Relationship between Heart Rate Turbulence and Local Physiological Variables in Heart Failure Patients

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Abstract

Heart Rate Turbulence (HRT) is a powerful risk stratification criterion in patients with cardiac disorders. Several physiological factors affect HRT, e.g., previous cardiac cycle (CC), coupling interval (CI), and compensatory pause (CP). However, classical HRT measurements often use an average of the available individual tachograms that might blur relevant physiological relationships. We hypothesized that filtering individual tachograms, by using robust signal processing techniques, would allow to compute local HRT measurements and to relate them with their local physiological conditions. In this paper, a denoising procedure based in support vector machine (SVM) estimation was used. HRT indices, Turbulence Slope (TS) and Tubulence Onset (TO), were computed in filtered individual tachograms by using 24-h Holter recordings from Congestive Heart Failure (CHF) patients. The relationship between local TS and TO parameters and their physiological conditions (CC, CI and CP) was quantified by linear regression. SVM filtering procedure might allow taking into account the local physiological conditions, which modulate the HRT response, and give a way to quantify this modulation. This approach could complete the current HRT assessment methods, and yield a clearer physiological interpretation of the HRT parameters.

1. Introduction

Heart Rate Turbulence (HRT) is the physiological response to a spontaneous ventricular premature complex (VPC). In normal subjects, it consists of an initial acceleration and its subsequent deceleration of the sinus heart rate. It has been shown to be a powerful risk stratification predictor in patients with high-risk of cardiac disease [1–3]. Assessment of the HRT is often performed by using the so-called VPC-tachogram, which is constructed by averaging the RR-intervals sequences surrounding isolated VPCs, thit is, local VPC tachograms. The aim of this averaging procedure is to reduce the noise that masks the HRT pattern in isolated VPCs tachograms.

The HRT is mostly assessed from two parameters, namely, the Turbulence Onset (TO) and the Turbulence Slope (TS). The former represents the amount of sinus acceleration following a VPC, and it is defined as the percentage difference between the heart rate immediately following the VPC and the heart rate immediately preceding the VPC. The later represents the rate of sinus deceleration that follows sinus acceleration, and it is defined as the maximum positive regression slope assessed over any 5 consecutive sinus rhythm RR-intervals within the first 15 sinus rhythm RR-intervals after the VPC [2]. In normal subjects, the initial sinus acceleration following the VPC is characterized by negative values of TO parameter, whereas the subsequent sinus deceleration is characterized by positive values of TS parameter.

The influence of several physiological factors on the HRT has been well documented [2]. The heart rate modulates the strength of the HRT response, thus, HRT is reduced at high heart rate. There exist approaches to correct HRT indexes for heart rate, or to propose new ones [3, 4]. VPC prematurity modulates the HRT response, and hence, in agreement with the baroreflex source of HRT, the more premature the VPC, the stronger the HRT response.

The usual procedure to assess the HRT implies averaging all available isolated VPC tachograms to construct the VPC-tachogram, used to compute TS and TO. However, this procedure might mask the influence of different physiological factors, since it considers all HRT responses to isolated VPC as equivalents, when they may have different physiological conditions, leading to different HRT patterns, and therefore different TS and TO values.

In this work, we propose to efficiently filter the noise in each isolated VPC tachograms to obtain reliable local TS and TO parameters, this is, computed from the denoised isolated VPC tachograms. This approach will allow us to study the relationship between the HRT characterization parameters and the underlying physiological conditions in

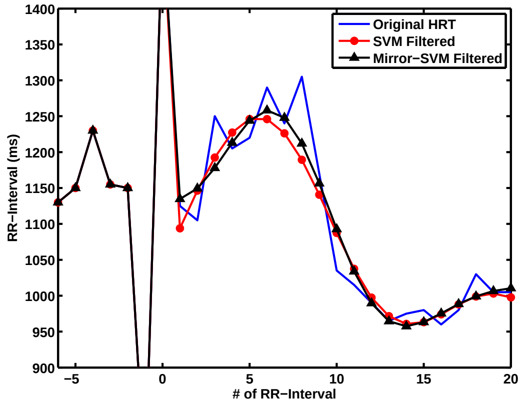

Figure 1. *HRT denoising using SVM filtering method, with and without mirrorizing the edges.*

which the VPC occurs. We use a database with 24-Holter recordings from Congestive Heart Failure (CHF) patients. We propose to use a filtering method based on support vector machine (SVM) regression, which is a robust denoising method especially suitable in problems with few samples, as in isolated VPC tachograms where only 20 samples are available [5].

