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Univariate and multivariate conditional entropy measures for the characterization of short-term cardiovascular complexity under physiological stress

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Abstract

Objective: A defining feature of physiological systems under the neuroautonomic regulation is their dynamical complexity. The most common approach to assess physiological complexity from short-term recordings, i.e. to compute the rate of entropy generation of an individual system by means of measures of conditional entropy (CE), does not consider that complexity may change when the investigated system is part of a network of physiological interactions. This study aims at extending the concept of short-term complexity towards the perspective of network physiology, defining multivariate CE measures whereby multiple physiological processes are accounted for in the computation of entropy rates. *Approach*: Univariate and multivariate CE measures are computed using state-of-the-art methods for entropy estimation and applied to time series of heart period (H), systolic (S) and diastolic (D) arterial pressure, and respiration (R) variability measured in healthy subjects monitored in a resting state and during conditions of postural and mental stress. *Main results*: Compared with the traditional univariate metric of short-term complexity, multivariate measures provide additional information with plausible physiological interpretation, such as (i) the dampening of respiratory sinus arrhythmia and activation of the baroreflex control during postural stress; (ii) the increased complexity of heart period and blood pressure variability during mental stress, reflecting the effect of respiratory influences and upper cortical centers; (iii) the strong influence of D on S, mediated by left ventricular ejection fraction and vascular properties; (iv) the role of H in reducing the complexity of D, related to cardiac run-off effects; and (v) the unidirectional role of R in influencing cardiovascular variability. *Significance*: Our results document the importance of employing a network perspective in the evaluation of the short-term complexity of cardiovascular and respiratory dynamics across different physiological states.

1. Introduction

Physiological systems exhibit complex dynamical behaviors, resulting from the combined effect of multiple regulatory mechanisms, coupling effects and feedback interactions among structural units (Glass 2001, Burggren and Monticino 2005). In addition, physiological dynamics are subject to modifications under different physiological states or pathological conditions which are reflected in the output signals of the different physiological systems. As a consequence, the study of the temporal dynamical structure of physiological signals has raised great interest in both research and clinical communities.

In this context, different and sometimes elusive meanings have been proposed for the concept of 'physiological complexity'. On the one hand, there exists a body of research that relates physiological complexity to the presence of long-range fractal correlations and nonlinear interactions in physiological signals (Hausdorff *et al* 1995, Ivanov *et al* 1999). This definition of complexity stems from the observation that healthy physiological systems (e.g. heartbeat fluctuations, interstride interval fluctuations) show self-similarity properties over multiple time scales, and that when these multiscale properties are disrupted the capability of systems to respond to external challenges is reduced (Lipsitz and Goldberger 1992, Goldberger *et al* 2002, Schumann *et al* 2010). Measures quantifying this type of complexity are applied to long recordings, that allow the observer to study physiological dynamics happening at a wide range of different time scales. On the other hand, a different approach is adopted by techniques that aim to quantify the short-term complexity of physiological signals, spanning time scales in the order of a few minutes. In this case, complexity is associated to the concept of regularity of the temporal patterns found in the observed signals, and typically quantifies the unpredictability of the present sample of a physiological time series given a small number of its past samples (Porta *et al* 2007b). Paradoxically, long-range correlations may represent a confounding factor for this type of analysis, being represented by slow trends that are commonly treated as non-stationarities to be filtered out through appropriate preprocessing (Xiong *et al* 2017). The most used approaches for the quantification of short-term complexity belong to the information-theoretic domain and stem from the work of Pincus, who devised a family of metrics to be applied to short, noisy and stochastic signals, measuring the rate of generation of new information, named approximate entropy (Pincus 1991). Subsequent refinements of this pioneering work led to the development of a range of measures, among which sample entropy (Richman and Moorman 2000), corrected conditional entropy (Porta *et al* 1998), fuzzy entropy (Chen *et al* 2007) and permutation entropy (Bandt and Pompe 2002) are the most popular. All these measures are subsumed by the general notion of entropy rate, computed as the conditional entropy (CE) of the present value of a time series given its own past values (Faes and Porta 2014).

A typical application of entropy-based short-term complexity analysis is the study of spontaneous fluctuations of the heart period, for the characterization of autonomic function and its changes associated with cardiovascular diseases, stress conditions, ageing, etc (Porta *et al* 2009). Besides heart rate variability, conditional entropy measures have been applied to assess the short-term complexity of other physiological signals such as arterial blood pressure (Angelini *et al* 2007, Turianikova *et al* 2011), respiration (Dragomir *et al* 2008, Papaioannou *et al* 2011), and others (Burioka *et al* 2005, Mansur *et al* 2010, Karmakar *et al* 2013). Even though the short-term complexity analysis of individual systems has provided helpful markers of health and disease, recent evidence highlights the fundamental importance of studying physiological phenomena within a network perspective (Ivanov *et al* 2016). This perspective arises from the knowledge that physiological systems do not evolve in isolation, but rather are highly interconnected and mutually interdependent of each other, showing patterns of interaction that are subject to changes depending on physiological states or pathological conditions (Bashan *et al* 2012, Bartsch *et al* 2015). It is therefore likely that the complexity of the dynamical behavior of a target physiological system is reduced when the joint dynamics observed from mutually connected systems are taken into account. On this basis, the present work aims to extend the concept of short-term complexity, traditionally defined for the dynamics of a single physiological system, to a more general concept of multivariate complexity, to be defined when the observed system is the target of a network of physiological interactions. To this aim, a multivariate extension of the univariate definition of CE is proposed, which allows to quantify how systems in the network contribute to predict the dynamics of the target system.

In this work, univariate and multivariate definitions of CE are exploited to study the complexity of the time series of the heart period, systolic blood pressure, diastolic blood pressure and respiratory volume measured from healthy subjects in resting condition and during commonly studied physiological stressors, i.e. orthostatic stress and mental stress. This is in line with recent approaches developed in the time, frequency or information domain (non-linear prediction, phase synchronization, Granger causality) that employ multivariate descriptions to characterize cardiovascular and cardiorespiratory interactions under the principles of network analysis and have proven their effectiveness in extracting physiologically relevant indices of system functioning and dysfunctioning (Schulz *et al* 2013, Porta and Faes 2016). A comparison between univariate and multivariate approaches for the assessment of complexity of short-term cardiovascular control has been carried out in Porta *et al* (2012) using linear prediction models, but here nonlinear features are accounted for by the proposed model-free information-theoretic approach. The objective is to characterize the physiological function in well-known conditions of postural stress or under less-established mentally challenging paradigms, emerging from modifications in the complexity of cardiac, blood pressure and respiratory dynamics. Cardiovascular and respiratory systems are known to reflect autonomic changes that are involved in the physiological response to stress and show behaviors that are highly dependent on each other (Haken and Koepchen 1991, Eckberg 2000). In this context, the proposed multivariate approach may help in typifying the autonomic response to postural or mental challenge, unravelling the physiological interaction mechanisms underlying the changes in the complexity of individual control systems.

2. Materials and methods

2.1. Complexity measures

Short-term physiological complexity is quantified in this work in the information-theoretic domain using measures of conditional entropy applied to the study of temporal dynamics, as defined in the following.

