Investigating Cardiac and Respiratory Determinants of Heart Rate Variability in an Information-Theoretic Framework*

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***Abstract*— This study was aimed at comparing two alternative information-theoretic approaches for the combined analysis of heart rate variability (HRV) and respiration variability (RV). The approaches decompose the predictive information about HRV in two terms, quantifying respectively the information stored into HRV and that transferred to HRV from RV. Storage and transfer were assessed by the popular self entropy (SE) and transfer entropy (TE) measures, as well as by the alternative conditional SE (cSE) and cross entropy (CE) measures. The comparison was performed at a theoretical level, computing the exact values of the four measures for simulated cardiorespiratory dynamics, and on real data, estimating the measures from RV and HRV time series taken from healthy subjects during head-up tilt and paced breathing protocols. Both analyses suggested that, for the study of cardiorespiratory interactions which are mostly unidirectional from RV to HRV, the decomposition evidencing cSE and CE is more suitable to describe respiratory sinus arrhythmia and its modifications related to changes in cardiorespiratory interactions.**

I. Introduction

Heart rate variability (HRV) is known to reflect the short-term cardiac autonomic control as the result of the combined activity of several physiological regulation mechanisms [1]. Respiratory sinus arrhythmia (RSA), i.e. the component of HRV which occurs in synchrony with respiration, is of particular importance as it has been reported to be a meaningful indicator of vagal activity [2]. In recent years, several time series analysis methods have been proposed to study the short-term dynamics of HRV, as well as to assess their link with respiration variability (RV), in an attempt to describe RSA in quantitative terms [3]. A popular approach is that framed in the information domain, which provides entropy-based measures of regularity of HRV and of RV-HRV coupling indicative of cardiorespiratory interactions [4]. The information-theoretic framework allows to quantify in a natural way the *predictive information* carried by HRV, and to decompose it in two terms, related to the *storage of information* within HRV dynamics and to the *information transfer* from RV to HRV [5]. The latter term is commonly quantified by means of the well-known transfer entropy (TE) [6], while information storage is assessed by the so-called self entropy (SE), a quantity complementary to popular measures of complexity like approximate entropy, sample entropy, or corrected conditional entropy [5,7].

Instead of using TE and SE, the predictive information about HRV can be also decomposed eliciting alternative measures of information transfer and storage, known as cross entropy (CE) and conditional SE (cSE), which result from inverting the factors of entropy decomposition [5]. The aim of this study is to test whether, in the context of cardiorespiratory variability analysis, CE and cSE quantify better than TE and SE the information transfer from RV to HRV reflecting RSA, and the information storage reflecting predictable HRV dynamics unrelated to RV. To this end, the two information decompositions are compared in synthetic coupled processes for which the exact values of TE, SE, CE and cSE can be computed numerically, and in real RV and HRV time series measured from healthy subjects during tilt test and paced breathing protocols.

II. Methods

A. Entropy Decomposition in Bivariate Systems

The goal of entropy decomposition applied in the framework of *information dynamics* [7] is to identify the causal sources of the temporal statistical structure of a dynamical system interacting with other systems. Here we consider the case of two dynamical systems described by the bivariate stochastic process $\{X,Y\}$. Let us denote as X_n and Y_n the random variables obtained by sampling the processes at the present time n, and as $X_n^-=[X_{n-1}\ X_{n-2}\ \cdots]$ and $Y_n^-=[Y_{n-1}\ Y_{n-2}\ \cdots]$ the vector variables describing the past of the processes up to time n–1. The uncertainty about the present state of an assigned target process, say Y, is quantified by its entropy, $H(Y_n)$, and the amount of uncertainty about Y_n that is resolved by the past of the whole bivariate process is quantified by the so-called prediction entropy (PE)

$$P_Y = I(Y_n ; X_n^- \oplus Y_n^-) , \quad (1)$$

where $I(\cdot;\cdot)$ stands for mutual information (MI) and $\oplus$ denotes vector concatenation. Exploiting the chain rule for MI, the PE can be decomposed as (decomposition D1)

$$P_Y = S_Y + T_{X\to Y} , \quad (2)$$

where $S_Y = I(Y_n ; Y_n^-)$ is the SE of Y, measuring how much of the uncertainty about the present of Y can be resolved by its own past, and $T_{X\to Y} = I(Y_n ; X_n^- \mid Y_n^-)$ is the TE from X to Y, measuring how much of the uncertainty about Y_n – that was not resolved by its own past – can be resolved by the past of X ($I(\cdot;\cdot|\cdot)$ denotes conditional MI (CMI)). The formulation in

