A Study of Probabilistic Models for Characterizing Human Heart Beat Dynamics in Autonomic Blockade Control

Zhe Chen, Emery N. Brown, and Riccardo Barbieri

***Abstract*— In this paper, we compare and validate different probabilistic models of human heart beat intervals for assessment of the electrocardiogram data recorded with varying conditions in posture and pharmacological autonomic blockade. The models are validated using the adaptive point process filtering paradigm and Kolmogorov-Smirnov test. The inverse Gaussian model was found to achieve the overall best performance in the analysis of autonomic control. We further improve the model by incorporating the respiratory covariate measurements and present dynamic respiratory sinus arrhythmia (RSA) analysis. Our results suggest the instantaneous RSA gain computed from our proposed model as a potential index of vagal control dynamics.**

***Index Terms*— Heart rate variability, point processes, adaptive filters, autoregressive processes.**

I. Introduction

Heart rate (HR) and heart rate variability (HRV) are important quantitative markers of cardiovascular control, as regulated by the autonomic nervous system [1]. It has long been understood that the healthy heart is influenced by multiple neural and hormonal inputs that result in variations of duration in the interbeat intervals (R-R intervals). Studying the R-R intervals is a standard way to analyze the heart beat dynamics. In the literature, numerous methods have been proposed for HRV analysis, including point process analysis [2, 3], frequency-domain analysis [4], and nonlinear dynamics analysis [8]. In this paper, we investigate different probabilistic models for the human heart beat interval with the adaptive point process filtering paradigm [2], utilizing the electrocardiogram (ECG) and lung volume data from a previous study [9] under an autonomic blockade assessment protocol. In addition, we extend the inverse Gaussian model to take into account the influence of respiration on HRV. Modeling accuracy is evaluated via goodness-of-fit tests, and spectral analysis and physiological interpretations are presented for the reported results.

II. Point Process Probabilistic Models

In this section, we conduct the probabilistic analysis of heart beat data with the stochastic point process paradigm. The major advantage of casting the heart beat interval within the point process framework is to allow the possibility to model and evaluate the *instantaneous* heart rate statistics at arbitrary fine time resolution. In addition, the continuous heart beat values (in contrast to the interpolated R-R interval values) offer the convenience for frequency analysis.

A. Heart Beat Interval

Suppose we are given a set of R-wave events $\{u_j\}_{j=1}^J$ detected from the ECG, let $RR_j = u_j - u_{j-1} > 0$ denote the jth R-R interval, or equivalently, the waiting time until the next R-wave event. By treating the R-wave as discrete events, we propose different parametric point process probabilistic models (Table I) in the continuous-time domain.

As an example, assuming history dependence, the waiting time $t - u_t$ until the next R-wave event may be modeled as the following inverse Gaussian model:

$$p(t) = \Big(\frac{\theta}{2\pi t^3}\Big)^{\frac{1}{2}} \exp\Big(-\frac{\theta(t-u_t-\mu_t)^2}{2\theta^2(t-u_t)}\Big) \quad (t > u_t),$$

where u_t denotes the previous R-wave event occurred before time t, $\theta > 0$ denotes the shape parameter, and μ_t denotes the instantaneous R-R mean that is defined as

$$\mu_t \equiv \mu_{\text{RR}}(t) = a_0 + \sum_{i=1}^{p} a_i RR_{t-i}. \tag{1}$$

Here, the mean value is modeled by a univariate p-order autoregressive (AR) process, which is assumed (approximately) to be influenced by the past p R-R values. Similarly, we can derive the mean and variance of R-R interval for all probabilistic models, such as the Gaussian, lognormal, and gamma models (Table I).

B. Instantaneous Indices of HR and HRV

Heart rate is defined as the reciprocal of the R-R intervals. For RR measured in seconds, $r = c(t-u_t)^{-1}$ (where $c = 60$ s/min) is a physiological measurement in beats per minute (bpm). By the *change-of-variables* formula, the HR probability $p(r) = p(c(t-u_t)^{-1})$ is given by

$$p(r) = \Big|\frac{\mathrm{d}t}{\mathrm{d}r}\Big| p(t), \tag{2}$$

and the mean and the standard deviation of heart rate r can be derived (see Table I). Essentially, the instantaneous indices of HR and HRV are characterized by the mean μ_{HR} and standard deviation σ_{HR}, respectively (see [2, 3] for details).