Let us consider a dynamical system $\mathcal{Y}$ represented by the dynamical process Y, whose present outcomes at time n are described by the scalar random variable $Y' = Y_n$, while the past outcomes are modelled by the vector random variable $\mathbf{Y}^- = [Y_{n-1}, Y_{n-2}, \ldots]$. Stationary and ergodic assumptions hold for process Y, so that the dependence on the time index n is dropped in Y' and $\mathbf{Y}^-$.

The traditional approach to evaluate short-term complexity considers the process Y in isolation, so that the (univariate) conditional entropy of its present on the past is computed as (Faes and Porta 2014)

$$H(Y'|\mathbf{Y}^-) = -\mathbb{E}[\log p(y'|\mathbf{y}^-)], \tag{1}$$

where H stands for the Shannon entropy, y' is an observation of the random variable Y', $\mathbf{y}^-$ is an observation of $\mathbf{Y}^-$ and the expectation $\mathbb{E}[\cdot]$ is taken over all possible values of y' and $\mathbf{y}^-$. $H(Y'|\mathbf{Y}^-)$ quantifies how much uncertainty remains in Y' after $\mathbf{Y}^-$ is known, or equivalently the information contained in the present of process Y that cannot be explained by the knowledge of its past.

Here, we extend the definition of complexity to a multivariate setting. Let us suppose that a network $\mathcal{Z}$ of M interacting systems is considered, composed of system $\mathcal{Y}$, called *target*, and $M-1$ other systems, here denoted as $\mathcal{X}_1, \mathcal{X}_2, \ldots, \mathcal{X}_{M-1}$, represented by the dynamical processes $X_1, X_2, \ldots, X_{M-1}$ and called *drivers*. The multivariate process representing the time evolution of the whole network is indicated as $Z = \{Y, X_1, X_2, \ldots, X_{M-1}\}$ and stationary and ergodic assumptions are assumed to be verified. Within this setting, multivariate complexity can be defined as the conditional entropy of the present of Y on the past of all processes in the network as

$$H(Y'|\mathbf{Z}^-) = -\mathbb{E}[\log p(y'|\mathbf{z}^-)], \tag{2}$$

where $\mathbf{Z}^- = [\mathbf{Y}^-, \mathbf{X}_1^-, \mathbf{X}_2^-, \ldots, \mathbf{X}_{M-1}^-]$ is the collection of the vector variables describing the past of Z and $\mathbf{z}^-$ is an observation of it. $H(Y'|\mathbf{Z}^-)$ quantifies how much uncertainty remains in Y' after $\mathbf{Z}^-$ is known, or equivalently the information contained in the present of process Y that cannot be explained by the knowledge of the past of all processes in the network. In other words, $H(Y'|\mathbf{Z}^-)$ represents the complexity of process Y when the past of the whole network is supposed to be known.

It is important to notice that $H(Y'|\mathbf{Y}^-)$ represents an upper bound to the complexity computed as in (2), that holds when the driver processes do not concur to resolve the uncertainty about the target process, i.e. when $p(y'|\mathbf{z}^-) = p(y'|\mathbf{y}^-)$ for all possible values of $\mathbf{y}^-$ and $\mathbf{z}^-$.

Generalizing (1) and (2), let us define W as the process composed of a subset of processes in the network Z. The conditional entropy of Y' given the past vector variable $\mathbf{W}^-$ is defined as

$$H(Y'|\mathbf{W}^-) = -\mathbb{E}[\log p(y'|\mathbf{w}^-)], \tag{3}$$

where $\mathbf{w}^-$ is an observation of $\mathbf{W}^-$. $H(Y'|\mathbf{W}^-)$ quantifies how much uncertainty remains in Y' after the past of the subset W of processes in the network Z is known. Note that (3) particularizes to the Shannon entropy of Y, $H(Y)$, when $W = \{\cdot\}$, to (1) when $W = Y$ and to (2) when $W = Z$. This generalization is used in the following paragraph for the outline of an iterative algorithm used to explore the contributions of systems in the network in yielding the multivariate conditional entropy of the target.

The algorithm starts with an M-dimensional set $\mathbf{C}^- = \{\mathbf{Y}^-, \mathbf{X}_1^-, \mathbf{X}_2^-, \ldots, \mathbf{X}_{M-1}^-\}$ of candidate vectors, collecting the past vector variables of all processes in the network, and an empty set $\mathbf{S}^- = \{\cdot\}$ of selected vectors. At each iteration i, the conditional entropy $H(Y'|[C^-, \mathbf{S}^-])$ is computed for each candidate vector $C^- \in \mathbf{C}^-$ and the candidate C_i^- bringing the minimum value of conditional entropy is selected as $C_i^- = \arg\min H(Y'|[C^-, \mathbf{S}^-])$. Then, the reduction in entropy associated to the selection of C_i^- is computed as $\Delta H_i = H(Y'|\mathbf{S}^-) - H(Y'|[C_i^-, \mathbf{S}^-])$ and C_i^- is removed from $\mathbf{C}^-$ and added to $\mathbf{S}^-$. The algorithm terminates when $\mathbf{C}^-$ is empty. The order in which systems are added to $\mathbf{S}^-$ is indicative of the relative contribution to the entropy reduction of the target, while the reduction in entropy that is obtained at each step represents the mutual information shared between Y' and C_i^-, conditioned to the knowledge of $\mathbf{S}^-$.

It is necessary to point out that this selection method is not exhaustive and, even though it leads to the minimum entropy when all systems have been selected, it may incur in local minima along the procedure. This means that the order in which systems are selected does not necessarily imply that at each step the global minimum of the conditional entropy is found, e.g. it is possible that there exist another set of systems (not meeting the requirement of being sequentially updated) that minimizes conditional entropy globally. Nevertheless, this approach provides a relevant indication about the systems that are involved in the reduction of the entropy of the target and may be preferred over exhaustive search methods for computational reasons, especially when the number of systems in the network is large.

2.2. Estimation strategy

In practical applications, information-theoretic measures need to be estimated from experimental data, available in terms of time series, i.e. finite-length time-ordered collections of observations of the processes under study. In this work, conditional entropy was estimated using a model-free approach based on nearest neighbors (Kozachenko and Leonenko 1987, Kraskov *et al* 2004, Faes *et al* 2015). Since conditional entropy, as defined in (3), can be expressed as a difference of entropy terms as

$$H(Y'|\mathbf{W}^-) = H(Y', \mathbf{W}^-) - H(\mathbf{W}^-), \tag{4}$$

let us first consider the nearest neighbor approach for the estimation of Shannon entropy. Given a generic d-dimensional random variable $\mathbf{V}$ having a continuous probability density $p_V(\mathbf{v})$ of observation of its outcomes $\mathbf{v}$, Shannon entropy is defined as $H(\mathbf{V}) = -\int p_V(\mathbf{v}) \log p_V(\mathbf{v}) d\mathbf{v}$. When N finite samples $\mathbf{v}_i, i = 1, \ldots, N$ drawn from $p_V(\mathbf{v})$ are available, it is possible to approximate $H(\mathbf{V})$ via a Monte-Carlo method as $\hat{H}(\mathbf{V}) = -\frac{1}{N}\sum_{i=1}^{N} \log \hat{p}_V(\mathbf{v}_i)$, where $\hat{p}_V(\mathbf{v}_i)$ is estimated from the k nearest neighbors of $\mathbf{v}_i$. The nearest neighbor estimator (Kozachenko and Leonenko 1987) is based on the following assumptions:

- the distance between each sample and its kth nearest neighbor is treated as a random variable, here named ϵ, with probability density $p(\epsilon)$ that follows a trinomial distribution;
- $\hat{p}_V(\mathbf{v}_i)$ is supposed to be constant within a ball having radius ϵ and centered in $\mathbf{v}_i$, whose probability mass is given by $P_i(\epsilon) = c_d \epsilon^d \hat{p}_V(\mathbf{v}_i)$, where c_d is the volume of the d-dimensional unit ball, $c_d = 1$ when maximum norm is used as a distance measure.

