Quantification of Linear and Nonlinear Cardiorespiratory Interactions Under Autonomic Nervous System Blockade

Carolina Varon[1], Dries Hendrikx[1], Juan Bolea[2,3], Pablo Laguna[2,3], Raquel Bailón[2,3]

[1] KU Leuven, Department of Electrical Engineering (ESAT), STADIUS Center for Dynamical Systems, Signal Processing and Data Analytics, and imec, Leuven, Belgium
[2] BSICoS Group, I3A, IIS Aragón, University of Zaragoza, Zaragoza, Spain
[3] CIBER - Biengineering, Biomaterials and Nanomedicine (CIBER-BBN), Madrid, Spain

Abstract

This paper proposes a methodology to extract both linear and nonlinear respiratory influences from the heart rate variability (HRV), by decomposing the HRV into a respiratory and a residual component. This methodology is based on least-squares support vector machines (LS-SVM) formulated for nonlinear function estimation. From this decomposition, a better estimation of the respiratory sinus arrhythmia (RSA) and the sympathovagal balance (SB) can be achieved. These estimates are first analyzed during autonomic blockade and an orthostatic maneuver, and then compared against the classical HRV and a model that considers only linear interactions. Results are evaluated using surrogate data analysis and they indicate that the classical HRV and the linear model underestimate the cardiorespiratory interactions. Moreover, the linear and nonlinear interactions appear to be mediated by different control mechanisms. These findings will allow to better assess the ANS and to improve the understanding of the interactions within the cardiorespiratory system.

1. Introduction

It is well-known that the classical heart rate variability (HRV) analysis might lead to the wrong assessment of the autonomic nervous system (ANS) when the respiratory influences are not taken into account [1, 2]. These, possibly nonlinear, respiratory influences, or so-called respiratory sinus arrhythmia (RSA), are mediated by the parasympathetic branch of the ANS [3], and are often quantified using the power of the HRV in the classical high frequency band (HF: 0.15 Hz to 0.4 Hz). This is based on the assumption that the spectrum of the HRV can be divided into the low frequency band (LF: 0.04 Hz to 0.15 Hz), which quantifies both sympathetic and parasympathetic activity, and the HF band, which mainly reflects the modulation of the parasympathetic branch of the ANS. Despite the popularity of this spectral division, multiple studies have shown that the estimation of both the RSA and of the balance between both ANS branches (or so-called sympathovagal balance, SB=LF/HF) is inadequate in cases when the respiratory rate falls outside the HF band [1, 2].

Different approaches have been proposed to better estimate the RSA under different conditions such as stress, autonomic blockade, tilt-table test, among others. These approaches, however, either rely on a linear model (e.g., [2]), hence only considering linear effects of respiration on heart rate, or they are able to quantify up to second order interactions (e.g., [4]), by detecting and quantifying the quadratic phase coupling. In this context, this work aims at improving the quantification of cardiorespiratory interactions, taking into account both linear and (all) nonlinear effects. An approach based on least-squares support vector machines (LS-SVM) [5] will be proposed to decompose the heart rate into a respiratory component and a residual component. Moreover, the separation of linear and pure nonlinear cardiorespiratory interactions will be made.

2. Methodology

2.1. Data

The dataset used in this study was acquired at the Massachusetts Institute of Technology and it consists of ECG and respiratory effort signals recorded from 13 male volunteers (ages 19-38 years, 21 ± 4.4 years) with no history of cardiopulmonary disease. The experimental protocol, described in [6], includes an orthostatic maneuver and single pharmacological blockade of the sympathetic and the parasympathetic branches of the ANS. A control phase was initially recorded, where subjects were first in a supine position (SUC) and the signals were recorded for 7 minutes. Then, subjects were moved to a standing position (STC) and after 5 minutes of adaptation, the signals were again recorded for 7 more minutes. This procedure was repeated 10 minutes after administering either atropine (0.03 mg/kg) or propranolol (0.2 mg/kg) for complete vagal or sympathetic blockade, respectively. These new phases will be referred as SUA and STA for atropine and SUP and STP for propranolol. In total, 4 segments of 7 minutes were an-

 ISSN: 2325-887X DOI: 10.22489/CinC.2019.329

alyzed per subject, 2 control segments and 2 with single blockade. 7 subjects received atropine and 6 propranolol. During the entire protocol, subjects were asked to follow an irregular breathing cycle, where they were allowed to vary the depth and shape of each breath so that normal ventilation was guaranteed. As a result, the power spectrum of the respiratory drive was nearly flat [6].