It is known from the point process theory [2, 3] that, the *conditional density function* (CIF) $\lambda(t)$ is related to the inter-event probability $p(t)$ with a one-to-one relationship:

$$\lambda(t) = \frac{p(t)}{1 - \int_{u_t}^{t} p(\tau)\mathrm{d}\tau}. \tag{3}$$

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TABLE I

COMPARISON OF 4 TWO-PARAMETER PARAMETRIC PROBABILISTIC MODELS FOR THE HEART BEAT R-R INTERVAL AND HEART RATE (HR).

	R-R interval model $p(t\|\theta_1,\theta_2)$	$\mathbb{E}[t]$	var$[t]$	HR model $p(r\|\theta_1,\theta_2)$	Note: $c = 60$ s/min
Gaussian	$\frac{1}{\sqrt{2\pi\theta_2}}\exp\left(-\frac{(t-\theta_1)^2}{2\theta_2}\right)$	θ_1	θ_2	$\frac{c}{\sqrt{2\pi\theta_2 r^2}}\exp\left(-\frac{(cr^{-1}-\theta_1)^2}{2\theta_2}\right)$	
invGaussian	$\left(\frac{\theta_2}{2\pi t^3}\right)^{\frac{1}{2}}\exp\left(-\frac{\theta_2(t-\theta_1)^2}{2\theta_1^2 t}\right)$	θ_1	θ_1^3/θ_2	$\left(\frac{\theta_2^*}{2\pi r}\right)^{\frac{1}{2}}\exp\left(-\frac{\theta_2^*(1-\theta_1^* r)^2}{2\theta_1^{*2} r}\right)$	$\theta_1^* = \theta_1/c, \theta_2^* = \theta_2/c$
lognormal	$\frac{1}{\sqrt{2\pi\theta_2}t}\exp\left(-\frac{(\log(t)-\theta_1)^2}{2\theta_2}\right)$	$e^{\theta_1+\theta_2/2}$	$e^{2\theta_1+\theta_2}(e^{\theta_2}-1)$	$\frac{1}{\sqrt{2\pi\theta_2 r}}\exp\left(-\frac{(\log(cr^{-1})-\theta_1)^2}{2\theta_2}\right)$	
gamma	$\frac{\theta_2^{\theta_1}}{\Gamma(t\theta_1^{-1})}\exp(-\theta_2 t)$	θ_1/θ_2	θ_1/θ_2^2	$\frac{\theta_2^{*\theta_1}}{\Gamma(\theta_1)r^{\theta_1+1}}\exp(-\theta_2^*/r)$	$\theta_2^* = c\theta_2$

The estimated CIF can be used to evaluate the goodness-of-fit of the probabilistic model for the heart beat dynamics.

C. Adaptive Point Process Filtering

Let $\boldsymbol{\theta}$ denote the unknown parameters in the parametric probabilistic model, we can use recursively estimate them via adaptive point process filtering [2]:

$$\boldsymbol{\theta}_{k|k-1} = \boldsymbol{\theta}_{k-1|k-1} \quad (4)$$

$$P_{k|k-1} = P_{k-1|k-1} + W \quad (5)$$

$$\boldsymbol{\theta}_{k|k} = \boldsymbol{\theta}_{k|k-1} + P_{k|k-1}(\nabla \log\lambda_k)[n_k - \lambda_k\Delta] \quad (6)$$

$$P_{k|k} = \left[P_{k|k-1}^{-1} + \nabla\lambda_k\nabla\lambda_k^T\frac{\Delta}{\lambda_k} - \nabla^2\log\lambda_k[n_k-\lambda_k\Delta]\right]^{-1} \quad (7)$$

where P and W denote the parameter and noise covariance matrices, respectively; $\Delta = 0.005$s denotes the time bin size; $\nabla\lambda_k = \frac{\partial\lambda_k}{\partial\boldsymbol{\theta}_k}$ and $\nabla^2\lambda_k = \frac{\partial^2\lambda_k}{\partial\boldsymbol{\theta}_k\partial\boldsymbol{\theta}_k^T}$ denotes the first- and second-order partial derivatives of the CIF w.r.t. $\boldsymbol{\theta}$ at time $t = k\Delta$, respectively. The indicator variable $n_k = 1$ if a heart beat occurs in time $((k-1)\Delta, k\Delta]$ and 0 otherwise.