Shannon entropy is then estimated as

$$\hat{H}(\mathbf{V}) = \psi(N) - \psi(k) + \log(c_d) + \frac{d}{N}\sum_{i=1}^{N} \log \epsilon(i), \tag{5}$$

where $\psi(\cdot)$ is the digamma function and $\epsilon(i)$ is twice the distance from $\mathbf{v}_i$ to its kth nearest neighbor. The entropy terms in (4) could in principle be estimated using (5), however there exist two limitations that need to be dealt with. First, the infinite-dimensional vector variable $\mathbf{W}^-$ needs to be approximated using a finite number of past samples L, as $\mathbf{W}^- \approx \mathbf{W}^L$. A procedure for the selection of the L past samples is described in the next section. Secondly, the different dimensions of the estimation spaces of the entropy terms ($1 + L$ and L respectively) result in different biases affecting the estimates that need to be corrected if terms are to be subtracted. These different biases can be compensated following the strategy proposed in Kraskov *et al* (2004), that consists in performing the traditional *neighbor search* in the highest dimensional space only and compute the distances $\epsilon(i)$, then projecting the computed distances in the lower dimensional spaces and compute the corresponding number of neighbors for each low dimensional sample (*range search*). As a result, conditional entropy is obtained as

$$\hat{H}(Y'|\mathbf{W}^L) = \frac{1}{N}\sum_{i=1}^{N} \left[\psi(k_{\mathbf{w}_i^L} + 1) + \log \epsilon(i)\right] - \psi(k) + \log(c_1), \tag{6}$$

where $\mathbf{w}_i^L$ is the ith realization of $\mathbf{W}^L$, $k_{\mathbf{w}_i^L}$ is the number of neighbors having distance $<\epsilon/2$ from $\mathbf{w}_i^L$ and c_1 is the volume of the monodimensional unit ball. In this study the maximum norm was used as a distance measure, so that $\log(c_1) = 0$.

2.2.1. *Approximation of the vector of past values*

The nearest neighbor estimator is based on the assumption that $\mathbf{W}^L$ is a finite-dimensional vector variable of dimension L, where L represents the number of past samples that are considered in the conditional entropy estimate. This number can be fixed, performing a uniform embedding. In case $W = [W_1, W_2, \ldots, W_m]$ is composed of m processes, the uniform embedding consists in selecting l past samples for each process, so that $L = ml$ and $\mathbf{W}^L = [W_{1,n-1}, \ldots, W_{1,n-l}, W_{2,n-1}, \ldots, W_{2,n-l}, \ldots, W_{m,n-1}, \ldots, W_{m,n-l}]$. However, this is not the best choice in terms of estimation accuracy, because of the likely inclusion of irrelevant and redundant components in $\mathbf{W}^L$, that do not effectively contribute to reduce the uncertainty of the target process, but result in an increase of the dimension of $\mathbf{W}^L$. This issue is particularly critical in the analysis of short time series, where the dimension of the embedding space (L) should be kept sufficiently low in order not to incur in the curse of dimensionality, i.e. a decrease of estimation performance that affects most entropy estimators at increasing dimensions.

In order to solve for this issue, the non-uniform embedding procedure proposed in Faes *et al* (2011a) is used here. The procedure works as follows. First, a set C of candidate past terms is built taking $l_{\max}$ past samples for each process belonging to W, so that $C = \{W_{1,n-1}, \ldots, W_{1,n-l_{\max}}, W_{2,n-1}, \ldots, W_{2,n-l_{\max}}, \ldots, W_{m,n-1}, \ldots, W_{m,n-l_{\max}}\}$ and an empty set $S = \{\cdot\}$ of selected terms is defined. Then, at each iteration, the conditional entropy $H(Y'|[c, S])$ is computed for each element $c \in C$ and the candidate c^* bringing the minimum value of conditional entropy is

selected as $c^* = \arg\min H(Y'|[c, S])$ and tested for statistical significance against a set of conditional entropies obtained from surrogate time series. In case the significance is verified, c^* is removed from C and added to S. The procedure stops either when significance of a candidate is not met or when the vector C is empty.

The non-uniform embedding allows to form a vector of past values that only includes past terms that are useful to explain the dynamics of the target process and can be related to physiologically relevant phenomena (as will be shown in figure 3 and discussed in section 4), thus keeping the dimension of the embedding space at its lowest while taking all relevant components into consideration.

2.3. Experimental protocol and data analysis

2.3.1. Subjects

Sixty-one healthy volunteer subjects (37 female, 24 male) aged 17.5 years ±2.4 years took part to this study. All subjects were normotensive and within the normal range of body mass index (19–25 kg m^{-2}). Subjects were instructed not to use substances influencing autonomic nervous system activity or cardiovascular system activity. Female subjects were examined in the proliferative phase (6th–13th day) of the menstrual cycle. All procedures were approved by Ethical Committee of the Jessenius Faculty of Medicine, Comenius University, Bratislava and all participants signed a written informed consent. When the subject was a minor (less than 18 years of age), parental or legal guardian permission was obtained for the child to participate in the study.

2.3.2. Experimental protocol

Volunteers were positioned on a motorized tilt table with foot support and secured to it with a restraining strap at the thigh level. During the experiment, subjects were asked to avoid disturbing movements or speaking. The study protocol consisted of four phases. First, subjects underwent 15 min of rest in the supine position (REST), aimed at stabilizing physiological parameters on a baseline level. After that, a head-up tilt (HUT) test was performed tilting the motorized table to 45 degrees for 8 min, in order to evoke mild orthostatic stress. The transition from 0 to 45 degrees took approximately 5 s. The procedure was followed by 10 min of supine rest, to allow physiological parameters to recover a baseline value. Finally, a mental arithmetic (MA) test (WQuick software with WIN 5 PMT test, Psycho Soft Software, s.r.o., Brno, Czech Republic) lasting 6 min was administered while subjects were lying in the supine position, aimed at evoking mild cognitive load. The test consisted of a repeated display of random three-digit numbers on the ceiling of the examination room by a data projector. Subjects were asked to mentally sum up the three digits and, if the result was a two-digit number, keep summing up until a one-digit number was reached. After that, they were asked to decide if the result was odd or even by clicking the corresponding virtual button projected on the ceiling by means of a computer mouse. Subjects were asked to perform mental computations as quickly as possible and with the minimum number of errors, with the purpose of providing a further increase in the stress level.

