Assessment of Cardiorespiratory Interactions During Spontaneous and Controlled Breathing: Non-linear Model-free Analysis*

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Abstract— **In this work, nonlinear model-free methods for bivariate time series analysis have been applied to study cardiorespiratory interactions. Specifically, entropy-based (i.e. Transfer Entropy and Cross Entropy) and Convergent Cross Mapping asymmetric coupling measures have been computed on heart rate and breathing time series extracted from electrocardiographic (ECG) and respiratory signals acquired on 19 young healthy subjects during an experimental protocol including spontaneous and controlled breathing conditions. Results evidence a bidirectional nature of cardiorespiratory interactions, and highlight clear similarities and differences among the three considered measures.**

I. Introduction

Although the interactions between cardiovascular and respiratory systems in humans have been long studied [1], [2], the underlying mechanisms that drive these interactions are still debated. The modulation of the heart rate caused by respiration, i.e. the so-called respiratory sinus arrhythmia (RSA), is the most prominent of such interactions. It causes the heart rate to decrease during inspiration and to increase during inspiration, and accounts for 20-60% of short-term heart rate variability at rest [2]. Other forms of cardio-respiratory interaction include the synchronization between the heart beat and the onset of inspiration and the constant phase difference between the right and the left stroke volumes over a respiratory cycle [2]. Different approaches have been employed in the literature to assess synchronization, coordination and coupling between cardiac and respiratory signals in various physio-pathological conditions, also including causality measures and asymmetric coupling measures [2]–[6], which led to observe that the coupling between the cardiovascular and respiratory system is not always unidirectional from respiration to heart rate.

Given that the dynamics of cardiorespiratory system is often regarded as nonlinear [6], in this work we apply three different nonlinear measures of causality (i.e. Transfer Entropy (TE)) or asymmetric coupling (i.e, Cross-Entropy (CE) and Convergent Cross Mapping (CCM)), to assess the closed-loop interactions between respiration and heart period during spontaneous and controlled breathing.

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II. Materials and Methods

The analyzed data consisted of electrocardiographic (ECG) and respiratory flow signals acquired on 19 healthy subjects (8 males; age: 27-35 years) with a sampling rate of 300 Hz. Signals were recorded on subjects lying in a resting supine position; after a first phase of spontaneous respiration (SR), they were asked to perform controlled breathing at 10 (R10), 15 (R15) and 20 (R20) breaths/minute in a random order. R-R interval (RRI) time series were extracted as time intervals between two consecutive ECG R peaks, while breathing (RESP) time series were defined by sampling the respiratory flow signal at ECG R peaks. For each subject and phase, a stationary artifact-free time window of N=255 heartbeats was selected and then normalized to zero mean and unit variance. Further details on ethical approval, data acquisition and pre-processing can be found in [3], [4].

Three non-linear model-free measures (CCM, TE and CE) were applied to the RRI and RESP time series to investigate on the directionality and strength of cardiorespiratory interactions. CCM is a method based on nonlinear state space reconstruction that identifies causality in complex dynamical systems [7]. Given two time series $\boldsymbol{X}$ and $\boldsymbol{Y}$ of length N, the algorithm first generates the manifolds M_x and M_y as time-lagged embedding vectors $X_{n,\tau}^m = [X_n, X_{n-\tau}, \dots X_{n-(m-1)\tau}]$ and $Y_{n,\tau}^m = [Y_n, Y_{n-\tau}, \dots Y_{n-(m-1)\tau}]$ for each point n, with m the embedding dimension and τ the embedding lag. In order to determine how $\boldsymbol{X}$ influences $\boldsymbol{Y}$, the $m+1$ nearest neighbors of $Y_{n,\tau}^m$ (i.e. $Y_{n_i,\tau}^m$, i=1,…,$m+1$) are found, then $\hat{X}_n$ is estimated from the determined manifold M_y using a locally weighted sum: $\hat{X}_n | M_y = \sum_{i=1}^{E+1} w_i X_{n_i}$, where $w_i = \frac{e^{d_i/d_1}}{\sum_{j=1}^{m+1} e^{d_j/d_1}}$ is a weight based on the Euclidean distance d_i between $Y_{n,\tau}^-$ and $Y_{n_i,\tau}^-$. The estimated values $\hat{X}_n$ are then compared to the original observed sequence X_n computing the Pearson correlation coefficient $\rho(X_n, \hat{X}_n | M_y)$. The same steps are applied to determine how $\boldsymbol{Y}$ influences $\boldsymbol{X}$, thus computing $\rho(Y_n, \hat{Y}_n | M_x)$.