2.2. Pre-processing

The ECG signals were used to find the location of the R-peaks, which were then corrected for ectopic, missed, and false peaks using the integral pulse frequency modulation (IPFM) model [7]. After that, the resulting HRV signals were resampled at 4 Hz and band-pass filtered using a Butterworth band-pass filter with cutoff frequencies of 0.03 Hz and 0.9 Hz. The same filter was applied to the respiratory signals, which were then downsampled at 4 Hz and normalized with zero mean and unit variance.

2.3. Quantification of Cardiorespiratory Interactions

The cardiorespiratory interactions were quantified using two different approaches. On the one hand, the *linear interactions* were extracted using orthogonal subspace projections as described in [2]. In this approach, the heart rate signal defined as $\mathbf{y} = [y(1), \ldots, y(N)]^T$, is decomposed into a respiratory component $\mathbf{y_x}$ and a residual component $\mathbf{y}_\perp$, with $\mathbf{x} = [x(1), \ldots, x(N)]^T$ the respiratory signal, N the length of the signals, and $x(n), y(n) \in \mathbb{R}$.

The combined *linear and nonlinear interactions*, on the other hand, were quantified using kernel regression for nonlinear function estimation. Here, a novel approach based on LS-SVM [5] is proposed to perform the heart rate decomposition. The problem of nonlinear function estimation can be formulated as $y_{\mathbf{x}}(i) = \mathbf{w}^T\boldsymbol{\varphi}(\mathbf{x}(i)) + b$, with $\mathbf{x}(i) \in \mathbb{R}^m$, $\mathbf{x}(i) = [x(i), x(i-1), \ldots, x(i-m)]^T$, m the model order, $\boldsymbol{\varphi}(\cdot) : \mathbb{R}^m \rightarrow \mathbb{R}^{m_h}$ the (possibly nonlinear) mapping to a high dimensional feature space of dimension m_h, $\mathbf{w} \in \mathbb{R}^{m_h}$, and $b \in \mathbb{R}$ the bias term. This problem can then be formulated in the framework of LS-SVM as

$$\begin{aligned} \min_{\mathbf{w},b,\mathbf{e}} J_P(\mathbf{w},\mathbf{e}) &= \frac{1}{2}\mathbf{w}^T\mathbf{w} + \gamma\frac{1}{2}\sum_{i=1}^{N} e(i)^2 \qquad (1) \\ \text{s.t.} \quad & y_x(i) = \mathbf{w}^T\boldsymbol{\varphi}(\mathbf{x}(i)) + b + e(i), \end{aligned}$$

with γ a positive regularization constant and $e(i)$ the error terms that are assumed to be i.i.d. with zero mean and constant variance. After formulating the Lagrangian $\mathcal{L}$ of (1) and satisfying the conditions for optimality given by

$$\begin{cases} \frac{\partial \mathcal{L}}{\partial \mathbf{w}} = 0 \rightarrow & \mathbf{w} = \sum_{i=1}^{N} \alpha(i)\boldsymbol{\varphi}(\mathbf{x}(i)) \\ \frac{\partial \mathcal{L}}{\partial b} = 0 \rightarrow & \sum_{i=1}^{N} \alpha(i) = 0 \\ \frac{\partial \mathcal{L}}{\partial e(i)} = 0 \rightarrow & \alpha(i) = \gamma e(i), \quad i = 1, \ldots, N \\ \frac{\partial \mathcal{L}}{\partial \alpha(i)} = 0 \rightarrow & y_x(i) = \mathbf{w}^T\boldsymbol{\varphi}(\mathbf{x}(i)) + b + e(i), \end{cases} \qquad (2)$$

the dual problem becomes

$$\left[\begin{array}{c|c} 0 & \mathbf{1}_N^T \\ \hline \mathbf{1}_N & \boldsymbol{\Omega} + \mathbf{I}/\gamma \end{array}\right] \left[\begin{array}{c} b \\ \hline \boldsymbol{\alpha} \end{array}\right] = \left[\begin{array}{c} 0 \\ \hline \mathbf{y_x} \end{array}\right], \qquad (3)$$