Physiological signals were recorded non-invasively from the volunteer subjects for the duration of the whole experiment. The electrocardiographic signal was obtained through a horizontal bipolar thoracic lead (CardioFax ECG-9620, NihonKohden, Japan), the continuous finger arterial blood pressure was measured by the photoplethysmographic volume-clamp method (Finometer Pro, FMS, Netherlands), while the respiratory volume signal was collected through respiratory inductive plethysmography (RespiTrace 200, NIMS, USA) employing thoracic and abdominal belts. All signals were digitalized at 1kHz sampling rate.

2.3.3. Time series extraction

Segments of 300 heart beats were extracted from the recorded signals starting 8 min after the beginning of the first phase (REST window), 3 min after the beginning of the second phase (HUT window) and 2 min after the beginning of the fourth phase (MA window), being representative of the physiological state during supine rest, orthostatic posture and mental arithmetic task respectively. The windows were selected at physiological equilibrium in order to avoid transition effects from one phase to another and thus favour the stationarity of the extracted segments. The time series of the consecutive heart periods (H) was extracted from the ECG after locating the R peaks and computing the duration of successive RR intervals. The respiratory volume signal was sampled at the onset of each RR interval, so that one respiratory volume sample (R) was available for each H value. The beat-to-beat systolic blood pressure (S) was computed as the maximum value of blood pressure signal within a given RR interval, while the beat-to-beat diastolic blood pressure (D) as the minimum value of blood pressure following the current S value and preceding the next one. Figure 1(a) shows the employed conventions for the measurement of H, S, D and R. The correct detection of the R peaks was visually checked in order to avoid erroneous or missed beats, and the occurrence of isolated ectopic beats was corrected by linearly interpolating with the closest unaffected values in all time series and conditions. In order to fulfill stationarity criteria, slow trends were removed from each time series by means of an autoregressive IIR zero-phase high-pass filter (cutoff frequency: 0.015 Hz) (Nollo *et al* 2000). Moreover, outliers (mainly affecting the R time series) were identified using Tukey's test (Tukey 1977) and removed, for a maximum of 42 removed samples per time series. An example

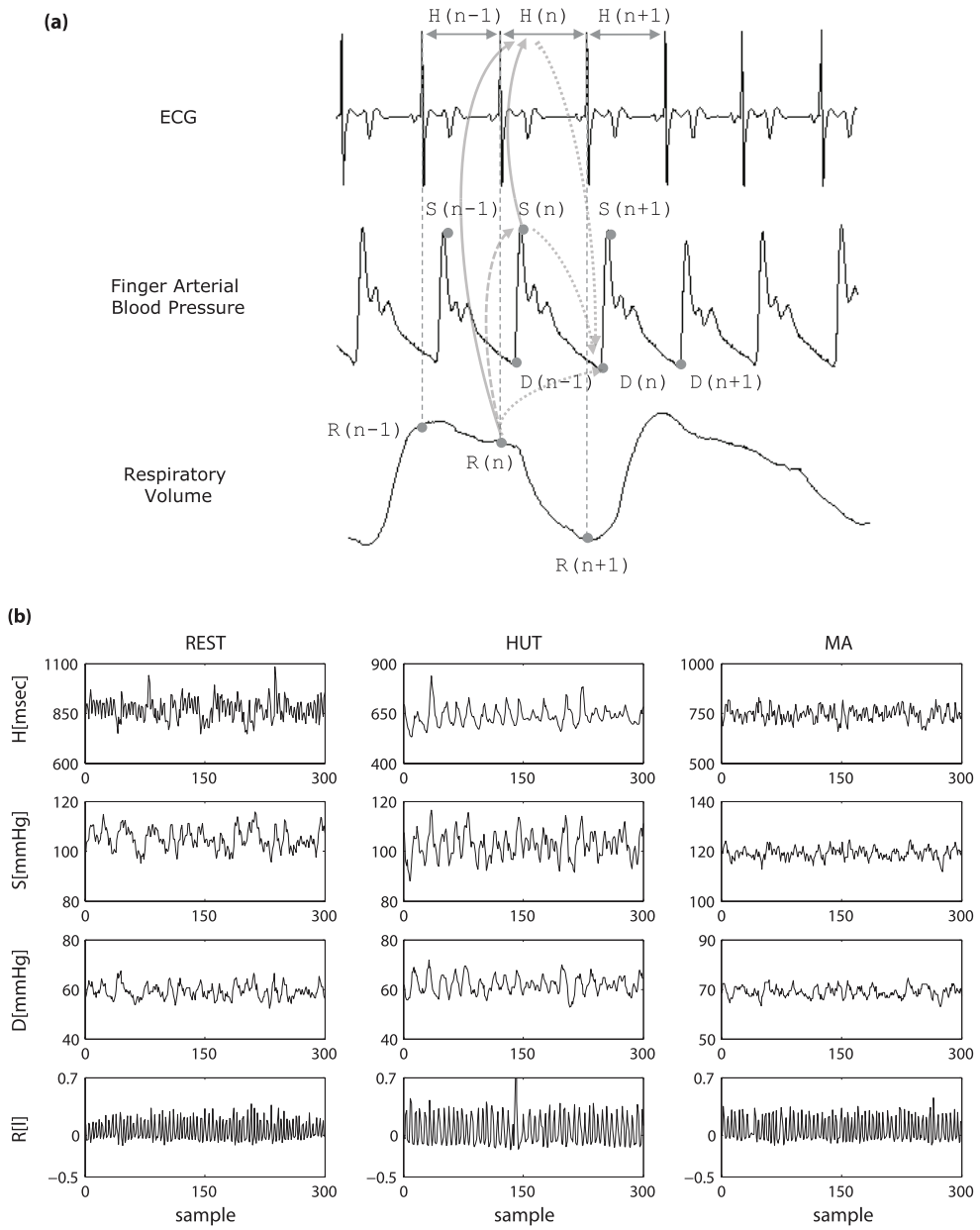

Figure 1. (a) Schematic representation of the measurement of beat-to-beat time series of heart period (H), systolic blood pressure (S), diastolic blood pressure (D) and respiratory volume (R). Light-grey arrows indicate the presence of instantaneous effects (i.e. occurring within the same heart beat) from S and R to H (solid arrows), from R to S (dashed arrow) and from H, S and R to D (dotted arrows). (b) Example of the four measured time series for a subject undergoing supine rest (REST), head-up tilt test (HUT) and mental arithmetic task (MA). Slow trends are removed implementing a high-pass filter.

of four measured time series of a subject during the three experimental protocol phases is shown in figure 1(b). The subsequent information-domain analysis was performed after normalizing time series to zero mean and unit variance.

2.3.4. *Information-domain analysis*

The complexity of H, S, D and R was computed in the REST, HUT and MA conditions using the univariate and the multivariate formulations of conditional entropy described in section 2.1 and considering the network $\mathcal{Z}$ as being composed of all the measured systems, i.e. H, S, D and R. Because of how time series were constructed, instantaneous effects (i.e. effects occurring within the same heart beat) from drivers to target systems were considered in the multivariate computation, by including zero-lagged samples in the candidate vector C of past samples to be used in the non-uniform embedding procedure. In particular, instantaneous effects were set from S and R to H (figure 1(a), solid arrows), from R to S (figure 1(a), dashed arrow) and from H, S and R to D (figure 1(a), dotted arrows). The non-uniform embedding procedure was initialized using a candidate vector including $l_{\max} = 10$ past samples for each past variable considered in the computation, and the number of selected samples was counted for each experimental condition and target signal. A number of $k = 10$ neighbors was used in the

Table 1. Time-domain indices of mean (μ) and standard deviation (σ) of heart period (H), systolic blood pressure (S), diastolic blood pressure (D) and respiration (R) time series in the REST, head-up tilt (HUT) and mental arithmetic (MA) protocol phases. The distribution of each index across subjects is described as the median and IQR (25th—75th percentile).

