesting the possible presence of HOBs arising from HOMs, is supported by the nonlinear and non-additive underlying structural relation, and by the known correlation existing between D_n and the ratio of P_n and L_n [39]. On the other hand, the negative Δ_{MP} values, together with the positive and more significant values for Δ_{MI} observed especially at rest for the system $\{M, S, D\}$, agree with the known presence of a linear and additive relation between SAP and DAP in determining MAP [38]. In fact, when non-continuous blood pressure measurements are available, MAP values are usually estimated from SAP and DAP through the relation $M_n = \frac{2}{3}S_n + \frac{1}{3}D_n$, which – in accordance

of our definition of HOMs – suggests that the high-order characterization of the relation between arterial pressure components does not depend on a joint influence of SAP and DAP, but just from their additive effect. Nevertheless, it is interesting to note how the modulation between the two experimental phases is coherent with the two WMS measures, revealing a decrease during HUT for the system $\{M, S, D\}$. This shift towards less synergistic interactions can be attributed to the impact of the mechanisms that act in response to orthostatic stress on arterial pressure dynamics – such as baroreflex mediated sympathetic activation – which in turn lead to alterations in arterial stiffness and vasomotion probably weakening the relation between the three arterial pressure components [41]. Moreover, in line with our observations in Section III-A, this decrease could be also be ascribed to the similar influence that such regulatory mechanisms have on SAP and DAP values strengthening their positive correlation.

Our observations on both simulated and physiological data converge in identifying the predictability measure Δ_{MP} as a less sensitive quantity for detecting HOBs in absence of HOMs and, conversely, the information measure Δ_{MI} as a measures able to highlight the presence of HOBs, regardless of whether these are generated by hidden structural laws implying groupwise interactions or simple additive effects generating emergent statistical dependencies. Accordingly, using the WMS measures based on nonlinear predictability and information-theoretic frameworks in parallel presents a well-founded engineering approach for identifying the presence of HOBs and providing possible insights into the statistical or structural nature of the resulting high-order effects. The robustness of the achieved results, as well as the straightforward computation of Δ_{MP} and Δ_{MI} measures based on simple MP and MI terms, suggest the efficacy of our approach in the broad field of HOIs. In this regard, it is noteworthy to highlight that the methodologies currently used to explore these interactions are often based on a-priori assumptions about the system, computationally demanding approaches, or measures that are difficult to extend to high-dimensional systems [12], [45], [46].

Nevertheless, it is also important to acknowledge the potential limitations of the proposed approach and the required improvements. First, estimation bias and variance must be considered, as these factors can obscure the results, particularly in the context of short-length data. Moreover, the limited robustness of the employed estimation strategies to noise should be carefully considered when investigating HOBs, since even low levels of noise affecting the system can hinder substantially the detection of synergistic interactions. Second, when interpreting results obtained from real-world data, the potential influence of unmeasured or disregarded variables acting as confounders on both target and source variables should be carefully considered, as these confounders may mask the detection of HOBs. For example, investigated physiological data may be influenced by physiological confounders such as total peripheral resistance (TPR) or the unmeasured sympathetic nervous activity [47], as well as by artifact-related confounders introduced during data acquisition. Finally, it should be acknowledged that, although the concept of WMS is easy to grasp and implement, it conflates

synergy and redundancy into a single metric, leading to an underestimation of the true high-order synergistic interactions. This issue is exacerbated at increasing the dimension of the system analyzed, because of the known effect of multiple counting redundancy within WMS measures at increasing the number of source variables. It has been indeed demonstrated that this problem already impacts the WMS measures computed for three source variables and grows proportionally with the number of sources [48], [49]. With this regard, future research should investigate the use of approaches able to differentiate the synergistic and redundant components of multivariate interactions, e.g. computed via the framework of Partial Information Decomposition [45], to more finely characterize HOBs arising from both structural or statistical dependencies.

VI. CONCLUSION

In conclusion, we propose using measures that implement the concept of WMS in analytical frameworks of nonlinear prediction and information theory to investigate HOBs in complex network systems. Our findings suggest that the information measure Δ_{MI} has a greater ability to observe higher-order effects when considering beyond-pairwise interactions and that the predictability measure Δ_{MP} is more sensitive in identifying HOBs arising from the presence of HOMs. Accordingly, the integrated perspective resulting from the proposed parallel approach rigorously exploits HOIs and possibly recognizes synergistic effects originating from system's underlying mechanisms or emergent behaviors.

Though preliminary, this work could enhance the ability to disambiguate the nature of the intricate interactions governing the physiological networks underlying the regulation of the homeostatic function of the human organism. This can provide significant advancements in modelling and interpreting poorly understood physiological interactions, as well as in developing new biomarkers to assess physio-pathological alterations of cardiovascular networks.

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