A MATHEMATICAL MODEL OF RESPIRATORY SINUS ARRHYTHMIA USING INTEGRAL PULSE FREQUENCY MODULATION

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Abstract: The modeling of the heart rate variability (HRV) found in the literature is most commonly based on the analysis of the interbeat time intervals in frequency domain or at discrete-time modeling. These approaches may fail if one is interested in generating the timing of the heartbeats. An alternative approach to model the HRV is the integral pulse frequency modulation (IPFM). The aim of this work was to evaluate a model of RSA based on IPFM, and a method to fit its parameters to experimental data. The transfer function \( H(s) \) between airflow and \( m(t) \), the modulating signal that represents the autonomic influences on the sinoatrial node, was modeled as a first order low-pass filter with DC gain \( G \). The results showed that the model was able to recover the power spectral density partially at the frequency band of interest, and only part of HRV could be explained by the respiratory signal. Further studies are necessary to improve the model.

Keywords: heart rate variability, respiratory sinus arrhythmia, integral pulse frequency modulation, modeling.

Introduction

The heart rate variability (HRV) can be used as a noninvasive tool to assess the autonomic nervous system. HRV analysis has been employed not only as an index of autonomic activity, but also to provide information on the physiological and pathological processes and their predictions [1, 2]. HRV modulation by breathing, called respiratory sinus arrhythmia (RSA), can also be used to evaluate changes in cardiac autonomic regulation.

The modeling of the HRV found in the literature is most commonly based on the analysis of the interbeat time intervals (RR) in the frequency domain. Also, it is usual to employ discrete-time modeling, in which the RR intervals are considered as the output of a process at a low sampling rate [3].

These approaches, however, may fail if one is interested in generating the timing of the heartbeats with arbitrary time resolution, especially in real-time. Such situation can be found in the simultaneous modeling of RSA and cardioventilatory coupling (CVC). The CVC is the apparent triggering of the onset of respiratory cycles by the heart beats [4]. Some groups have presented evidence, although not yet with a functional or anatomical explanation, that heart beats may anticipate the beginning of their subsequent inspiration [5], and this effect seems to be modulated by factors such as level of conscience and stress [6].

There has been efforts to model the CVC. For instance, Galletly et al. [7] presented a model of the CVC, which requires the generation of the heart beat timings. That model accounted for the RSA, with a very simplified approach in which the heart beats occur at two fixed rates, one during inspiration and other during expiration. However, the experimentally observed RSA is more complex than that, since the respiratory modulation of the RR interval behaves like a dynamic process depending on factors such as the tidal volume and respiratory frequency.

An alternative approach to model the HRV is the integral pulse frequency modulation (IPFM). In this model, an integrator receives as input a modulating signal, and its output is continuously compared to a threshold. When that threshold is reached, the integrator is reset and a pulse is generated, indicating the occurrence of a heart beat. The modulating signal is thus responsible for the variability of the interval between pulses. This continuous time model seems to meet the requirements for the generation of heart beats, at the same time including a more accurately modeled respiratory influence on the heart rate.

The objective of this study was to evaluate a model of RSA based on IPFM that could be used in a broader model including CVC, and a method to fit its parameters to experimental data.

Materials and Methods

The IPFM model - The IPFM model is based on the hypothesis that the autonomic influences on the sinoatrial node can be represented by a modulating signal, \( m(t) \), and the beat trigger impulse is generated when the integral of this function reaches a threshold [9, 10].

In this model, the time \( t_k \) of the occurrence of the \( k \)-th heart beat is generated by the equation (1):

\[
\int_0^{t_k} \frac{1+m(t)}{T} \, dt = k
\]

where \( m(t) \) is a modulating signal, \( k \) is the number of the beat and \( T \) is the mean heart period.
Solving for \( m(t) \), the equation (2) is obtained:

\[
\int_{t_k}^{t_k+1} m(t) \, dt = k \cdot \bar{T} - t_k
\]  

(2)

The transfer function \( H(s) \) between airflow and \( m(t) \) is modeled here as a first order low-pass filter with DC gain \( G \) and cutoff frequency \( f_c \), according to the equation (3):

\[
H(s) = \frac{G}{s + 1}
\]  

(3)

The model is represented in the diagram in Figure 1.