	REST		HUT		MA	
μ_H	**916**	**(862–965)**	**724**[a]	**(664–760)**	**794**[a, b]	**(751–856)**
μ_S	**120.7**	**(115.4–127–3)**	**113.4**[a]	**(106.1–120.8)**	**130.4**[a, b]	**(125.4–139.8)**
μ_D	**70.1**	**(66.1–75.5)**	**71.3**	**(63.4–75.4)**	**78.1**[a, b]	**(72–82.5)**
μ_R	—	—	—	—	—	—
σ_H	**60.4**	**(42.8–82.3)**	**40.9**[a]	**(33.9–51.7)**	**45.5**[a, b]	**(36.3–59)**
σ_S	**4.3**	**(3.5–5)**	**4.8**[a]	**(3.9–5.6)**	**3.1**[a, b]	**(2.7–3.9)**
σ_D	**3.0**	**(2.6–3.4)**	**3.4**[a]	**(3–4)**	**2.7**[a, b]	**(2.4–3.1)**
σ_R	**0.139**	**(0.113–0.163)**	**0.163**[a]	**(0.141–0.211)**	**0.137**[b]	**(0.113–0.155)**

[a] $p < 0.05$ REST versus HUT or REST versus MA.
[b] $p < 0.05$ HUT versus MA.

conditional entropy estimates (Faes *et al* 2015). The iterative procedure described in section 2.1 was applied to the network composed of H, S, D and R in the REST, HUT and MA conditions, alternatively setting each system as target.

2.4. Statistical analysis

Significant modifications in univariate and multivariate complexity across the three experimental conditions included in the protocol were assessed via the Kruskal–Wallis ANOVA test, followed by Wilcoxon signed rank test used as post-hoc test on pairs of distributions of conditional entropy values across the 61 subjects of the study. Significance level was set at $p < 0.05$ and Bonferroni correction for multiple comparisons was applied in post-hoc testing, which consisted of three comparisons between pairs of conditions. A one-tailed Wilcoxon signed rank test was applied to check the significance of the difference between the multivariate and the univariate approach for the computation of complexity, by pooling REST, HUT and MA conditions. The same statistical tests were applied to the distributions of the number of lagged components selected by the non-uniform embedding procedure.

3. Results

Table 1 provides a time-domain characterization of the four measured time series in terms of traditional time-domain indices of mean and standard deviation, expressed as the median and IQR (25th–75th percentiles) of the distributions across subjects. Significant modifications of the indices across conditions were assessed as detailed in section 2.4. The mean of the respiratory signal is omitted as it only depends on the measurement procedure. The expected cardiac response to physiological stress is reflected in the reduced duration of mean heart period (tachycardia) during both HUT and MA when compared to resting state. In addition, both conditions result in a reduction of the standard deviation of the RR intervals, a parameter that was previously associated to decreased vagal tone and/or increased cardiac sympathetic activity (Kleiger *et al* 1987, Rothschild *et al* 1988), common indicators of stress reaction. The mean systolic blood pressure is found to be lower during HUT than at baseline, but is kept within a normal physiological range. This decrease is compatible with the HUT protocol, triggering a drop in blood pressure that is restored to normal values through the activity of the baroreceptors. The variability (standard deviation) of both blood pressure variables is increased with HUT, consistent with previous studies (Faes *et al* 2011b, Porta *et al* 2012). Contrarily to the HUT stress, the MA task results in increased mean values and decreased variability of systolic and diastolic blood pressure. The respiratory volume pattern shows an increased variability with HUT, reflecting an increased tidal volume.

Figure 2 shows the results of the univariate (three bars on the left of each panel) and multivariate (three bars on the right of each panel) complexity analysis of the heart period, systolic blood pressure, diastolic blood pressure and respiration time series in the three experimental conditions elicited in the protocol. The multivariate complexity of H, S and D is found to be significantly lower than the univariate, independently of the condition ($\Delta H = 0.11$, $p = 8.4 \times 10^{-25}$ for H; $\Delta H = 0.23$, $p = 6.2 \times 10^{-32}$ for S; $\Delta H = 0.13$, $p = 6.3 \times 10^{-16}$ for D). On the contrary, univariate and multivariate complexity of R are not found to differ significantly ($\Delta H = -0.05$, $p > 0.05$). Considering the traditional univariate approach, the conditional entropy (CE) of H and of D is found to significantly decrease with HUT when compared to the REST condition (figures 2(a) and (c)). On the other hand, MA results in a significantly increased complexity of the blood pressure variables (S and D) and of R with respect to REST (figures 2(b)–(d)). Similar results are obtained when the multivariate conditional entropy is computed, showing significantly reduced complexity of the heart period control with HUT and significantly increased blood pressure and respiratory complexity with MA. In addition, the multivariate approach identifies

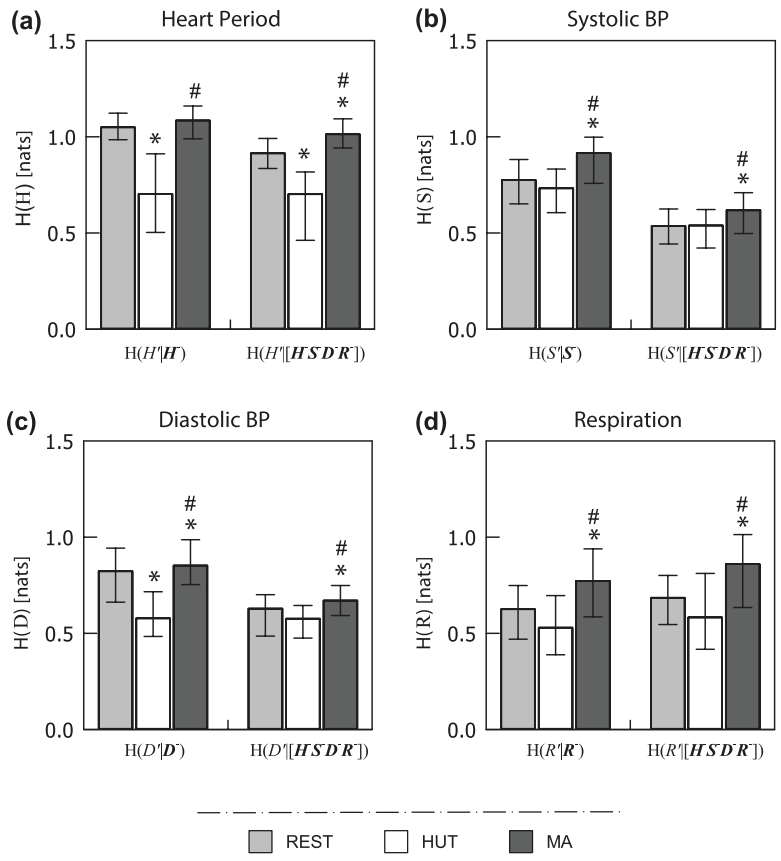

Figure 2. Complexity of the heart period (a), systolic blood pressure (b), diastolic blood pressure (c) and respiration (d) time series computed using the traditional univariate approach (on the left) and its multivariate extension (on the right) in the REST, head-up tilt (HUT) and mental arithmetic (MA) protocol phases. Bar plots show the median and IQR of the distributions of conditional entropy across the 61 subjects of the study. $*$ $p<0.05$ REST versus HUT or REST versus MA. # $p<0.05$ HUT versus MA.

an increased complexity of H when MA is performed (figure 2(a)). When HUT and MA are compared, significant differences in complexity are found for all time series and using either univariate or multivariate approach.