D. Goodness-of-fit Tests

The goodness-of-fit of the model is tested with the *time-rescaling theorem* [7]. Given a point process specified by J discrete events: $0 < u_1 < \cdots < u_J < T$, define the random variables $z_j = \int_{u_{j-1}}^{u_j}\lambda(\tau)\mathrm{d}\tau$ for $j = 1, 2, \ldots, J-1$. Then the random variables z_js are independent, unit-mean exponentially distributed. By introducing the variable of transformation $v_j = 1-\exp(-z_j)$, then v_js are independent, uniformly distributed within the region [0, 1]. Let $g_j = \Phi^{-1}(v_j)$ (where $\Phi(\cdot)$ denotes the cumulative density function (cdf) of the standard Gaussian distribution), then g_js will be independent standard Gaussian random variables. The *Kolmogorov-Smirnov* (KS) test is used to compare the cdf of v_j against that of the random variables uniformly distributed in [0, 1]. The KS statistic is the maximum deviation of the empirical cdf from the uniform cdf. To compute it, v_js are sorted from the smallest to the largest value, then we plot values of the cdf of the uniform density defined as $\frac{j-0.5}{J}$ against the ordered v_js. The points should lie on the 45 degree line. In Cartesian plot of the empirical cdf as the y-coordinate versus the uniform cdf as the x-coordinate, the 95% confidence interval lines are $y = x \pm \frac{1.36}{(J-1)^{1/2}}$. The KS distance, defined as the maximum distance between the KS plot and the 45° line, is used to measure the lack-of-fit between the model and the data.

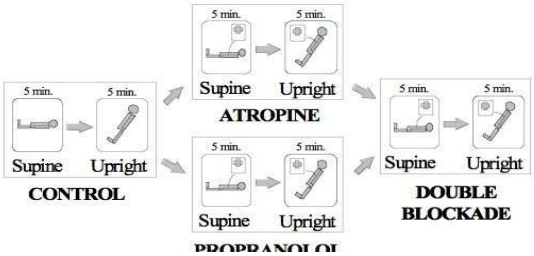

Fig. 1. Diagram of the autonomic blockade protocol.

In addition, we also compute the autocorrelation function of g_js: ACF$(m) = \frac{1}{J-m}\sum_{j=1}^{J-m} g_j g_{j+m}$. If g_js are independent, they are also uncorrelated; hence, ACF(m) shall be small (around 0 and within the 95% confidence interval $\frac{1.96}{(J-1)^{1/2}}$) for all values of m.

III. EXPERIMENTAL PROTOCOL AND DATA

The experimental data were recorded under the "autonomic blockade assessments of the sympatho-vagal balance and RSA" protocol [9] (Fig. 1). In each epoch, 5 min segments of continuous ECG and lung volume were recorded. In the drug administered state, either *atropine* (ATR, 0.04 mg/kg iv over 5 min, parasympathetic blockade) or *propranolol* (PROP, 0.2 mg/kg iv over 5 min, sympathetic blockade) was delivered to the subject. In the double blockade (DB), the inputs from both sympathetic and parasympathetic branches of the autonomic nervous system were suppressed [9]. A total of 17 healthy young and old volunteers participated in the study. Here we focus on two representative subjects.

The order of the AR model was determined based on the *Akaike information criterion* (AIC) (by pre-fitting a subset of the data) as well as the KS distance in the post hoc analysis. In all univariate AR cases, the order $p = 8$ was chosen from $\{2, 4, 6, 8, 10\}$. In bivariate AR analyses, the order $p = q = 8$ was used. The initial AR coefficients are estimated by solving the *Yule-Walker equation* using about 40-50 seconds of the initial recordings [5].

IV. IMPROVED BIVARIATE MODEL AND FREQUENCY ANALYSIS

The comparative results of four probabilistic models for the heart beat data are presented in Table II. It is noted that although we only present the results from 2 subjects (due to space limit), similar observations are also found for other subjects. As seen from Table II, the inverse Gaussian

TABLE II

COMPARISON OF THE KS DISTANCE BETWEEN 4 PROBABILISTIC MODELS FOR 2 SUBJECTS. THE VALUES OF HR AND HRV ARE THE AVERAGES OF μ_{HR} AND σ_{HR} WITHIN 5 MIN. EPOCH.