The structure of the paper is as follows. In Section 2, the method to assess the relationship between HRT and the physiologica variables is presented, as well as the data used in the work, and in Section 3 the results are reported. Finally, in Section 4, conclusions are summarized.

2. Methods and Data

2.1. Relationship between HRT and Physiological Variables

HRT represents a biphasic response of sinus rhythm to a single VPC. The turbulence signal consists of a fast initial acceleration, followed by an oscillation in RR intervals, which usually lasts no longer than about 15-20 beats. The HRT pattern is influenced by a number of physiological factors, and so are the parameters used to assess this pattern, i.e. TS and TO.

In order to quantify the relationship between HRT response and some of the local physiological variables that modulate it, we obtained the TS parameter in each individual filtered VPC tachogram for each patient. Then, for those patients with 4 or more individual tachograms, we computed the Pearson's correlation coefficient, r, between TS and the following physiological factors: previous cardiac cycle, CC, coupling interval, CI, and compensatory pause, CP. Whenever $r >= 0.5$, the slope of the regression line was computed to characterize how these three local variables modulate the HRT as assessed by the TS.

2.2. SVM Filtering Method

The HRT signal comprises no more than 15-20 beats, so it is an extremely short signal duration for conventional denoising or filtering techniques. The signal model considered represents the RR intervals in the local tachogram under study, denoted by $\{x_n, n = 1, \ldots, 20\}$, as composed by two contributions: one given by the actual HRT response to be estimated, given by $\{s_n, n = 1, \ldots, 20\}$, and the other given by noise contributions from different sources, denoted by $\{e_n, n = 1, \ldots, 20\}$, which is the part to be filtered out. The HRT signal model is then:

$$x_n = s_n + e_n, \quad n = 1, \ldots, 20 \tag{1}$$

The filtering method used in this paper is based on a SVM modeling approach, previously developed in [5]. The SVM regressor can be seen as a nonparametric procedure, in the sense that it does not rely on any specified form of the HRT. Also, we propose to consider the ε-Huber cost [6], which represents a cost function that can adapt itself to the noise distribution. Due to the short length of the signal, nonparametric bootstrap resampling is used for free parameter tuning. The SVM model for HRT denoising can be described as follows. The nonlinear regression model is given by

$$x_n = s_n + e_n = \langle \boldsymbol{w}, \phi(n) \rangle + b + e_n \tag{2}$$

where $\phi(n)$ is a nonlinear application of n to a possibly high-dimensional (say P-dimensional) feature space $\mathfrak{F}$, where a linear approximation is built by the dot product with vector$\boldsymbol{w} \in \mathfrak{F}$. This model can be seen as a nonlinear interpolation. Following the conventional SVM methodology, a regularized cost function of the residuals is to be minimized. In [6], the following robust cost function of the residuals was proposed,

$$L(e_n) = \begin{cases} 0, & |e_n| \leq \varepsilon \\ \frac{1}{2\delta}(|e_n| - \varepsilon)^2, & \varepsilon \leq |e_n| \leq e_C \\ C(|e_n| - \varepsilon) - \frac{1}{2}\delta C^2, & |e_n| \geq e_C \end{cases} \tag{3}$$

where $e_C = \varepsilon + \delta C$; ε is the insensitive parameter; and δ and C control the trade-off between the regularization and the losses. The ε-insensitive zone ignores errors lower than ε; the quadratic cost zone uses the L_2-norm of errors, which is appropriate for Gaussian noise; and the linear cost zone controls the effect of outliers. The SVM coefficients are estimated by minimizing the previous loss function regularized with the squared norm of model coefficients,

$$\frac{1}{2}\sum_{p=1}^{P} w_p^2 + \frac{1}{2\delta}\sum_{n\in I_1}(\xi_n^2 + \xi_n^{\star 2}) + C\sum_{n\in I_2}(\xi_n + \xi_n^{\star}) - \sum_{n\in I_2}\frac{\delta C^2}{2} \tag{4}$$