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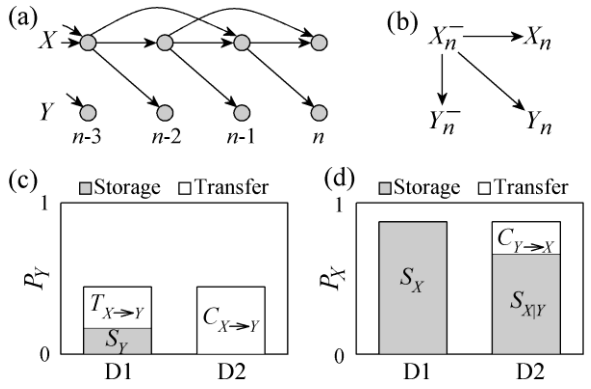

Figure 1. Graphical representation and entropy decomposition for the bivariate process $\{X, Y\}$ defined in (5). The causal statistical structure of the joint process is depicted as a time series graph showing all time-lagged effects (a), and as a condensed graph showing only the effects between the present and the whole past of X and Y (b). The PE decompositions evidencing TE and SE (D1), or cSE and CE (D2), are shown for the target process Y (c) and for the target process X (d).

(2) is very popular because it evidences SE and TE, which are known measures of information storage and transfer [5-7] widely used in the study of dynamical processes. A less popular, yet equally valid, way to decompose the PE is to use the following decomposition (D2) [5]

$$P_Y = C_{X\to Y} + S_{Y|X}, \tag{3}$$

where $C_{X\to Y} = I(Y_n ; X_n^-)$ is the CE from X to Y, measuring information transfer as the uncertainty about Y_n that can be resolved by the past of X, and $S_{Y|X} = I(Y_n ; Y_n^- \mid X_n^-)$ is the cSE of Y given X, measuring information storage as the amount of uncertainty about Y_n that was not resolved by the past of X but is resolved by the past of Y.

B. Computation of Information Dynamics Measures

The practical computation of the measures appearing in (2) and (3) presupposes to estimate the CMI of high-dimensional vector variables. While model-free approaches are recommended when nonlinear effects are relevant, a conspicuous amount of cardiorespiratory variability can be explained by linear models [8-10]. Therefore in this study we adopt the assumption of Gaussianity and use the exact expressions that hold in this case [8]. The use of exact expressions has also the advantage of allowing analytical comparison of the measures of transfer and storage.

If the bivariate process $\{X,Y\}$ has a joint Gaussian distribution, the MI between Y_n and the generic vector variable V, and the CMI between Y_n and V conditioned to the vector variable W can be written as

$$\begin{aligned} I(Y_n;V) &= \frac{1}{2}\ln\frac{\sigma(Y_n)}{\sigma(Y_n \mid V)} \\ I(Y_n;V \mid W) &= \frac{1}{2}\ln\frac{\sigma(Y_n \mid W)}{\sigma(Y_n \mid V \oplus W)} \end{aligned}, \tag{4}$$

where $\sigma(Y_n)$ is the variance of Y_n and $\sigma(Y_n \mid V)$ is the partial variance of Y_n given V, i.e., the variance of the residuals of a linear regression of Y_n on V. Additionally, under the Gaussian assumption the process $\{X,Y\}$ can be fully represented as a bivariate vector autoregressive (VAR) process, and this allows expressing $\sigma(Y_n \mid V)$ in terms of the VAR coefficients for any conditioning vector V; the procedure is essentially based on solving the Yule-Walker equations that relate the covariance of $\{X,Y\}$ to the VAR coefficients (details can be found in Ref. [8]). With this procedure, computation of the terms of D1 and D2 entails identification of the VAR model fitting the available data, followed by computation – starting from the estimated VAR coefficients – of the partial variances to be used as in (4) to yield estimates of PE, SE, TE, CE and cSE.