prob. model	HR±HRV (bpm)	KS dist.	within 95% conf. bound
supine, control, $J = 229$ (subject 15)			
Gauss	56±2.17	0.0900	No
invGauss	56±2.38	0.0590	**Yes**
lognormal	56±4.96	0.1189	No
gamma	56±2.54	0.1820	No
supine, ATR, $J = 440$ (subject 15)			
Gauss	107±1.17	0.1224	No
invGauss	106±0.76	0.1277	No
lognormal	106±0.61	0.0953	No
gamma	105 ±1.21	0.1583	No
supine, DB, $J = 394$ (subject 15)			
Gauss	88±0.68	0.1578	No
invGauss	88±0.55	0.1584	No
lognormal	88±0.31	0.0754	No
gamma	88±0.62	0.1582	No
upright, control, $J = 337$ (subject 15)			
Gauss	80±1.72	0.1117	No
invGauss	78±1.73	0.0765	**Yes**
lognormal	78±3.42	0.1045	No
gamma	78±2.34	0.1487	No
upright, ATR, $J = 440$ (subject 15)			
Gauss	114±1.17	0.1186	No
invGauss	114±0.91	0.1339	No
lognormal	113±0.93	0.1010	No
gamma	114±1.21	0.1289	No
upright, DB, $J = 375$ (subject 15)			
Gauss	85±0.67	0.1298	No
invGauss	85±0.65	0.1540	No
lognormal	85±0.41	0.1323	No
gamma	85±0.53	0.1441	No
supine, control, $J = 383$ (subject 20)			
Gauss	68±3.56	0.1114	No
invGauss	69±3.83	0.0416	**Yes**
lognormal	68±8.69	0.0728	No
gamma	68±3.21	0.1552	No
supine, PROP, $J = 276$ (subject 20)			
Gauss	67±3.15	0.0929	No
invGauss	67±2.75	0.0721	**Yes**
lognormal	67±6.55	0.0514	**Yes**
gamma	67±3.54	0.1667	No
supine, DB, $J = 440$ (subject 20)			
Gauss	107±1.44	0.0864	No
invGauss	107±1.36	0.1026	No
lognormal	107±1.80	0.0846	**Yes**
gamma	107±1.52	0.1543	No
upright, control, $J = 376$ (subject 20)			
Gauss	86±2.48	0.1090	No
invGauss	86±2.76	0.0599	**Yes**
lognormal	86±6.08	0.0923	No
gamma	86±2.35	0.1223	No
upright, PROP, $J = 301$ (subject 20)			
Gauss	72±2.62	0.1184	No
invGauss	71±2.55	0.0994	No
lognormal	71±6.18	0.1140	No
gamma	72 ±3.21	0.1821	No
upright, DB, $J = 440$ (subject 20)			
Gauss	106±1.27	0.1437	No
invGauss	106±0.97	0.1010	No
lognormal	106±1.37	0.0907	No
gamma	106±1.08	0.1625	No

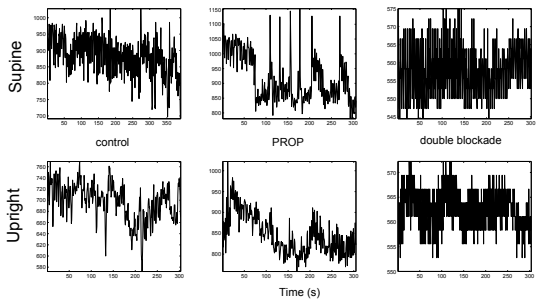

Fig. 2. A snapshot of R-R intervals (in msec) under 6 different conditions (subject 20). *Top 3 panels*: supine posture. *Bottom 3 panels*: upright posture.

TABLE III

IMPROVED GOODNESS-OF-FIT (OF INVERSE GAUSSIAN MODEL) BY USING THE RESPIRATION COVARIATE.

subject	epoch	KS distance	95% conf. bound
15	ATR, supine	0.1277→0.1155	No
15	ATR, upright	0.1339→0.1199	No
15	DB, supine	0.1584→0.0941	No
15	DB, upright	0.1540→0.1070	No
20	PROP, upright	0.0994→0.0531	**Yes**
20	DB, supine	0.1026→0.0796	No
20	DB, upright	0.1010→0.0980	No

model achieves the overall best fit in terms of the smaller KS distance, especially during the control and PROP epochs, in both supine and upright positions. The lognormal model achieves better performance during the DB epochs. The gamma model has the worst performance among the four probabilistic models tested here. All models perform rather poorly during the ATR epochs.

The lack of fit in the KS plots in the absence of parasympathetic modulation suggests that dynamics related to sympathetic influence may require a more complex stochastic model or structure. Furthermore, physiology suggests that HR is influenced by other cardiovascular covariates, such as the change of lung volume [4, 5]. Specifically, for the inverse Gaussian model, we replace the instantaneous mean (1) by

$$\mu_t = a_0 + \sum_{i=1}^{p} a_i RR_{t-i} + \sum_{j=1}^{q} b_j RP_{t-j}, \tag{8}$$

where RP_{t-j} denotes the previous jth respiration measurement before time t. Eq. (8) is motivated by the reports in the literature that the cardiovascular system is modulated and mutually influenced by many other covariates (e.g., systolic blood pressure, blood flow, and respiration). In our experiments, it was found that the inclusion of the respiration covariate helps to improve the KS fit (Table III) in all three pharmacological conditions (ATR, PROP, and DB). Fig. 3 illustrates a comparative example between using (1) and (8) in the "upright+PROP" condition.

