Point Process Modeling of R-R Interval Dynamics during Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia, and one of the main causes of ictus and strokes. Effective treatments for AF are still unknown, as its effects on the heart substrate have not been clearly quantified yet. One of the main lines of investigation aims at characterizing ventricular response by looking at its effects on heartbeat interval dynamics. Most of the standard approaches have focused on RR interval (RRI) histogram parameters albeit with several shortcomings, such as bin width dependence or lack of attention to the time-varying dynamical structure. In this study, we model heartbeat interval series as a history-dependent inverse Gaussian (HDIG) point process where the history for each RRI prediction is a linear regression of the previous RRIs. As opposed to classical non-parametric methods, the heart rate (HR) variability features derived from the proposed parametric model provide a physiologically more consistent characterization during AF, and can clearly discriminate AF from sinus rhythm (SR) subjects. Analysis of 36 patients affected by persistent AF and 18 controls shows that RRI distributions are more right-skewed and affected by higher variability during AF (skewness of 0.63 ± 0.29 in AF and of 0.17 ± 0.16 in SR, p=$7.6 \cdot 10^{-8}$; HR standard deviation of 18.73 ± 10.64 bpm in AF and 4.66 ± 4.75 bpm in SR, p=$2.3 \cdot 10^{-6}$). Our results demonstrate that we can extract valuable information associated with AF from RRI series by using a point process framework.

1. Introduction

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function [1]. Ischaemic stroke episodes in association with AF are more and more recurrent, and patients who survive are more likely to experience a recurrence than patients with other causes of stroke [2]. Hence, there is a need for a prompt diagnosis and a suitable therapy to treat this pathology. Despite the recent advances in understanding AF, its electrophysiological dynamics have not been completely clarified yet. One of the most common lines of research focuses on ventricular response analysis based on knowledge about heartbeat interval statistical properties.

Previous electrocardiogram (ECG) based studies have pointed out that changes in atrioventricular (AV) node function and its refractoriness during AF are reflected on the irregularity of the RR interval (RRI) distribution [3]. Similarly, in [4] these properties are estimated from the RRIs using maximum likelihood estimation and the RRI Poincaré plot. In [5], heartbeat interval variability allows the estimation of the effects of several pharmacological therapies [5]. However, these results are merely based on visual inspection of the RRI histogram, and no quantitative assessment of the statistical features is presented. A probabilistic analysis of RRIs has been attempted in [6], although such approach is highly dependent on histogram bin width, thus making it hard to generate univocal results. In addition, all these methods prove their efficacy on long ECG recordings (at least 10 minutes up to 24-hour Holter recordings) not always available in daily clinical practice.

The present study puts forward a novel method which models RRI probability distribution as a history-dependent Gaussian (HDIG) point process [7]. Such dependence resumes effects of sino-atrial (SA) node response to sympathetic and parasympathetic inputs from the autonomous nervous system, as well as changes in AV node refractory period and effects of concealed conduction typical of AF. This characterization enables the computation of heart rate (HR) and heart rate variability (HRV) features which may better distinguish AF from sinus rhythm (SR) conditions, thus providing a more accurate characterization of this disease and a better comprehension of its dynamics.
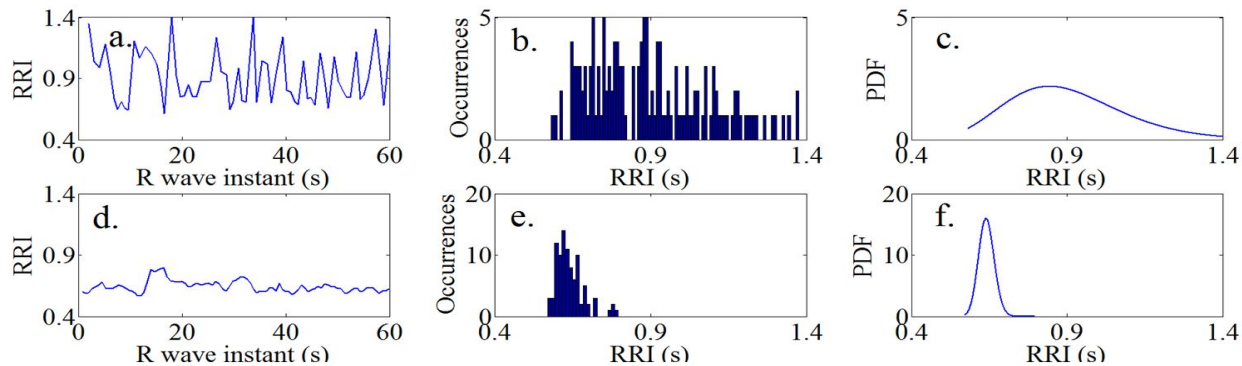
Figure 1. Examples of RRI time series (a.-b.) and the related histogram (c.-d.) and probability distribution (e.-f.). Top: AF, subject 2; Bottom: SR, subject 14.