Figure 3 shows, for each assigned target series, the number of lagged components selected by the non-uniform embedding procedure from the past of the target series only (univariate approach, left part of each panel) or from the past of all series (multivariate approach, right part of each panel). For all target time series, the multivariate approach selected a significantly higher number of components than the univariate approach (Wilcoxon signed rank test for pooled data, $p = 3.3 \times 10^{-14}$ for H, $p = 4.9 \times 10^{-29}$ for S, $p = 5.2 \times 10^{-24}$ for D, $p = 1.6 \times 10^{-18}$ for R). Looking at the differences across conditions, the number of components selected to predict H decreased significantly moving from REST to HUT, and increased significantly moving from HUT to MA using both approaches (figure 3(a)). HUT was associated also with the selection of more components using the univariate approach for the prediction of S (figure 3(b)), and with the selection of less components using the multivariate approach for the prediction of D (figure 3(c)). On the other hand, MA was associated with the selection of a large number of components for the prediction of R using the multivariate approach (figure 3(d)).

Figure 4 shows the results of the application of the iterative procedure for the evaluation of the contributions to entropy reduction to the heart period, systolic blood pressure, diastolic blood pressure and respiration time series in the three experimental conditions included in the protocol. On the x axis, the sequence of systems C_i^- that are selected at each iteration (the ones minimizing conditional entropy) are shown, while the y axis reports the corresponding reduction in the entropy ΔH_i of the target that is obtained at each iteration. The results show that in three out of four target systems (H, D and R) the first iteration selects the past of the target system itself, independently of the condition (figures 4(a), (c) and (d)). The entropy of S instead is mostly reduced by the knowledge of the past of D, regardless of the condition (figure 4(b)). At the second iteration, the entropy of the heart period is mostly reduced by R at REST and during MA, and by S during HUT (figure 4(a)). The entropy of the systolic blood pressure is self explained at the second iteration, regardless of the condition (figure 4(b)). The entropy of the diastolic blood pressure is mostly reduced at the second iteration by H, but only at REST and during MA (figure 4(c)). When the respiration time series is set as target, no further significant reduction in entropy is obtained at the second iteration, regardless of the condition (figure 4(d)); the third and fourth iterations do not

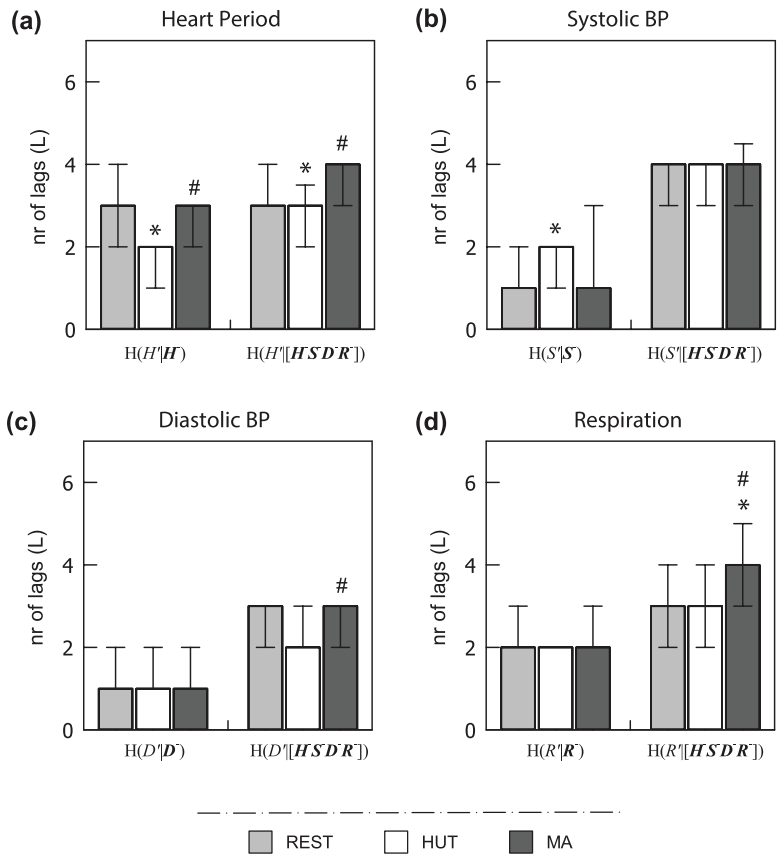

Figure 3. Number of lagged components selected by the non-uniform embedding procedure as best predictors of the dynamics of the target time series of the heart period (a), systolic blood pressure (b), diastolic blood pressure (c) and respiratory volume (d) from the past of the target itself (on the left) or from the past of the whole network (on the right) in the REST, head-up tilt (HUT) and mental arithmetic (MA) protocol phases. Bar plots show the median and IQR of the distributions of the number of lagged components (L) across the 61 subjects of the study. ∗ $p<0.05$ REST versus HUT or REST versus MA. # $p<0.05$ HUT versus MA.

bring additional entropy reductions and reflect estimation errors for most time series and conditions, as highlighted by the presence of negative values, that would not be theoretically admitted.

4. Discussion

This study was aimed at exploring univariate and multivariate approaches for the characterization of short-term physiological complexity quantified by the information-theoretic measure of conditional entropy. Whereas the univariate approach represents a standard method that is applied to isolated systems, the multivariate approach is defined here in the perspective of networks of interacting systems. Even though points in common can be found between the two methods, the discrepancies emerging from the analysis are informative about the role that the network has in driving the dynamics of a target system. Conditional entropy measures have been used in this study to characterize modifications in the complexity of the cardiac chronotropic control, blood pressure control and respiratory activity under conditions of postural and mental stress.

4.1. Comparison of univariate and multivariate approaches for the evaluation of complexity

Our results show that the multivariate approach yields significantly lower values of conditional entropy with respect to the univariate approach in the assessment of the complexity of H, S and D. This finding is indicative of the fact that the network significantly contributes to reduce the complexity of the heart period and blood pressure dynamics (figures 2(a)–(c)); it is further supported by the significantly higher number of components that are used in the multivariate entropy estimates when compared to the univariate (figures 3(a)–(c)). On the contrary, univariate and multivariate complexity of R are not found to significantly differ, meaning that the network does not provide a significant contribution in reducing the complexity of the respiratory dynamics, despite the higher number of lagged samples that are selected using the multivariate approach.