Figure 1. The transfer function of RSA coupled to the IPFM model. \( F(t) \) is the respiratory flow, \( H(s) \) is the transfer function, \( m(t) \) is the modulating function, \( \bar{T} \) is the mean heart period, \( y(t) \) is an intermediary signal and \( b(t) \) is a signal with pulses at times \( t_k \), \( t_{k+1} \) and \( t_{k+2} \) representing the instants of the heart beats.

**Model fitting** - We used experimental data from the work of Granja-Filho et al. [8]. Eighteen (nine men and nine women) young healthy adults participated in this study. The weight of the subjects ranged from 54.0 kg to 99.3 kg (median 66.5 kg), age ranged between 22-31 years (median 23 years) and height ranged from 1.56 m to 1.92 m (median 1.70 m). One derivation of ECG and respiratory airflow were acquired at a sampling rate of 512 Hz during spontaneous breathing in seated position. The times of the occurrences of the R waves were detected, giving the series of \( t_k \). The value of \( \bar{T} \) was calculated as the mean difference between consecutive values of \( t_k \). The modulating signal \( m(t) \) was calculated at the same sampling rate of the flow signal by interpolating the right branch of (2) with a cubic spline, which was then analytically differentiated. The segments of \( m(t) \) and flow from the first to the last heart beat were used to avoid influences from parts of respiratory flow not related in time with the cardiac tachogram. Flow was processed to remove the DC level.

To remove nonrespiratory contributions to \( m(t) \), it was filtered by a first-order bandpass Butterworth filter with cutoff frequencies of 0.95 and 1.05 times the frequency of highest coherence between \( m(t) \) and flow. The coherence was calculated with a subroutine in MatLab v. R2007a (MathWorks) as the magnitude squared coherence estimated using Welch's averaged periodogram method, with sections of 30,000 samples windowed by a Hanning window, with 50\% overlapping, at sampling rate of 512 Hz. The signal \( m(t) \) was forward and backward filtered, to keep zero phase distortion. The signals were acquired for 315.34 ±9.25 seconds.

To estimate \( f_c \) and \( G \), flow was filtered with a low-pass first-order Butterworth filter, with cutoff frequencies ranging from 0.001 to 1.0 Hz in steps of 0.001 Hz. The gain was calculated by linear regression between the low-pass filtered flow and the modulating function according to the equation (4):

\[
m(t) = G \cdot F_c(t) + C
\]  

(4)

where \( m(t) \) is the modulating function, \( G \) is the gain, \( F_c(t) \) is the low-pass filtered flow and with \( C \) accounting for a possible offset. The objective criterion chosen to select the cutoff frequency and gain was the minimization of the sum of the squared differences between \( m(t) \) and its estimated version obtained with the linear regression, \( m_\text{est}(t) \). Thus, the individual parameters \( G \) and \( f_c \) were established.

The signal \( m_\text{est}(t) \) was then used as the input to the IPFM model, generating a simulated time series of heart beats and the corresponding tachogram, that is, the RR interval series.

**Evaluation of the model** - to evaluate the simulated tachograms, parameters were calculated according to Task Force [11]. In the time domain, it was used the standard deviation of the RR intervals (SDNN), the square root of the mean squared differences of successive RR intervals (RMSSD), the standard deviation of differences between adjacent RR intervals (SDSD) and the rate of number of pairs of adjacent RR intervals differing by more than 50 ms in the entire recording (pNN50); in frequency domain, the power spectral density (PSD), calculated by Welch periodogram method. All the processing was performed in MatLab v. R2007a (MathWorks).

**Results**

The results of time domain analysis for some subjects are presented, with real and simulated results. Graphs depicting the cardiac tachograms and power spectral densities are also presented, comparing real and simulated values. Signals from 18 volunteers were studied. Two representative cases, which present one of the best and one of the worst results, are shown in detail. The results for subject F1224 are shown in Table 1 (analysis in the time domain) and Figure 2 (analysis in frequency domain). The tachograms are also shown for comparison. The results for subject M1522 are shown in Table 2 (analysis in the time domain) and Figure 3 (analysis in frequency domain).