III. Simulation Study

In order to investigate the differences between the two entropy decompositions presented above, the theoretical profiles of the measures of information dynamics were studied in simulated VAR processes. First, we considered the simple bivariate process of order 2 defined as

$$\begin{aligned} X_n &= a_1 X_{n-1} + a_2 X_{n-2} + \varepsilon_n \\ Y_n &= c X_{n-1} + \xi_n \end{aligned}, \tag{5}$$

where ε_n and ξ_n are independent Gaussian white noise processes with zero mean and unit variance. The causal statistical structure of the process (5) is fully determined by the autodependency of X on its past at lags 1 and 2, and by the coupling from X to Y at lag 1. This structure is conveniently represented in the time series graph of Fig. 1a showing all time-lagged effects, and in the condensed graph of Fig. 1b reporting only the causal relations between the past and present of the two processes. From these representations one would expect that, for the process Y, the predictive information is entirely due to information transfer from X to Y, manifested through the effect $X_n^- \to Y_n$, and that the information storage is null because of the absence of an effect from Y_n^- to Y_n. Looking at the values of information dynamics measures of Fig. 1c (computed with a_1=1.27, a_2=-0.81, c=0.5) we see that these expectations are met only when D2 is adopted to decompose the PE, as in this case we have $S_{Y|X}$=0 and P_Y=$C_{X\to Y}$. On the contrary, D1 yields a misleading indication about the presence of information storage (S_Y>0) and a consequent underestimation of the information transfer ($T_{X\to Y}$<P_Y). In this case, even though $Y_n^- \to Y_n$ does not exist, Y_n^- and Y_n are not independent because they are both caused by X_n^- (Fig. 1b): this common driver effect determines a nonzero SE; conversely, cSE is zero because X_n^- is conditioned out in the computation of information storage. On the other hand, D1 appears more suitable for decomposing the predictive information about the process X. Indeed, even if there is no causality $Y_n^- \to X_n$, the decomposition D2 yields nonzero information transfer and underestimates the storage ($C_{Y\to X}$>0, $S_{X|Y}$<P_X); again, these misleading values are due to common driver effects of X_n^-, in this case directed to both Y_n^- and X_n, originating a spurious transfer from Y_n^- to X_n. On the contrary, the fact that TE is formulated by conditioning on the past of the target process (in this case, X) prevents the information storage in X_n^- from being mistakenly interpreted as having been transferred from Y, so that D2 yields $T_{Y\to X}$=0 and S_X=P_X.

The analysis presented above suggests that the entropy decomposition D2 based on CE and cSE may be more

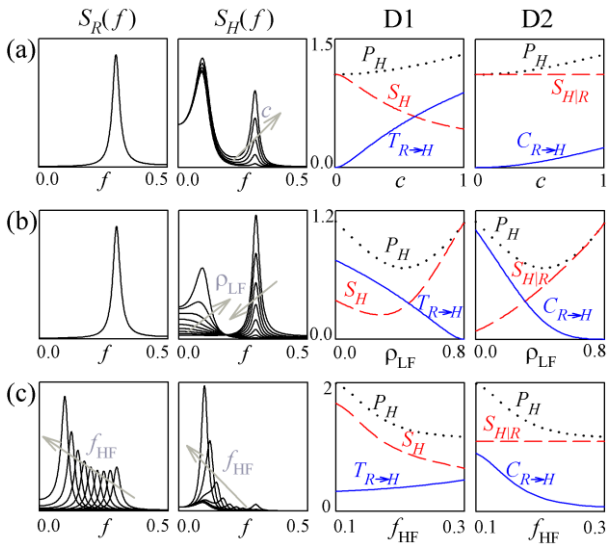

Figure 2. Entropy decomposition for different parameter settings of the bivariate process $\{R, H\}$ defined in (6). Profiles of the power spectral densities of the simulated RV ($S_R(f)$) and HRV ($S_H(f)$), and of the PE decompositions evidencing TE and SE (D1) or cSE and CE (D2), are depicted while simulating an increased RSA (a), a shift in the symphato-vagal balance (b), and a shift in the respiratory frequency (c).

appropriate than the classic decomposition D1 based on SE and TE when the target process does not have feedback causal effects on the source process, i.e., when interactions are unidirectional from source to target. This situation is expected to occur in cardiorespiratory variability where respiration acts as an exogenous signal on cardiac dynamics, i.e. RV affects HRV without being affected by it [9,11]. To perform further investigation of information dynamics in this context, we studied the simulated VAR process designed to reproduce realistic cardiorespiratory interactions:

$$\begin{aligned} R_n &= a_1 R_{n-1} + a_2 R_{n-2} + \varepsilon_n \\ H_n &= \sum_{k=1}^{4} b_k H_{n-k} + c\left(R_{n-1} - R_{n-2}\right) + \xi_n \end{aligned} \quad (6)$$