The TE is an information-theoretic measure which implements in a model-free fashion the Granger causality concept of predictability improvement. With the notation above, and measuring unpredictability by the conditional entropy $H(\cdot\,|\,\cdot)$, the TE from $\boldsymbol{X}$ to $\boldsymbol{Y}$ is defined as [8]:

$$TE_{X\to Y} = H\left(Y_{n+1} \middle| Y_{n,\tau}^{m-1}\right) - H\left(Y_{n+1} \middle| X_{n,\tau}^{m-1}, Y_{n,\tau}^{m-1}\right) \quad (1)$$

On the other hand, the CE is an information-theoretic asymmetric coupling measure that quantifies the concept of cross-predictability measuring the information shared between the current state of $\boldsymbol{Y}$ and the synchronous embedding vector of $\boldsymbol{X}$ [8]:

$$CE_{X \to Y} = H(Y_n) - H\left(Y_n \middle| X_{n,\tau}^m\right) \quad (2)$$

To make CE and CCM conceptually similar, differently from the existing definition of CE [8], in (2) we consider also the influence of the current state of the driver process X_n on the current state of the target one Y_n.

In this study, for each subject and condition, the TE, CE and CCM measures were computed on the RRI and RESP time series for both directions, i.e. considering RRI as the target and RESP as the driver and *vice versa*, to assess the bidirectional coupling between the respiratory and cardiac dynamics. To compute TE and CE measures, the k-nearest neighbor (kNN) [9] estimator was employed, setting the number of neighbors as k=10. All measures were computed using an embedding dimension $m = 3$ and an embedding delay $\tau = 1$, as is common in short-term cardiovascular variability analysis [8], [9].

The statistical significance of the differences between conditions of a given measure computed across subjects was performed through the non-parametric Kruskal-Wallis analysis of variance ($p<0.05$) followed by post-hoc Wilcoxon signed rank test with Bonferroni correction for multiple comparisons (n=6). Moreover, the statistical significance of estimated measures for each subject was tested generating 100 surrogate time series through the circular shift method with minimum shift set to 20; the significance threshold was set to 95% for a one-sided test.

III. Results

The results reported in Fig. 1 indicate that all measures detect statistically significant coupling between RRI and RESP, along both directions, in the majority of subjects. The coupling values are comparable for the two directions. The TE does not evidence any statistically significant difference across breathing phases (Fig. 1a). On the contrary, both CE (Fig. 1b) and CCM (Fig. 1c) show a higher degree of cardiorespiratory coupling at the slowest respiratory rate (R10) than in the other phases; CE and CCM are also higher from RESP to RRI during R15 when compared to R20.

IV. Discussion and Conclusion

The statistically significant values observed for the TE, CE and CCM measures, as well as the similar trends across experimental conditions obtained computing each measure in the two directions from RESP to RRI and from RRI to RESP, support the bidirectional symmetric nature of cardio-respiratory interactions and thus the hypothesis that cardiac activity also influences the respiratory rate.

The increase of CE and CCM during low frequency breathing can be ascribed to the heavier modulation of heart rate at the imposed respiratory frequency due to RSA. On the other hand, the inability of the TE to reveal variations across the breathing conditions may be due to the strong cardiorespiratory coupling in all conditions, which brings self-predictability to the target dynamics.

The different trends exhibited by CE and TE across conditions confirm their different nature, the former being an asymmetric measure of coupling and the latter a Granger causality measure. On the other hand, the similar behavior of CE and CCM suggests that the measures capture similar aspects of coupled dynamics. Future studies should investigate comparatively the ability of these measures to identify a prevailing coupling direction, also considering simulated systems, and should test potential causality links between RRI and RESP individually for each subject, given that the results may be affected by the different ability of the subjects to follow correctly the breathing protocol.

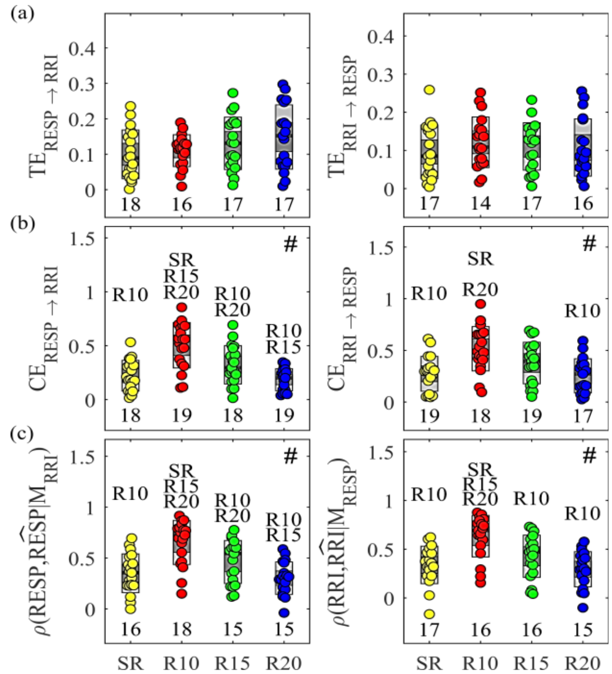

Fig. 1. Boxplot distributions (95% c.i. and 1 sd) and individual values of (a) TE, (b) CE (b) and (c) CCM correlation coefficient computed in the four breathing phases (SR, R10, R15, R20) from RESP to RRI (left) and from RRI to RESP (right). #, $p<0.05$, Kruskal-Wallis test; phase name, $p<0.05$ post-hoc Wilcoxon signed rank test with Bonferroni correction. Bottom: number of subjects (out of 19) with statistically significant coupling.

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