Recursive Model Identification for the Analysis of Cardiovascular Autonomic Modulation During Epileptic Seizure

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Abstract

Significant cardio-respiratory fluctuations are often observed during and after an epileptic seizure event. The mechanisms underlying these acute modifications are considered to be involved in sudden and unexpected death in epilepsy (SUDEP). We hypothesize that these acute events are mediated by specific dynamics of the autonomic nervous system (ANS). However, the evaluation of the ANS during seizures remains particularly challenging, mainly due to the lack of observability. Computational modelling could help to override these limitations, to assess ANS modulation and to evaluate this hypothesis. In this study, we propose and apply a recursive identification algorithm of a system-level model of the autonomic modulation of the sino-atrial node, integrating a Tikhonov regularization, in order to assess sympathetic and parasympathetic activities during ictal tachy-bradycardia events. We evaluate the feasibility of the method on heart rate (HR) data from 4 seizures observed in the same patient. After parameter optimization and identification we were able to reproduce observed HR data with a maximum root mean squared error equals to 1.7bpm. The estimated autonomic series show sympathetic activation and parasympathetic inhibition at the seizure onset, and a massive vagal discharge as the leading factor to ictal bradycardia.

1. Introduction

The autonomic function is usually altered during and after an epileptic seizure event. These alterations lead, between other effects, to a significant modification of heart rate [1], as well as other cardiac and respiratory functions [2]. Although the hypothesis of an autonomic dysfunction has been already proposed in the context of sudden and unexpected death in epilepsy (SUDEP) [3], the precise underlying mechanisms remain unknown. Autonomic analyses performed on SUDEP patients have shown severe autonomic dysfunctions [4][5]. Animal experiments demonstrated that seizures spread to the brainstem can lead to cardio-respiratory depression and death [6]. It has been also suggested that lethal events are mediated by seizure-induced brainstem depolarization which inactivates autonomic control centers [7]. In these cases, the assessment of autonomic nervous system (ANS) activity may be useful to better understand the underlying mechanisms of SUDEP. However, ANS activity is difficult to estimate during seizure. Classical heart rate variability (HRV) analysis tools are not adapted, due to the strong non-stationary character of these series and the suddenness of cardiovascular events. Furthermore, experimental recordings of ANS activity are difficult to acquire.

The objective of this paper is to evaluate the feasibility of a new model-based method to assess sympathetic and parasympathetic dynamics from non-stationary HR series observed during an epileptic seizure event. The method relies on a system-level model of the autonomic modulation of the sino-atrial node, and a recursive identification algorithm. In particular, we propose in this publication a Tikhonov-like regularization approach to enhance the identification process in such an under-determined problem, and provide a method to optimize the regularization parameters. The proposed method was applied to 4 seizures of one patient presenting acute and transient cardiovascular ictal events.

2. Methods

2.1. Clinical Data

From a clinical research database acquired at CHU of Rennes with the authorized consent of the patient, we selected a patient with no other pathology but epilepsy, presenting transient seizure-induced acute cardio-respiratory events. Complete polysomnography (PSG) recordings were analyzed to extract 4 seizures with recurrent patterns of ictal tachycardia arising at the onset of the seizure and followed by a transient, significant bradycardia. An example of such events is shown in Fig.1.

2.2. Data Processing

RR series were extracted from the available PSG ECGs. Ectopic beats were removed and QRS complex detection were manually corrected to avoid detection errors due to epilepsy-related artefacts. The heart rate series was then
calculated, interpolated, and resampled at 100 Hz, so as to keep a sufficient temporal resolution for the recursive identification method.

2.3. Computational Model

The proposed computational model is focused on efferent nervous activity and is based on a widely used approach [8–10]. Both sympathetic and vagal branches are modeled by first-order filters, characterized by gains \( K_s, K_v \) and time constants \( (T_s, T_v) \) (Fig. 2). The polynomial \( P_{HR} \) characterizes the chronotropic response to both sympathetic \( (F_s) \) and vagal \( (F_v) \) activities [8]. The inputs of the model, \( f_s \) and \( f_v \), stand respectively for the sympathetic and parasympathetic efferent activities. These are time-varying variables that aggregate the influence of different sources (blood pressure fluctuations, central modulation, respiration, etc.). We defined the state vector \( \vec{S}_i = (f_{s,i}, v_{i}, F_{s,i}, F_{v,i}) \) as the representation of the state of the model at each instant \( t = iT \).

\[
\begin{align*}
   f_s = \frac{K_s}{1 + \tau_s \cdot p} & \quad F_s = P_{HR}(HR) \\
   f_v = \frac{K_v}{1 + \tau_v \cdot p} & \quad F_v = P_{HR}(HR)
\end{align*}
\]

\([K_s, K_v] = [1, 0.8]\)
\([\tau_s, \tau_v] = [6, 1.8]\)
\(HR = 35 + 140 \cdot F_s - 40 \cdot F_s^2 - 32 \cdot F_v + 10 \cdot F_s^2 + 20 \cdot F_v \cdot F_s\)

Figure 2. Block diagram of the system-level model, representing its parameters and main variables.