2. Methods

2.1. ECG Acquisition Protocol

We consider 36 patients (age 50 to 70 years) affected by persistent AF. One-minute standard ECG was acquired at a sampling rate of $F_S = 977$ Hz. ECG recordings of 18 control subjects are taken from the MIT-BIH Normal Sinus Rhythm Database. The group consists of 5 men, aged 26 to 45, and 13 women, aged 20 to 50.

2.2. Histogram Analysis of RRI

Preliminary analysis inspecting RR series and their respective histograms highlights asymmetric RRI distributions around their mean value for AF patients. In contrast, the histograms extracted in the SR control subjects appear more symmetric, thus confirming previous findings. An example is shown in Fig. 1. This can be explained by the rapid firing of atrial activations throughout the AV node typical of AF, inducing a correspondingly irregular ventricular activation, as reflected on RRI duration on ECG. Furthermore, as shown in Fig. 1a, during AF repetition rate of RRIs seems considerably higher, and their length values are more irregularly distributed, in contrast with SR where RRIs seem more evenly spaced. We hypothesize that these properties can be quantified more accurately by our point process approach.

2.3. Point Process Model of RRI

As stated in previous works [7], ventricular contractions (R waves on the ECG) can be effectively represented as a history dependent inverse Gaussian (HDIG) point process. Dependence on past RRIs reflect the sympathetic and parasympathetic dynamic inputs from the autonomic nervous system to the SA node, which can persist on the following heartbeats for several seconds. This model al-lows to explore if further effects due to AV node refractoriness and concealed conduction can contribute to RRI variability during AF. Within this framework, let us define the time occurrence of the k-th R wave as u_k and the k-th RRI as $w_k = u_k - u_{k-1}$. For any $t > u_k$, we assume that the probability density function of the RRI length follows a HDIG distribution:

$$f_{RR}(t, H_{u_k}, \theta) =$$
$$[\frac{\theta_{q+1}}{2\pi(t-u_k)^3}]^{\frac{1}{2}} \exp\{-\frac{1}{2}\frac{\theta_{q+1}[t-u_k-\mu_{RR}(H_{u_k},\theta)]^2}{\mu_{RR}(H_{u_k},\theta)^2(t-u_k)}\}$$
(1)

where $\theta = [\theta_0, \theta_1, \ldots, \theta_{q+1}]$ is a vector of model parameters, and μ_{RR} and θ_{q+1} stand for the first moment and the shape factor of the distribution, respectively. According to this model, each interval w_k is regarded as dependent on its previous history $H_{u_k} = (u_k, w_k, w_{k-1}, \ldots, w_{k-q+1})$, i,e., as a linear combination of the last q RRIs.

$$\mu_{RR}(H_{u_k}, \theta) = \theta_0 + \sum_{j=1}^{q} \theta_j w_{k-j+1} \qquad (2)$$

In this analysis, since we focus attention on the statistical properties rather than sympatho-vagal modulation, we fixed the regression order to $q = 1$ and the temporal window for local maximum likelihood estimates to 30 seconds (about half length of each available ECG segments) [7].