where $\boldsymbol{\alpha} = [\alpha_1, \ldots, \alpha_N]^T$ are the Lagrange multipliers, $\mathbf{1}_N = [1, \ldots, 1]^T$, $\mathbf{I}$ the identity matrix, and $\boldsymbol{\Omega}$ the kernel matrix with entries $\boldsymbol{\Omega}_{ij} = \boldsymbol{\varphi}(\mathbf{x}(i))^T\boldsymbol{\varphi}(\mathbf{x}(j)) = K(\mathbf{x}(i), \mathbf{x}(j)) = \exp(-\|\mathbf{x}(i) - \mathbf{x}(j)\|_2^2/\sigma^2)$, $i, j = 1, \ldots, N$, and σ^2 the kernel bandwidth selected using cross-validation. The resulting LS-SVM model defined as $\mathbf{y_x} = \boldsymbol{\Omega}\boldsymbol{\alpha} + \mathbf{b}$, with $\mathbf{b} = [b, \ldots, b]^T$, allows to extract all possible linear and nonlinear influences of $\mathbf{x}$ on $\mathbf{y}$, i.e., the respiratory component. The residual component is then obtained as $\mathbf{y}_\perp = \mathbf{y} - \mathbf{y_x}$.

After decomposing the heart rate, either by means of the linear or the nonlinear approach, the relative power of the respiratory component ($\mathcal{P}_\mathbf{x}$) as an estimate of the RSA and the unconstrained estimation of the sympathovagal balance ($\mathrm{SB}_\mathbf{u}$) are computed as proposed in [2]:

$$\mathcal{P}_\mathbf{x} = \frac{\mathbf{y_x'y_x}}{\mathbf{y'y}}, \qquad \mathrm{SB}_\mathbf{u} = \frac{\mathrm{LF}_\perp}{\mathrm{LF}_\mathbf{x} + \mathrm{HF}_\mathbf{x}}, \qquad (4)$$

with $\mathrm{LF}_\mathbf{x}$ and $\mathrm{HF}_\mathbf{x}$ the powers in the LF and extended HF (HF: 0.15 Hz - half the mean heart rate) bands of $\mathbf{y_x}$. $\mathrm{LF}_\perp$ corresponds to the LF power of the residual component.

For both approaches, linear and kernel-based, the model order m was defined as the maximum value obtained using the minimum description length principle and the Akaike Information Criterion. The reason to use the more complex model relies on the fact that the PSD of the respiratory drive was nearly flat [6].

In order to differentiate between the pure linear methodology and the kernel-based one, the superscripts l and k will be used. For instance, the respiratory related components derived with the linear and the kernel method will be denoted as $\mathbf{y}_\mathbf{x}^l$ and $\mathbf{y}_\mathbf{x}^k$, respectively. Finally, the pure nonlinear effects on the RSA will be estimated as $\mathbf{y}_\mathbf{x}^{nl} = \mathbf{y}_\mathbf{x}^k - \mathbf{y}_\mathbf{x}^l$.

2.4. Statistical Analysis

Two different analyses will be performed. First, the significance of the kernel-based estimations will be assessed by means of *iteratively refined surrogates* for multivariate

data as described in [8]. The main idea is to generate a surrogate time series for both the heart rate and respiratory signal of each phase (e.g., SUC). The pair of surrogates will be generated in such a way that all the nonlinear interactions will be destroyed. This will be guaranteed by randomising the data so that their phase information is destroyed. At the same time the individual distributions will be matched and the autocorrelation function of each signal as well as the cross-correlation function between the pairs will be kept. This will be performed 19 times (see [8]) for each pair of signals. Then, for each set of surrogates both $\mathcal{P}_{\mathbf{x}}^{k}$ and $\mathrm{SB}_{\mathbf{u}}^{k}$ will be computed and if they are larger than the values calculated from the surrogates, the parameters will be considered to be significant and nonlinear interactions can be assumed to be present in the data. Instead, when this condition is not satisfied, the interactions are considered to be purely linear.

The second analysis will deal with the ability of the proposed parameters, namely, linear, kernel-based, and pure nonlinear, to quantify the RSA and the SB under complete parasympathetic withdrawal during STA (i.e. pure sympathetic modulation), and during SUP where there is pure vagal modulation. The extended HF parameter and the classical SB will be used for comparison. This analysis will be performed using the Friedman test for repeated measures with $\alpha = 0.05$ and, when required, a multicomparison test will be implemented with the Bonferroni correction.