2.4. Recursive Identification

The objective here is to estimate the time series \( f_s \) and \( f_v \) that minimize the error between the simulated HR signal \( (HR_{sim}) \) and the observed HR \( (HR_{ref}) \). The cost function (1) is calculated on overlapping segments, as:

\[
\epsilon_i = \frac{1}{n} \sum_{t_e=iT}^{iT+\Omega} (HR_{sim}(t_e) - HR_{ref}(t_e))^2 + \Gamma_{s,i} + \Gamma_{v,i}
\]

\(1\)

\[
\Gamma_{s,i} = \alpha \sum_{t_e=iT-\tau_s}^{iT} (f_s(t_e) - f_s(t_e))^2
\]

\(2\)

\[
\Gamma_{v,i} = \beta \sum_{t_e=iT-\tau_v}^{iT} (f_v(t_e) - f_v(t_e))^2
\]

\(3\)

where \( i \) is the step of the identification process, \( t_e \) is the time elapsed since the onset of the identification period, \( \Omega \) is the duration of each interval, \( T \) corresponds to the overlap time between each interval, \( n \) is the number of samples during \( \Omega \). \( \Gamma_s \) and \( \Gamma_v \) are two regularization terms, inspired from the Tikhonov regularization method and introduced to face the under-determination of the problem. They respectively weigh the dynamics of the \( i^{th} \) candidates regarding the past identified values, on a segment of duration equal to their respective time constant \( \tau_s \) and \( \tau_v \), so as to privilege smoother solutions. The main procedure of the identification process is described in [9] and depicted in figure 3. At each step \( i \), the best set of \( \{f_v, f_s\} \) was identified within \([0, 1]\) by applying a self-adaptive differential evolution algorithm (jDE)[11]. The model was then updated with these inputs to start a new simulation that will generate the new state vector \( \vec{S}_{i+1} \) at \( t = (i + 1)T \). Between the \( i^{th} \) and the \((i + 1)^{th}\) steps of the algorithm, the sliding window was shifted of \( T \) seconds and the new step was initialized with \( \vec{S}_{i+1} \). This procedure was executed until all the samples of \( HR_{ref} \) had been covered.

Figure 3. Representation of sliding windows of length \( \Omega \) where input values are estimated. For each step, the sliding window is shifted of \( T \) seconds and states of the algorithm are set to the latest optimal solution at \( t = (i + 1)T \).
2.4.1. Cost function optimization

Performance of the identification is highly dependent on parameters $\Omega$ and $T$. In fact, the overlap time $T$ should be able to capture rapid events in $HR_{ref}$, partly due to the vagal modulation, and acts as the sampling period of the method. The identification interval $\Omega$ should be defined to take into account the slowest dynamics, which could be associated with sympathetic modulation. Constants $\alpha$ and $\beta$, associated with regularization terms, also had an impact on the results. In order to find optimal identification results, an exhaustive exploration of $\Omega$, $T$, $\alpha$ and $\beta$ was performed by executing the recursive identification procedure for each combination of these identification parameters within a discrete grid. From each execution, a simulated heart rate $\hat{HR}_{sim}$ was constructed from state vectors $\hat{S}$. The optimal values of $\Omega$ and $T$ were chosen in order to minimize the root mean squared error (RMSE) between $\hat{HR}_{sim}$ and $HR_{ref}$ (eq.4) where $t_s$ is the sampled time, $N$ is the total number of samples and $t_{tot}$ corresponds to signal duration.

$$RMSE = \sqrt{\frac{1}{N} \sum_{t_s=0}^{t_{tot}} (\hat{HR}_{sim}(t_s) - HR_{ref}(t_s))^2}$$  \hspace{1cm} (4)

Parameters $\alpha$ and $\beta$ were selected in such a way that the identification procedure gives a realistic autonomic activity without degrading the efficiency of the identification process.

3. Results and Discussion

The cost function optimization process was applied to the four available HR series, corresponding to four epileptic seizures of a given patient. Figure 4 illustrates an example of RMSE values calculated for different values of $T$ and $\Omega$ for one seizure. Results showed the existence of a global minimum in the range of parameters delimited by time constants of the model. We chose $\alpha = \beta = 0.1$. These weights give both the ability to the process to fit the input data, and to give a realistic sympathetic and parasympathetic identified activities [12].

Figure 5 shows the results of the recursive identification procedure on each of the four seizures analyzed. Results show, i) the comparison between simulated and observed HR signals, ii) the dynamics of $f_s$ and $f_o$ as identified with the proposed approach and iii) the optimal values of $T$ and $\Omega$ for each case. A close match was observed between simulated and observed signals, with an average RMSE of 0.52bpm. In the case of seizure 2, the error is three times greater than this mean value. The identification process didn’t succeed to fit the bradycardia, and the identified ANS activities lead to saturation of the model.

4. Conclusions

In this paper we proposed a model-based method relying on a recursive stochastic algorithm to estimate ANS dynamics from non-stationary, observed HR series. We proposed a method to better condition this process, to reproduce HR, and to estimate realistic ANS activity. Results warrant further investigation to enhance identification of ANS activity, especially to study the underlying mechanisms of SUDEP.

Acknowledgements

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References

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Figure 5. Identification results over four seizures showing the reference HR signal (black dashed), the simulated HR signal (solid black) and the identified sympathetic (red) and vagal (blue) activities.