with respect to w_p, $\{\xi_n^{(\star)}\}$ (notation for both $\{\xi_n\}$ and $\{\xi_n^\star\}$), and b, and constrained to

$$x_n - \langle \boldsymbol{w}, \phi(n)\rangle - b \leq \varepsilon + \xi_n \quad (5)$$

$$-x_n + \langle \boldsymbol{w}, \phi(n)\rangle + b \leq \varepsilon + \xi_n^\star \quad (6)$$

$$\xi_n, \xi_n^\star \geq 0 \quad (7)$$

for $n = 1, \cdots, 20$; $\{\xi_n^{(\star)}\}$ are *slack variables* or *losses*, which are introduced to handle the residuals according to the robust cost function; and I_1, I_2 are the sets of samples for which losses have a quadratic or a linear cost.

By including linear constraints (5)-(7) into (4), the primal-dual functional (or Lagrange functional) is obtained:

$$L_{PD} = \frac{1}{2}\sum_{p=1}^{P} w_p^2 + \frac{1}{2\delta}\sum_{n\in I_1}(\xi_n^2 + \xi_n^{\star 2}) + C\sum_{n\in I_2}(\xi_n + \xi_n^\star) - \\ - \sum_{n\in I_2}\frac{\delta C^2}{2} - \sum_{n=1}^{20}(\beta_n\xi_n + \beta_n^\star\xi_n^\star) - \varepsilon\sum_{n=1}^{20}(\alpha_n + \alpha_n^\star) + \\ + \sum_{n=1}^{20}(\alpha_n - \alpha_n^\star)(x_n - \langle \boldsymbol{w}, \phi(n)\rangle - b - \xi_n) \quad (8)$$

constrained to $\alpha_n^{(\star)}, \beta_n^{(\star)}, \xi_n^{(\star)} \geq 0$. By making zero the gradient of L_{PD} with respect to the primal variables [6], we obtain $\alpha_n^{(\star)} = \frac{1}{\delta}\xi_n^{(\star)}(n \in I_1)$, $\alpha_n^{(\star)} = C - \beta_n^{(\star)}(n \in I_2)$, to be fulfilled, and if these constrains are included into (8), primal variables can be removed. The correlation matrix of input space vectors can be identified, and denoted as $\boldsymbol{R}(t,u) \equiv \langle \phi(t), \phi(u)\rangle$. The dual problem can now be obtained and expressed in matrix form, and it corresponds to the maximization of

$$-\frac{1}{2}(\boldsymbol{\alpha}-\boldsymbol{\alpha}^\star)^T\left[\boldsymbol{R} + \delta\mathbf{I}\right](\boldsymbol{\alpha}-\boldsymbol{\alpha}^\star) + (\boldsymbol{\alpha}-\boldsymbol{\alpha}^\star)^T\boldsymbol{y} - \varepsilon\mathbf{1}^T(\boldsymbol{\alpha}+\boldsymbol{\alpha}^\star) \quad (9)$$

constrained to $C \geq \alpha_n^{(\star)} \geq 0$, where $\boldsymbol{\alpha}^{(\star)} = [\alpha_1^{(\star)}, \cdots, \alpha_{20}^{(\star)}]^T$; $\boldsymbol{x} = [x_1, x_2, \ldots, x_{20}]^T$; and $\mathbf{1}$ denotes a column vector of ones. After obtaining Lagrange multipliers $\boldsymbol{\alpha}^{(\star)}$, the time series model for a sample at time instant m is:

$$\hat{s}_m = \sum_{n=1}^{20}(\alpha_n - \alpha_n^\star)\langle \phi(n), \phi(m)\rangle + b \quad (10)$$

which is a weighted function of the nonlinearly observed times in the feature space. Note that only a reduced subset of the Lagrange multipliers is nonzero, which are called the *support vectors*, and the HRT solution is built in terms of them.