3. Results and Discussion

The relative power of the respiratory component calculated using LS-SVM ($\mathbf{y}_{\mathbf{x}}^{k}$) was always larger than its linear counterpart ($\mathbf{y}_{\mathbf{x}}^{l}$). However, according to the surrogate data analysis this increase was not significant ($p > 0.05$) for some segments. In total, 3 (SUC), 2 (STC), 2 (SUA), 4 (STA), 3 (SUP), and 1 (STP) segments were identified as having only linear cardiorespiratory interactions. It is important to remember that the parameters calculated using LS-SVM take into account both the linear and nonlinear interactions between heart rate and respiration. Therefore, for these segments with no significant increases, the kernel-based estimates, namely $\mathbf{y}_{\mathbf{x}}^{k}$ and $\mathrm{SB}_{\mathbf{u}}^{k}$ were replaced by their corresponding linear values. As a consequence, $\mathbf{y}_{\mathbf{x}}^{nl} = 0$ for some cases.

After correcting for non significant values, the parameters were compared for each phase and the results are shown in Figure 1. It is clear that the quantification of the cardiorespiratory interactions is underestimated by the linear model in all phases since there is often a nonlinear part that can be quantified using LS-SVM. Furthermore, the HF parameter tends to underestimate the vagal modulation on HRV, in particular during autonomic blockade, as well as overestimate the sympathovagal balance. At this point, it is clear that HF is not the most optimal parameter as it has been already established in literature [1, 2]. This again, is due to the presence of respiratory influences outside the HF band, as can be seen in Figure 2. The figure shows the PSDs of a pair of signals from one subject during STC. It is evident that the dynamics of the respiratory signal fall within the LF band, which can only be taken into account by the proposed estimations of RSA. Additionally, the wide bandwidth of the respiratory signals in this data [6] can also be observed in this example, which justifies, as mentioned before, the selection of the more complex model for the estimation of the parameters.

Concerning the differences between the phases, especially those between supine and standing position, the novel indices were able to capture the vagal withdrawal during this orthostatic maneuver. There was a clear trend in all parameters towards a lower cardiorespiratory interactions and an increased sympathovagal balance when going from supine to standing. For instance, in the estimation of vagal activity, for the control phases before both single blockades, only the relative power of the respiratory component extracted using LS-SVM was able to capture this difference ($p < 0.05$). The linear model, on the other hand, was only successful in the control phases before atropine administration while no significant difference was obtained with the classical HF in any of the cases. When looking at the sympathovagal balance during contol phases, the classical SB increased significantly when going from SUC to STC. This was also the case for the linear model, whereas the LS-SVM model could only capture this change before atropine administration.

In the case of complete parasympathetic withdrawal (SUA-STA), only the linear model could capture the orthostatic change in both the vagal activity and the sympathovagal balance. Moreover, both estimations of RSA, $\mathcal{P}_{\mathbf{x}}^{l}$ and $\mathcal{P}_{\mathbf{x}}^{k}$, were larger than HF, with only $\mathcal{P}_{\mathbf{x}}^{k}$ significant for both cases. One important result at this point is that the pure nonlinear influences denoted by $\mathcal{P}_{\mathbf{x}}^{nl}$ make up for a big part of the cardiorespiratory interactions during the atropine phases. During control phases SUC and STC, these interactions are significantly lower than the pure linear ones, while during SUA and STA they become more relevant. This, however, does not seem to be the case during sympathetic blockade (SUP and STP). These interactions tend to be larger when going from supine to standing independently of the administered drug, but the percentage of pure nonlinearities is larger during atropine administration. In [4], the quadratic cardiorespiratory interactions were quantified using real wavelet biphase during a tilt-table test. The study reported a reduction of quadratic interactions when going from supine to standing, which is somehow the case during control phases. Nevertheless, here not only second order interactions are studied but other possibly higher order ones, which indicates that the nonlinearities might account for more of the dynamics of the HRV. These results suggest that there is a close relationship between nonlinear respiratory influences on HRV and sympathetic modulation. Furthermore, a different mechanism appears to be responsible for the nonlinear