In addition, univariate and multivariate approaches were also found to differ in the ability to detect significant modifications in complexity across conditions. Whereas this does not happen for S and R, where the same pattern of significant changes is detected using either approach, univariate and multivariate approaches provide

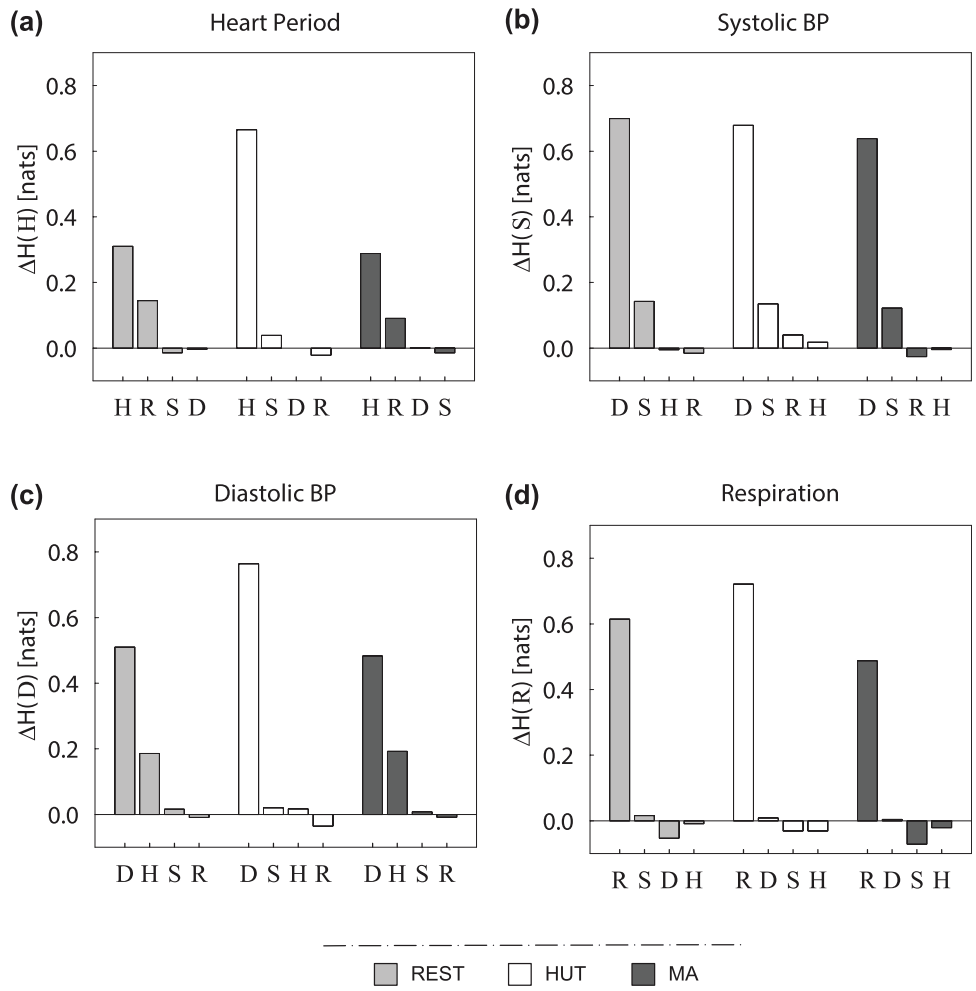

Figure 4. Contribution of driver effects in the physiological network composed of the systems regulating heart period (H), systolic blood pressure (S), diastolic blood pressure (D) and respiratory volume (R) in reducing the entropy of the target systems, represented alternatively by H (a), S (b), D (c) and R (d), in the rest (REST), head-up tilt (HUT) and mental arithmetic (MA) protocol phases. For each panel and bar group, the label associated to the *i*th bar indicates the system that is selected at the *i*th iteration, while the height of the *i*th bar indicates the reduction in entropy of the target that is obtained by conditioning on the past of the selected system, given the knowledge of all the previously selected systems. The median of the distribution across the 61 subjects of the study is shown.

different outcomes for H and D, that are indicative of the contribution of the network in determining the complexity of the target system under different conditions. In particular, the significantly increased complexity of H during MA detected only by the multivariate approach reflects a strong contribution of the network at REST that is reduced during MA (figure 2(a)). Similarly, the significantly decreased complexity of D during HUT detected only by the univariate approach is the result of a more important contribution of systems in the network at REST than during HUT (figure 2(c)). Both these results suggest that the application of a physiological stress seems to favour the isolation of systems by reducing the influences from the connected network nodes.

An alternative interpretation of these results in terms of flow of information between systems can be made observing that the difference between univariate and multivariate conditional entropy is formally defined as the transfer entropy (Schreiber 2000) from the driver systems in the network to the target system. From this perspective, it is possible to infer that (i) there is a joint transfer of information from H, D and R to S that is manifested to a comparable extent in all conditions; (ii) no information seems to be transferred to R from the cardiovascular variables; (iii) the amount of information that is jointly transferred to H from S, D and R at REST undergoes a significant reduction with MA; and (iv) the amount of information that is jointly transferred to D from H, S and R at REST undergoes a significant reduction with HUT. Similar findings are present in recent studies, that report an almost unchanged amount of information transferred to the systolic blood pressure regulation from cardiac and respiratory regulation mechanisms as a consequence of either mental or postural challenge when compared to resting state (Faes *et al* 2017), a significant decrease of joint information transferred from respiratory and blood pressure control systems to the cardiac process as a consequence of mental stress (Faes *et al* 2017) and a significant reduction of the information transferred to the diastolic blood pressure dynamics from the heart period oscillations as a consequence of postural challenge (Javorka *et al* 2017).

4.2. Contributions of the network to entropy reduction of the target

The results of the iterative procedure presented in section 2.1 provide a further level of detail about the dominant contributions of systems in the network in yielding the complexity quantified by the multivariate approach. Figure 4 shows, for each target system and experimental condition, the subsequent reductions in entropy that are obtained at each iteration conditioning the present of the target on the past of the system that is selected at the current iteration, given that the past of all the previously selected systems in the network is known. In particular, at each iteration the selected system is the one yielding the lowest conditional entropy, i.e. the one explaining the most the dynamics of the target system. As a consequence, the order in which systems are selected is indicative of their relative influence in reducing the complexity of the target, which is quantified as an entropy reduction. It is not surprising that H, D and R are best explained by their own past (the target system itself is selected at the first iteration in figures 4(a), (c) and (d)): this result supports conditional entropy approaches that evaluate the univariate complexity as the residual uncertainty that remains when past self dynamics are known. However, the use of multivariate approaches allows one to explore further information that is related to the reduction in complexity resulting from the effect of physiological interactions between systems, as it is detailed in the next section.