In this approach we used a *Gaussian* Mercer's kernel, given by

$$K_G(t,u) = \exp\left(-\frac{(t-u)^2}{2\sigma^2}\right) \quad (11)$$

	Slope ($\mathbf{ms^2/RR - Int}$)	N. of patients $\mathbf{r \geq 0.5}$
TS vs CC	0.05	4 out of 8
TS vs CI	0.30	2 out of 8
TS vs CP	0.04	3 out of 8

Table 1. *Mean slopes of regression lines between TS and its local physiological variables (CC, CI, and CP) for those patients with a Pearson's correlation coefficient greater than 0.5, and 4 or more individual VPC tachograms available, 8 out of 60.*

where σ is the width of the Gaussian kernel, and it must be properly chosen. For a fixed value of σ, it is fulfilled that $K_G(t,u) = \langle \phi(t), \phi(u)\rangle$ in some unknown feature space. Thus, the final solution of SVM for HRT denoising can be expressed simply as

$$\hat{x}_m = \sum_{n=1}^{20}(\alpha_n - \alpha_n^\star)K_G(n,m) + b \quad (12)$$

which is just a linear combination of shifted Gaussian kernels of a given width.

An issue that has to be taken into account is related to boundary conditions, it is mandatory to minimize errors propagations due to finite observation lengths. These errors are generally reflected in the HRT assessment as an overestimation in the TS parameter. To minimize this impact, we obtained good results by mirrorizing the extrema close to the edges. Figure 1 shows an example of HRT denoising using SVM approach, both with and without mirrorizing the edges.

2.3. Congestive Heart Failure Database

A database of 60 Holter recordings, from CHF patients, was assembled in the Arrhythmia Unit of Hospital Universitario Virgen de la Arrixaca (Spain). RR-interval series were previously filtered to identify reliable isolate VPC tachograms according to the criteria proposed in [2].

3. Results

Table 1 shows the mean slopes values of the regression lines fitted by least squares between TS parameter and physiological variables CC, CI, and CP, for those patients with a Pearson's correlation coefficient greater than 0.5. Only 8 patients, out of the 60 that comprised the database, had available 4 or more isolated VPC tachograms.

Regarding the relationship between TS and CC, the mean slope was 0.05, meaning that a change in 50 ms in the CC would lead to a change of 2.5 units in TS parameter. Regarding the relationship between TS and CI, the mean slope was 0.3, meaning that a change in 50 ms in

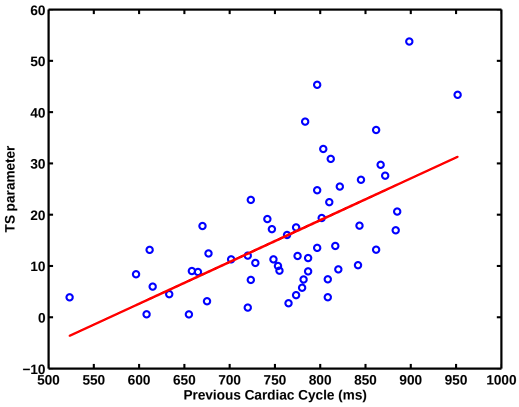

Figure 2. *Relationship between the TS parameter and the CC physiological variable characterized by the regression line fitted to the data.*

the CI would lead to a change of 15 units in TS parameter. Finally, regarding the relationship between TS and CP, the mean slope was 0.04, meaning that a change of 50 ms in the CP would lead to a change of 2 units in TS parameter.

Figure 2 shows a scatter plot representing the relationship between the TS parameter and the CC physiological variable as characterized by the slope of regression line.

4. Conclusions

We proposed a method to characterize the relationship between the HRT and the local physiological variables responsible for the modulation of the HRT response, using filtered individual VPC tachograms instead of an average VPC tachogram as the classical method.

It is well documented in the literature that the HRT response is modulated by different physiological factors, among them are the previous cardiac cycle, the coupling interval and the compensatory pause CP. The framework presented in this paper to assess the HRT allows to perform quantitative analysis to characterize the influence of these physiological variables on the HRT response in isolated VPC tachograms as quantified by TS parameter.

The Pearson's correlation coefficient was used to establish a significant relationship between local physiological variables and TS parameter, whereas the slope of the regression line was used to quantify this relationship.

The physiological variables studied had a significant influence on the HRT in half of the available patients. In those cases, the coupling interval had a major role modulating the HRT response as quantified by the TS parameter.

The study had some limitations due to the lack of patients with enough isolated VPC tachograms available, and the lack of a gold standard for the relationship between the local physiological variables studied and the HRT.

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