Given the parametric AR model (8), we can evaluate the frequency response for the R-R interval itself

$$H_1(\omega) = \left. \frac{1}{1 - \sum_{i=1}^{p} a_i(k) z^{-i}} \right|_{z=e^{j2\pi f_1}}, \tag{9}$$

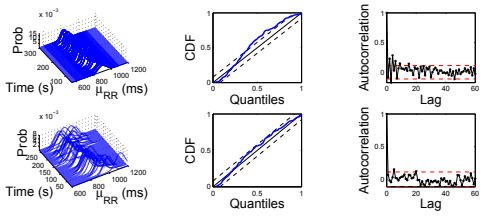

Fig. 3. Comparison of inverse Gaussian models with the mean as the univariate (top) and bivariate (bottom) AR models for subject 20 (upright, PROP). *Left panel*: estimated time-varying probability density function of the R-R interval. *Middle panel*: KS plot. *Right panel*: autocorrelation function. (Dashed lines indicate the 95% confidence bounds)

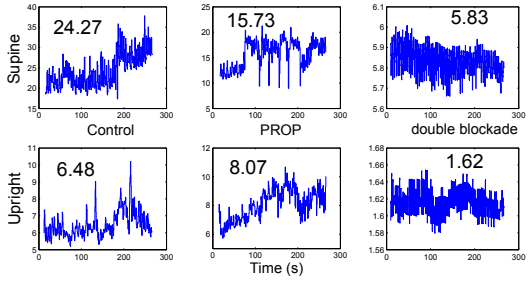

Fig. 4. The time-varying RSA gain at HF (0.15-0.5 Hz) range (subject 20). The number in each subplot indicates the mean value of the RSA gain.

as well as the frequency response for the *respiratory sinus arrhythmia* (RSA: RP→RR) [4]

$$H_{12}(\omega) = \frac{\sum_{j=1}^{q} b_j(k) z^{-j}\Big|_{z=e^{j2\pi f_2}}}{1 - \sum_{i=1}^{p} a_i(k) z^{-i}\Big|_{z=e^{j2\pi f_1}}}, \qquad (10)$$

where f_1 is the beat rate of the R-R and f_2 is the sampling rate (3 Hz) of the RP. With the estimated time-varying AR coefficients $\{a_i(k)\}$ and $\{b_j(k)\}$ at time $t = k\Delta$, we may evaluate the *instantaneous* gain (amplitude) and power spectrum in the frequency domain [6]. Since two major rhythms in cardiovascular variability analysis are the one occurring at the frequency of the Mayer waves (LF, 0.05-0.15 Hz) and the one triggered by respiration (HF, 0.15-0.5 Hz, $\pm$0.04 Hz around the respiratory rate) [1], we can compute the gain or the power over these frequencies over time for both (9) and (10). As an illustration, Fig. 4 plots the instantaneous RSA gain in HF while using a bivariate AR model (8). From (9) we also compute the dynamic LF/HF power ratio with the parametric autospectrum [1] (not shown here) A small (or large) LF/HF ratio indicates relatively predominant vagal (or sympathetic) control.

V. Discussion

In modeling the heart beat interval during the control epochs, the inverse Gaussian model achieves the best performance, which is in agreement with our earlier claims [2, 3]. The Gaussian model achieves a similar performance since when the random variable's mean is much greater than its variance, the inverse Gaussian can be well approximated by a Gaussian shape. In modeling the pharmacological autonomic blockade, the inverse Gaussian model is more suited for PROP than ATR—this suggests that the sympathetic influence requires more effort for modeling in the absence of parasympathetic modulation. The lognormal model is better fitted for the double blockade—this is partly due to the fact that during DB the lognormal model is more robust in characterizing the significant drop in HRV. With inclusion of the RP→RR interaction into the model, we both reflect a more accurate physiological model of cardiovascular control and we are able to explicitly monitor the respiratory effects and evaluate the instantaneous RSA gain. The RSA gain is a useful index of vagal control that often correlates with R-R interval modulation. This is also confirmed by our example (Fig. 4) where RSA values expectedly decrease in the upright position as compared to supine, and they show significant lower values in DB when vagal activity is absent.

The failure of the KS fit within 95% confidence interval in the ATR epochs still leaves us challenges in choosing proper probabilistic models. It is noted that thus far the model of μ_{RR}, transfer function, and frequency analysis are all limited by the assumption of a linear system, currently we are also investigating the nonlinear coupling and modulation effects among the cardiovascular/cardiorespiratory systems.

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