Goodness-of-fit of the point process model is evaluated by means of the time-rescaling theory and the KS test [7]. KS plots can be drawn by plotting the distribution function of the RRI series rescaled to the interval $(0, 1]$ against a uniform distribution defined in the same interval. A representative example is displayed for each group in Fig 2. We measure the maximum KS distance from the KS plot: the lower its value, the better the model fit.
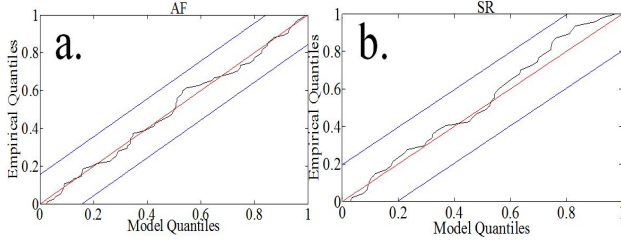
Figure 2. KS plots for one AF (a) and one SR (b) subject.

2.4. Heart Rate and Heart Rate Variability Feature Extraction

Several indices of HR and HRV are evaluated by both a simple non-parametric approach (the straightforward feature extraction from the heartbeat interval series, with no assumptions on its probability distribution) and the point process approach.

In the non-parametric approach these indices are:

1. **Mean RRI**: defined as the average value of all RRI lengths ($\overline{RR} = E\{(w_k)\}$).

2. **HR mean value**: conventionally assumed as the reciprocal mean RRI ($\overline{HR} = c\overline{RR}^{-1}$), scaled by the factor of conversion from seconds to beats per minute $c = 60min$.

3. **Skewness**: it provides a measure of asymmetry of the RRI distribution, defined as $Skewness = \frac{E\{(w_k-\overline{RR})^3\}}{E\{(w_k-\overline{RR})^2\}^{\frac{3}{2}}}$.

4. **RRI standard deviation**: it assesses the level of RRI length variability ($\sigma_{RR} = E\{(w_k - \overline{RR})^2\}$).

5. **HR standard deviation**: defined as the standard deviation of the reciprocal RRIs (σ_{HR}), adequately scaled by the conversion factor c.

In the HDIG framework, the following features are investigated:

1. **Mean RRI**: it is equal to the first moment of the HDIG distribution μ_{RR}.

2. **HR mean value**: $\mu_{HR} = c(\frac{1}{\mu_{RR}} + \frac{1}{\theta_{q+1}})$.

3. **Skewness**: $Skewness = 3\sqrt{\frac{\mu_{RR}}{\theta_{q+1}}}$.

4. **RRI standard deviation**: $\sigma_{RR} = \sqrt{\frac{\mu_{RR}^3}{\theta_{q+1}}}$.

5. **HR standard deviation**: $\sigma_{HR} = \frac{c}{\theta_{q+1}}\sqrt{2 + \frac{\theta_{q+1}}{\mu_{RR}}}$.

All parameters are averaged among each group ("AF" vs "SR") and referred to as mean $\pm$ standard deviation for each method (non-parametric vs point process approach). Interclass statistical differences are assessed by the p-value of the unpaired Student's t-test under a confidence level $\alpha = 0.05$.

3. Results

Results of goodness-of-fit estimation are shown in Table 1. The minimum and maximum KS distance, as well

Table 1. Assessment of Point Process Model Goodness-of-fit: KS distance evaluation.

	Mean $\pm$ Standard Deviation	Minimum	Maximum
AF	0.1045 ± 0.0626	0.0476 (subject 2)	0.3908 (subject 22)
SR	0.1051 ± 0.0400	0.0555 (subject 1)	0.1984 (subject 6)

as the mean $\pm$ standard deviation, are reported for each category under examination. The low KS distance values indicate a good agreement between our model and the considered heartbeat interval series. In 30 AF patients out of 36 KS plots fall entirely within the 95% confidence bounds. In patient 30 the model fit is also extremely accurate, since the percentage of KS plot points lying within the confidence bounds is considerably high (92.7273%). Only in AF subjects 7 and 22 the model less accurately describes RRI distribution. This is proven not only by the high values of the maximum KS distance, but also by the visual inspection of the related KS plot, as most of their points lie outside the confidence interval (69.6721% and 55%, respectively). Accordingly, these patients are not included in the statistical analysis of HRV features (thus reducing mean KS distance to 0.0951 ± 0.0393). Concerning the control group, the KS plots are entirely within the confidence interval in 15 subjects out of 18. However, in the remaining SR subjects estimation is also highly accurate, since deviations from the perfect fit are very limited (subject 3 = 76.7442%, subject 5 = 93.4783%, subject 6 = 76.9231%). In Fig. 1 we show two representative examples (one for AF and one for SR) of the estimated HDIG distribution functions.