<table>
<thead>
<tr>
<th>Index for F1224</th>
<th>Real</th>
<th>Simulated</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN (ms)</td>
<td>48.5321</td>
<td>32.7172</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>901.2037</td>
<td>782.4944</td>
</tr>
<tr>
<td>SDSD (ms)</td>
<td>47.3658</td>
<td>41.1836</td>
</tr>
<tr>
<td>pNN50 (%)</td>
<td>0.1648</td>
<td>0.1983</td>
</tr>
</tbody>
</table>
Figure 2: Tachograms and frequency domain analysis for subject F1224.

Table 2: Time domain analysis for subject M1522.

<table>
<thead>
<tr>
<th>Index for M1522</th>
<th>Real</th>
<th>Simulated</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN (ms)</td>
<td>94.8399</td>
<td>46.4605</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>1.4008e+003</td>
<td>936.4409</td>
</tr>
<tr>
<td>SDSD (ms)</td>
<td>75.8522</td>
<td>50.7856</td>
</tr>
<tr>
<td>pNN50 (%)</td>
<td>0.2682</td>
<td>0.2485</td>
</tr>
</tbody>
</table>

Figure 3: Tachograms and frequency domain analysis for subject M1522.

The results of the time domain analysis to the eighteen subjects are shown in Table 3.

Table 3. Comparison of real and estimated parameters in time domain for the eighteen volunteers.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Median [p25 – p75]</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN (ms)</td>
<td>71.9 [56.4 – 1.12e+2]</td>
</tr>
<tr>
<td>SDNN est (ms)</td>
<td>55.2 [41.3 - 83.1]</td>
</tr>
<tr>
<td>RMSSD</td>
<td>1.48e+3 [1.00e+3 - 2.16e+3]</td>
</tr>
<tr>
<td>RMSSD est (ms)</td>
<td>1.24 e+3 [8.51 e+2 - 1.56 e+3]</td>
</tr>
<tr>
<td>SDSD (ms)</td>
<td>79.3 [54.7 – 1.14e+2]</td>
</tr>
<tr>
<td>SDSD est (ms)</td>
<td>67.6 [46.6 – 86.2]</td>
</tr>
<tr>
<td>pNN50 (%)</td>
<td>0.262 [0.188 – 0.304]</td>
</tr>
<tr>
<td>pNN50 est (%)</td>
<td>0.291 [0.173 – 0.3364]</td>
</tr>
</tbody>
</table>

Discussion

The model was able to recover partially the power spectral density at the frequency band of interest. Comparison of tachograms showed that the model was not able to recover the base fluctuations in RR interval. Thus, it is necessary to implement a device in the model that simulates such oscillations.

The use of a low-pass filter was proposed as a constituent of the transfer function, particularly through its effect on the phase of the respiratory signal. This low-pass filtering would have its physiological counterpart anatomical and physiological interactions between the respiratory and cardiovascular systems. So, the cutoff frequency and the gain of the filter can be used as individual parameters.

A critical point of the model was the choice of the cutoff frequency of the low-pass filter. That choice was made by minimizing the squared error of the estimated and actual modulating functions, but an underestimation of the simulated values was observed, both in time as in the frequency domain. Hence, the option was to minimize after filtering the modulation function by a band-pass filter, using the spectral coherence as reference. The frequency of maximum coherence was chosen as the center frequency of the band-pass filter, with the limits of ± 5%, but other choices may provide different results. On the other hand, other objective criteria to adjust the parameters could be proposed, such as minimizing the differences between the actual and simulated tachograms instead of the modulating function. That could lead to different results.

This model has some limitations. The analysis showed that only a part of HRV could be explained by the respiratory signal. This is expected because other factors, like arterial blood pressure or endocrine fluctuations, also contribute to HRV and may not be directly related to respiration.

A large portion of the HRV lies at lower frequencies, which calls for the inclusion of further components in \( m(t) \). For that, models and estimation techniques must be studied. Also, the first order low-pass model of \( H(s) \) may prove insufficient to explain RSA; possibly higher order models, nonlinearities and other elements must be included. The approach to identify the cutoff frequency of \( H(s) \) may be substituted by other techniques that exploit the structure of the model; linear regression is a candidate, granting further research.

In conclusion, the present model could be able to simulate RSA and possibly be used in a larger model that includes cardioventilatory coupling, such as that proposed by Galletly et al. [7]. Further studies are necessary to improve the model and identification techniques.

Acknowledgments

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References