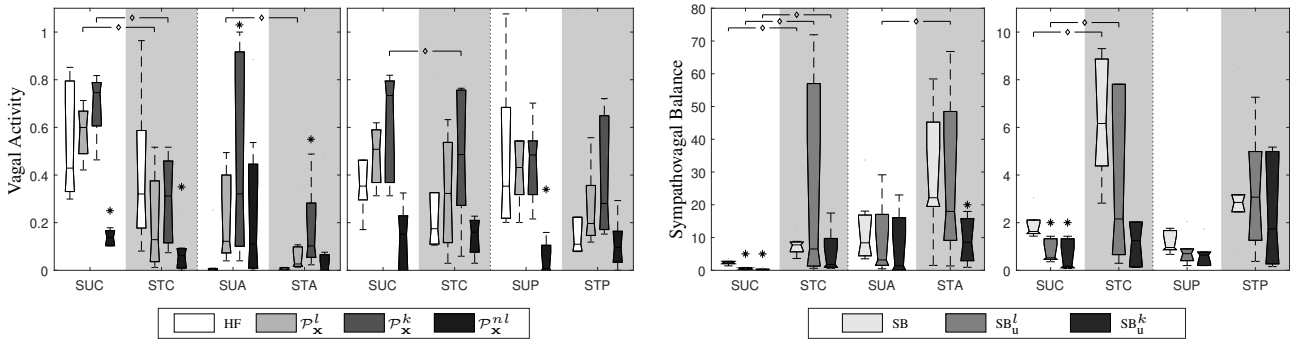

Figure 1. (left) Vagal activity quantified using the classical HF and the relative power of the respiratory component of the HRV ($\mathcal{P}_{\mathbf{x}}$). (right) Sympathovagal balance quantified by means of the classical SB=LF/HF and the proposed unconstrained versions ($SB_{\mathbf{u}}$). Significant differences between the phases are indicated by the diamonds, and differences with respect to the classical parameteres, either HF or SB, are indicated by *.

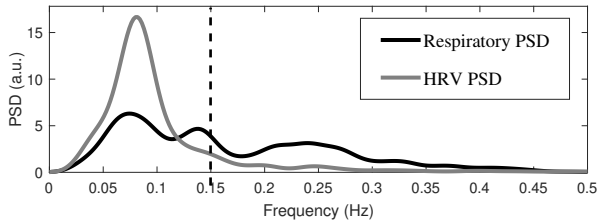

Figure 2. Power spectral density estimates of the respiratory signal and the HRV signal of a subject during STC. The dashed line indicates the lower limit of the HF band.

interactions. For instance, the nonlinear influences could be mediated by the respiratory pacemaker in the central nervous system [9] through the sympathetic modulation [6]. Additionally, they can be related to changes in blood pressure. However, no strong conclusions can be made on this point due to the low amount of subjects used in this study and the lack of other cardiovascular information.

4. Conclusions

The approach proposed here allows to quantify both linear and nonlinear cardiorespiratory interactions. In this way, a more complete picture of the cardiorespiratory system can be envisioned. The results presented here suggest that the linear and nonlinear interactions are mediated by two different mechanisms. Further studies need to be performed in order to identify these mechanisms. For instance, studies that include blood pressure recordings during stress tests and orthostatic maneuvers.

Acknowledgements

OSA+; imec ICON HBC.2016.0167; The research leading to these results has received funding from the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013) / ERC Advanced Grant: BIOTENSORS (n° 339804). This paper reflects only the authors' views and the Union is not liable for any use that may be made of the contained information; This work was partially funded by MINECO and FEDER through the project RTI2018-097723-B-I00. D.H. is a SB Ph.D. fellow and C.V. is a postdoctoral fellow, both of the Research Foundation-Flanders (FWO).

References

[1] Hernando A, et al. Inclusion of respiratory frequency information in heart rate variability analysis for stress assessment. IEEE JBHI 2016;20(4):1016–1025.

[2] Varon C, et al. Unconstrained estimation of HRV indices after removing respiratory influences from heart rate. IEEE JBHI Early Access 2018;.

[3] Berntson GG, et al. Respiratory sinus arrhythmia: autonomic origins, physiological mechanisms, and psychophysiological implications. Psychophysiology 1993;30(2):183–196.

[4] Kontaxis S, et al. Assessment of quadratic nonlinear cardiorespiratory couplings during tilt-table test by means of real wavelet biphase. IEEE TBME 2019;66(1):187–198.

[5] Suykens J, et al. Least squares support vector machines, volume 4. World Scientific, 2002.

[6] Saul JP, et al. Transfer function analysis of the circulation: unique insights into cardiovascular regulation. Am J Physiol Heart Circ Physiol 1991;261(4):H1231–H1245.

[7] Mateo J, Laguna P. Analysis of heart rate variability in the presence of ectopic beats using the heart timing signal. IEEE TBME 2003;50(3):334–343.

[8] Schreiber T, Schmitz A. Surrogate time series. Physica D Nonlinear Phenomena 2000;142(3-4):346–382.

[9] Peña F. Contribution of pacemaker neurons to respiratory rhythms generation in vitro. In Integration in Respiratory Control. Springer, 2008; 114–118.

Address for correspondence:
Carolina Varon
ESAT/STADIUS/KU Leuven
Kasteelpark Arenberg 10, bus 2446, 3001 Leuven, Belgium.
carolina.varon@esat.kuleuven.be