where the processes R and H represent respectively RV and HRV, and ε_n and ξ_n are independent Gaussian white noises with variances set to 2 and 1. The autodependency effects are set to generate autonomous oscillations in the two processes at the frequencies typical of cardiorespiratory variability. This was obtained placing pairs of complex-conjugated poles, of modulus ρ and phase $2\pi f$, in the complex plane representation of the processes. Specifically, very low frequency (VLF) and low frequency (LF) oscillations are obtained for the simulated HRV setting poles with ρ_{VLF}=0.2, f_{VLF}=0.03 and ρ_{LF}=0.8, f_{LF}=0.1 for the process H, and high frequency (HF) oscillations are obtained for the simulated RV setting poles with ρ_{HF}=0.9, f_{HF}=0.3 for the process R. The VAR coefficients resulting from this setting are a_1=-0.556, a_2=-0.81, b_1=1.687, b_2=-1.189, b_3=0.303, b_4=-0.026. Then, the HF rhythm is transmitted from RV to HRV imposing causality from R to H at lags 1 and 2, and weighing this simulated cardiorespiratory coupling by the parameter c. Fig. 2 shows the power spectral densities of RV and HRV obtained with different parameter settings.

The behavior of the information dynamics measures was studied at varying the simulation parameters. First, the coupling c was changed from 0 to 1 to simulate an increasing RSA, documented by the growing HF peak in the spectral density of the simulated HRV (Fig. 2a). This determined an increase of the PE, that was entirely interpreted as information transfer according to D2 ($C_{R\to H}$ increases with c, $S_{H|R}$ is kept constant); this interpretation is more meaningful than that provided by D1, which suggested a loss of storage (S_H decreases with c), and a consequent stronger transfer ($T_{R\to H}$ increases more than $C_{R\to H}$ to compensate the drop of S_H), not easy to explain because the internal dynamics of the process H were kept unchanged. Then, we simulated a shift in the sympatho-vagal balance toward sympathetic activation and vagal deactivation by setting ρ_{LF}=0,...,0.8 and c=1–ρ_{LF}, in order to get a rise in the LF power and a simultaneous fall in the HF power of HRV (Fig. 2b). Again, the imposed changes were documented well by decomposing the PE through D2, as we see an increasing information storage (higher $S_{H|R}$, reflecting the enhanced internal dynamics of H) and a decreasing transfer (lower $C_{R\to H}$, reflecting the weakened coupling from R to H); similar results were found using D1, though with a non-monotonic behavior of the SE which is of difficult interpretation. Finally, we simulated a shift in the respiratory frequency by decreasing f_{HF} from 0.3 Hz to 0.1 Hz. Slowing the HF rhythm of HRV determined its enhancement and its progressive entrainment with the LF rhythm (Fig. 2c) that was reflected by a higher predictive information (P_H increases for lower f_{HF}). This phenomenon is meaningfully explained in terms of cardiorespiratory interactions w D2 is used to decompose the PE, as the changes observed for the predictive information are fully seen as due to information transfer ($C_{R\to H}$ increases and $S_{H|R}$ is constant for lower f_{HF}). The use of D1 brings to an opposite interpretation, as the increased PE is ascribed to storage effects (S_H increases and $T_{R\to H}$ decreases for lower f_{HF}) although no changes in the internal dynamics of HRV, were simulated in this case.

IV. Application to Cardiorespiratory Variability

The two proposed entropy decompositions were applied to HRV and RV time series measured from young healthy subjects during head-up tilt (HUT, 15 subjects (9 males), 25.2±2.6 yrs) and paced breathing (PB, 16 subjects (7 males), 26.0±2.4 yrs) [11]. HRV and RV were measured respectively as the sequence of the consecutive RR interval durations from the ECG (series H), and as the values of the respiratory nasal airflow signal sampled at each R-peak of the ECG (series R). Synchronous time series of 300 beats were taken during HUT with subjects breathing spontaneously in the supine (SU) and 60° upright (UP) body positions, and during PB with subjects lying supine and breathing spontaneously (SP) or following a metronome oscillating at 0.2 Hz, 0.25 Hz or 0.3 Hz. The analysis was performed identifying a VAR model on each pair of series through least-squares estimation, and optimizing the model order by the Bayesian Information Criterion [10].