Similarly to the difference between univariate and multivariate conditional entropy, also the subsequent entropy reductions ΔH_i that are here regarded as decreases in complexity may be interpreted in the perspective of popular measures of information theory that are used for the study of information flows (Faes and Porta 2014). In particular, whenever a system is best explained by its own past at the first iteration (e.g. H is selected first when H itself is set as target, figure 4(a)), ΔH_i corresponds to the self entropy of the system. On the contrary, when it is best explained by another system (e.g. D is selected first when S is set as target, figure 4(b)), ΔH_i is equivalent to a cross entropy. At the second iteration, if the first case holds, then ΔH_i equals the transfer entropy from the selected system to the target (e.g. R is selected at the second iteration when H is set as target and REST condition is considered, figure 4(a)); on the other hand, if the second case holds, a conditional self entropy is obtained if the selected system is the target (e.g. S is selected at the second iteration when S itself is set as target, figure 4(b)).

4.3. Physiological mechanisms underlying stress

Analyzing the complexity of a physiological system from a network perspective helps in shedding light on the physiological regulatory mechanisms in the network that drive the changes related to the response to different physiological conditions. In the following, the physiological response to postural and mental stress is interpreted in the light of changes in complexity of heart period, blood pressure and respiratory dynamics, based on the results of our study.

4.3.1. Heart period dynamics

Heart period dynamics are strongly affected by postural stress, showing a significant reduction in complexity detected by both univariate and multivariate approaches (figure 2(a)). This finding is supported by previous studies (Porta *et al* 2007a, Faes *et al* 2011b) and can be explained by the shift in the sympathovagal balance driving the heart rate towards higher involvement of the sympathetic branch and vagal withdrawal as a consequence of baroreceptors unloading when HUT test is performed, that results in a net simplification of the heart period dynamics. The simplification of the temporal dynamics agrees with the selection of a lower number of lagged components by the non-uniform embedding with HUT (figure 3(a)). Vagal withdrawal and concomitant sympathetic activation are responsible for the dampening of high-frequency respiratory oscillations, a common estimate of the respiratory sinus arrhythmia (RSA), during HUT (Faes *et al* 2011b). RSA is reflected in a strong respiratory contribution as driver of the H dynamics at REST and during MA (figure 4(a), R is selected at the second iteration), that is suppressed when HUT is performed (figure 4(a), R is selected at the fourth iteration). On the other hand, the effect of baroreceptors unloading is reflected by the selection of S as driver of the H dynamics during HUT (figure 4(a), S is selected at the second iteration). These results agree with previous studies employing spectral (Montano *et al* 1994, Cooke *et al* 1999) or information-theoretic (Faes *et al* 2011b, 2012) indices.

As for the effect of mental stress, the significant increase in complexity that is detected using the multivariate approach (figure 2(a)) may be ascribed to a reduced contribution of the systems in the network in explaining the dynamics of More in detail, R appears to be the only significant driver of the H dynamics in REST and MA, showing a reduced amount of entropy reduction during MA when compared to REST (figure 4(a)) that results in the increased multivariate conditional entropy (figure 2(a)). It may be thus inferred that the increase in complexity is possibly reflecting vagal withdrawal as a consequence of the mental task (Berntson *et al* 1994).

4.3.2. Blood pressure dynamics

According to the analysis of univariate and multivariate complexity, it seems that postural stress alters the diastolic blood pressure regulation only, while both systolic and diastolic dynamics undergo an increase in complexity following mental stress.

Postural stress results in a reduced complexity of D detected by the univariate approach only (figure 2(c)), that is ascribed to the augmented contribution of self effects as drivers of the diastolic dynamics (figure 4(c), the entropy reduction associated to the selection of D is higher in HUT than in REST). This effect is somehow concealed when the multivariate approach is applied, by the presence of a considerable amount of information transferred from H to D at REST, that is suppressed when HUT is performed (figure 4(c)), yielding a net multivariate complexity that does not change significantly in the transition from REST to HUT. The increase of self-effects with HUT may be a possible consequence of the increased sympathetic activity. On the other hand, the transfer of information from H to D in REST and MA may be ascribed to the fast run-off effects of the cardiac cycle on the diastolic pressure, according to which a longer heart period results in a lower diastolic BP value (Westerhof *et al* 2009). This effect appears to be damped during HUT, as reported previously (Javorka *et al* 2017), documenting the possible involvement of other mechanisms driving blood pressure dynamics.

As far as mental stress is concerned, it is possible to infer that the combined effect of changes in the patterns of autonomic activation following a cognitive load which have been found to result in vasoconstriction in splanchnic region and vasodilation in limbs (Kuipers *et al* 2008), and of the involvement of higher brain areas in controlling the vascular dynamics (Lackner *et al* 2011), is responsible for the increased systolic and diastolic blood pressure dynamical complexity. However, it is worth noticing that interindividual differences arising in the response to mental stress may limit the generality of these results.

A further inference can be done with regards to the observation that the dynamics of S are strongly driven by the network independently of the experimental condition. This finding might be explained by the fact that the most important contribution to the entropy reduction of S is given by the past dynamics of D, given that D is selected in the first iteration when S is set as target (figure 4(b)). The diastolic drive of the systolic blood pressure dynamics is indicative of the strong connection that exists between the two variables and seems to act from D to S. The reason for such a strong connection may be physiologically explained by an interplay of left ventricular ejection and vascular properties (Stergiopulos *et al* 1996). This hypothesis, however, would require further investigations using appropriate measures of stroke volume or vascular resistance/compliance.

4.3.3. Respiratory dynamics

Our results show that the complexity of the respiratory system is not significantly affected by HUT, however it shows an increase with MA that might be explained by the appearance of long pauses or sighs in the respiration pattern when mental calculations are performed (Grassmann *et al* 2016), making it more erratic and thus complex. An increased randomness of the respiratory pattern during mental load has been previously reported (Vlemincx *et al* 2011). Another possible explanation may be given by the increased breathing rate during MA (results not shown), leading to a coarser sampling of the respiratory volume signal that results in a worse representation of the original dynamics and thus to an increased complexity.

Moreover, the comparison of univariate and multivariate conditional entropy, as well as the analysis of the contributions to entropy reduction, reveal that the network composed of H, S and D does not seem to transfer information to the respiratory system, as documented by the presence of self effects only as predictors of the system dynamics (figure 4(d), R is selected first and it is the only system yielding a substantial amount of entropy reduction). This result is in agreement with previous studies (Schulz *et al* 2013), suggesting that the respiratory system interacts exclusively in an open loop with the cardiovascular variables, acting as a driver but not being affected by their dynamics on the beat-to-beat time scale.

5. Conclusion

In the paradigm of network physiology (Bashan *et al* 2012), different organ systems continuously interact with each other to produce distinct physiological states and to drive the transitions from one physiological state to another. The present study documents that such interactions among physiological systems are crucial also to establish the level of complexity of the output dynamics of various systems, as well as to determine the changes in complexity related to specific types of physiological stress. Indeed, using a generalized measure of multivariate complexity applied to the network of cardiovascular and respiratory interactions, we find examples of physiological systems that—when considered as systems embedded in a network—do not change their short-term complexity (i.e. the respiratory system), reduce substantially their complexity (i.e. the systolic blood pressure control system), or reduce their complexity to an extent that varies with the physiological state (i.e. the heart rate control system during mental stress and the diastolic blood pressure control system during postural stress). These findings highlight the importance of looking at physiological complexity from a network perspective, and pose the basis for future investigations where this integrated perspective can be expanded further to investigate the transitions across physiological states or towards diseased conditions, to improve disease stratification, or to support clinical decisions.

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