Results of the unpaired statistical analysis are reported in Table 2. In particular, of all the considered features, the most discriminating ones were the skewness and the heart rate variance computed from the point process model. Of note, the respective non-parametric features are not significantly different between the two groups.

4. Discussion and Conclusions

In this work, we put forward a probabilistic approach aiming at AF characterization by analysis of the ventricular contractions (RRIs). To this extent, we propose a previously developed HDIG point process model of heartbeat dynamics. The model allows to compute instantaneous HR and HRV indices, is independent from histogram bin width, and proves to be effective also on short ECG recording. The rigorous assessment of model goodness-of-fit, an important feature of the point process framework, reveals an excellent agreement with the RRI series derived during AF, thus confirming its ability to accurately capture heartbeat statistical properties also in this important pathological state.

The point process approach enables an enhanced char-

Table 2. Unpaired Statistical Analysis of HR and HRV features (n.u.: normalized units).

	Non-parametric Analysis			HDIG Point Process		
	AF	SR	p-value	AF	SR	p-value
$\overline{RR} - \mu_{RR}$ [s]	0.74 ± 0.17	0.72 ± 0.13	$6.6 \cdot 10^{-1}$	0.75 ± 0.16	0.72 ± 0.13	$5.7 \cdot 10^{-1}$
$\overline{HR} - \mu_{HR}$ [bpm]	85.45 ± 20.12	85.81 ± 14.74	$9.5 \cdot 10^{-1}$	89.95 ± 20.99	86.2 ± 15.3	$5.1 \cdot 10^{-1}$
$Skewness$ [n.u.]	0.58 ± 1.08	0.76 ± 3.13	$7.7 \cdot 10^{-1}$	0.63 ± 0.29	0.17 ± 0.16	$7.6 \cdot 10^{-8}$
σ_{RR} [s]	0.16 ± 0.07	0.05 ± 0.02	$3.8 \cdot 10^{-7}$	0.16 ± 0.09	0.04 ± 0.04	$2.2 \cdot 10^{-6}$
σ_{HR} [bpm]	26.28 ± 55.92	7.75 ± 10.81	$1.7 \cdot 10^{-1}$	18.73 ± 10.64	4.66 ± 4.75	$2.3 \cdot 10^{-6}$

acterization of HR and HRV features based on RRI histogram properties, thus overcoming the limitations of more standard approaches. More specifically, even though differences in symmetry in RRI histogram between AF and SR subjects can be visually detected, no studies have so far quantitatively assessed such a difference. Indeed, our research reveals that the standard non-parametric analysis is not able to separate skewness characteristics of RRI distribution between AF and SR (see Table 2). By contrast, the point process characterization significantly differentiates such properties, thus confirming that during AF several factors contribute to make ventricular contraction more rapid and irregular, as reflected on the high proportion of short RRIs on the ECG and the higher skewness values. Of note, both methods do not underline significant differences in the mean RR interval and the mean heart rate, $\overline{RR}$ and $\overline{HR}$, respectively.

RRI irregularity observed in presence of AF can be also estimated by second-order statistics quantifying the degree of scattering of data distribution, e.g., σ_{RR} and σ_{HR}. Here, we can note that, while both parametric and point process RR standard deviation can significantly differentiate AF from SR (see p-values in Table 2), only the point process HR standard deviation shows significant values. This evidence confirms that RRI length distribution is affected by higher variability during AF. This increased variability is consistent with electrophysiological phenomena such as AV node refractoriness and effects of concealed conduction, namely, the incomplete penetration of atrial impulses into the AV node, resulting in a prolongation of the refractory period, which may block or delay the passage of subsequent atrial impulses during AF. In conclusion, differences in asymmetry and dispersion indices between AF and SR are significantly enhanced, and can be potentially applied to perform automatic AF detection and recognition. Future studies will explore if more refined point process HRV features can further improve AF characterization and classification, and will consider experimental data collected before and after radiofrequency catheter ablation in order to investigate if our methods can help improve ablation outcome prediction and therapy selection.

Acknowledgements

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