The results of entropy decomposition are shown in Fig. 3 for the HUT protocol, and in Fig. 4 for the PB protocol. During HUT (Fig. 3) the decompositions D1 and D2 yielded concordant results. The predictive information about HRV

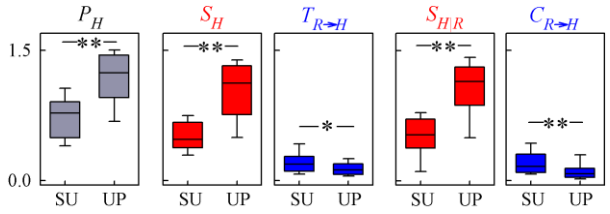

Figure 3. Entropy decomposition of HRV and RV for the HUT protocol. The PE of the HRV series, P_H, computed in the supine (SU) and upright (UP) conditions is decomposed through D1 evidencing SE and TE, or through D2 evidencing cSE and CE. * p<0.05, ** p<0.005 SU vs. UP (Wilcoxon sign rank test for paired data).

increased significantly with the transition from SU to UP, as a result of an increase of information storage (measured by SE or cSE) and a concomitant decrease of information transfer (measured by TE or CE). Similarly to what was shown at a simulation level in Fig. 2b, these trends can be ascribed to the rise of the LF component, and fall of the HF component, which are commonly observed after tilt. Physiologically, the higher storage and lower transfer are related to the reduced RSA, and the corresponding sympathetic activation and vagal deactivation, induced by the orthostatic stress [1,11].

During the PB protocol, the PE showed a tendency to increase for progressively lower breathing rates (Fig. 4). In this case, the two entropy decompositions yielded an opposite interpretation about how the predictable dynamics in HRV are explained in terms of information storage and of transfer from RV. Indeed, the higher PE observed during PB at 0.2 Hz compared to spontaneous breathing and to PB at 0.3 Hz was due to a higher storage component using D1 (Fig. 4a, S_H), and to a higher transfer component using D2 (Fig. 4b, $C_{R\to H}$). These different behaviors somewhat reflect what is observed in the simulation of Fig. 2c. The higher PE observed at 0.2 Hz is in line with previous findings reporting that RSA tends to be stronger during slow breathing [12]. Our results suggest that the enhanced RSA can be interpreted in terms of cardiorespiratory interactions only when the information transfer is assessed by the CE, while no changes are observed using TE. In the latter case, it is likely that cardiorespiratory interactions are incorporated, at least in part, in the SE and thus ascribed to information storage.

V. Conclusions

The aim of this study was to compare the measures of information storage and transfer resulting from the two possible entropy decompositions that can be applied to the predictive information about the target of a bivariate dynamical system. Our simulations showed that both decompositions have advantages and drawbacks, but – for the case of unidirectional interactions from source to target – the decomposition based on CE and cSE should be preferred. In this case, the more classic decomposition based on TE and SE is exposed to common driver effects determining changes in the SE (see, e.g., Figs. 1c and 2a,c) which are ascribed to information storage phenomena although they are not related to the internal dynamics of the target system.

The analysis of real RV and HRV time series suggested that the CE is more appropriate than the TE to quantify cardiorespiratory interactions, confirming the suitability of CE and cSE for decomposing the predictive information

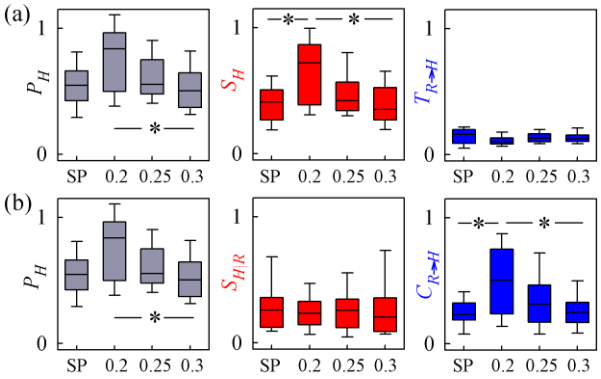

Figure 4. Entropy decomposition of HRV and RV for the PB protocol. The PE of the HRV series, P_H, computed during spontaneous (SP) and paced breathing at 0.2 Hz, 0.25 Hz and 0.3 Hz, is decomposed through D1 (a) or through D2 (b). * p<0.05, Kruskall Wallis ANOVA and post-hoc pairwise test with Tukey's honestly significant difference correction for multiple comparisons.

about HRV in cardiorespiratory analyses in which interactions are most likely unidirectional from RV to HRV.

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