A Point Process Model of Respiratory Dynamics in Early Physiological Development

Premananda Indic[Member, IEEE],
Department of Neurology, University of Massachusetts Medical School, MA 01655, USA
(Premananda.Indic @ umassmed.edu)

David Paydarfar[Senior Member, IEEE], and
Department of Neurology, University of Massachusetts Medical School, MA 01655, USA and also
with Wyss Institute, Harvard University, Boston, MA 02115, USA. (David.
Paydarfar@umassmed.edu)

Riccardo Barbieri[Senior Member, IEEE]
Neuroscience Statistics Research Laboratory, Massachusetts General Hospital, Harvard Medical
School, Boston, MA 02114 USA, and also with the Harvard-MIT Division of Health Science and
Technology, Massachusetts Institute of Technology, Cambridge, MA 02139 USA.
(barbieri@neurostat.mit.edu)

Abstract

Interbreath interval (IBI), the time interval between breaths, and its variations in time around the
mean, the IBI variability, are important measures associated with irregularity of breathing. The IBI
histogram generally follows a power law distribution with its characterizing parameters changing
with maturation. To assess the dynamics of breathing we propose a point process model of IBI
with a lognormal parametric structure to appropriately represent the stochastic nature of the IBI
distribution. We estimate the time varying evolution of the characterizing parameters to represent
the dynamic nature of breathing, and thereby provide a time-varying measure of irregularity in
breathing. The reliability of the model to capture the data is assessed using Kolmogorov-Smirnov
(KS) and independence tests. Our results validate the novel approach in the assessment of the
irregularity of breathing by analyzing respiratory recordings from newborn rats and preterm
infants.

I. INTRODUCTION

Infants with post-conceptional age of less than 36 weeks commonly have irregular breathing
patterns with periodic and sporadic pauses in breathing (apnea)[1]. The time interval
between breaths, called the interbreath interval (IBI), is an important measure for
understanding the irregularity of the breathing patterns. Standard statistical measures such as
mean and variance of the IBI have been employed to quantify the variability of breathing in
preterm infants.

However, preterm infant breathing patterns are highly non-stationary, with rapid changes in
measures of breathing and there is no model available that can provide information about
such dynamic changes. To understand the instability of breathing in infants, we propose a
point process model of IBI that can describe pathological instabilities of breathing and is
able to track the dynamics in real time.

Our model provides the precise probabilistic description of the IBI at any desired time
resolution. To characterize the stochastic nature of IBI, we assume a lognormal distribution
for the distribution of IBI. IBI is derived from the time interval between successive peaks of

the respiratory signal. We estimate the time varying parameters of the point process model by a maximum local likelihood approach, and assess the model goodness-of-fit by a Kolmogorov-Smirnov (KS) test derived from a time rescaling theorem [2]. We illustrate our approach using data from newborn rats as well as preterm infant recordings with apnea.

II. METHODS

A. Neurophysiology of Breathing

Respiratory rhythm in mammals is governed by neural circuits within the brainstem that signal the timing and depth of each breath. Continuous ventilation results from recurrent bursts of inspiratory neuronal activity that controls the diaphragm via discrete phrenic motor neuron activations [3].

A basic assumption of our point process model for breathing is that the peak of inspiration, marked by the peak of inhalation recorded non-invasively, is a discrete event that marks the timing of neuronal inspiratory bursts. A second assumption is that IBI dynamics are governed by continuous processes under the regulation of multiple feedbacks and feed forward loops impinging upon the respiratory oscillator.

B. A Probability Model of Interbreath Interval (IBI)

It has been shown that the IBI of the infant follows a power law distribution, and the characterizing parameters of the distribution are found to be sensitive to age (maturation) [4]. In an observation interval $(0, T)$, we consider the times where local maxima of the respiratory cycle occur (end of inspiration and onset of expiration) as $0, < u_1 < u_2 <, \ldots \ldots \ldots, < u_k <, \ldots \ldots \ldots, < u_k \quad T$. Then, we assume that at any given respiratory event u_k, the waiting time until the next event obeys a history dependent lognormal density $f(t|H_k, \theta)$ as

$$f(t|H_k, 0) = \left[\frac{1}{2\pi\sigma^2(t-u_k)^2} \right]^{\frac{1}{2}} exp \left\{ -\frac{1}{2} \frac{(ln(t-u_k) - \mu(H_k, \theta))^2}{\sigma^2} \right\} \quad (1)$$

where t is any time, $t > u_k$, H_k is the history of IBI up to represented as $H_k = \{ u_k, w_k, w_{k-1}, \ldots, w_{k-p+1} \}$ with $w_k = u_k - u_{k-1}$ is the kth IBI and θ is a vector of model $\sum_{j=1}^{p} \theta_j w_{k-j+1}$. The probability density in equation (1) defines the IBI distribution with μ and σ as the characterizing parameters. At each instant of time t, to estimate θ and σ, we employed local maximum-likelihood approach [5].

C. Local Maximum Likelihood Approach

To calculate the local maximum likelihood estimate of θ and σ, we defined the local joint probability density of u_{t-1} l being the length of the local likelihood observation interval. If we observe n_t peaks within this interval as $u_1 < u_2 <, \ldots \ldots \ldots, < u_{nt} \quad t$ and if θ as well as σ are time varying, then at time t, we estimate the maximum likelihood estimate of $\widehat{\theta_t}$ and $\widehat{\sigma_t}$ to be the estimate of θ and σ in the interval l. Considering the right censoring, local log likelihood is obtained as

$$\log f(u_{t-l:t}|\theta_t) = \sum_{i=2}^{n_t} w(t-u_i) \log f(u_i - u_{i-1}|H_{u_{i-1}}, \theta_t) + w(t-u_{n_t}) log \int_{t-u_{n_t}}^{\infty} f(\vartheta|H_{u_t}, \theta t) d\vartheta \quad (2)$$

where $w(t)$ is a weighting function to account for faster updates to local likelihood estimation and we selected as $w(t) = e^{-a(t-u)}$ with as the weighting time constant that assigns the influence of a previous observation on the local likelihood at time t. Since θ can be

estimated in continuous time, we can obtain the instantaneous estimate of μ, the mean, using the autoregressive representation. Similarly the local likelihood estimate provides the instantaneous estimate of variance σ^2.

D. Model Goodness-of-Fit

The IBI probability model along with the local maximum likelihood method provides an approach for estimating the instantaneous mean and instantaneous variance of the IBI. These measures provide information about the changes in the characteristics of the distribution, possibly due to irregularity of breathing. However, it is also essential to evaluate how well the model represents the IBI. To obtain a goodness-of-fit measure we compute the time-rescaled IBI defined as

$$\tau_k = \sum_{u_{k-1}}^{u_k} \lambda\left(t|H_t, \widehat{\theta_t}\right) dt \tag{3}$$

where the u_k represent the breathing events observed in (0,T) and $\lambda\left(t|H_t, \widehat{\theta_t}\right)$ is the conditional intensity function defined as

$$\lambda\left(t|H_t, \widehat{\theta_t}\right) = f\left(t|H_t, \widehat{\theta_t}, \widehat{\sigma_t}\right)\left[1 - \int_{u_{n_t}}^{t} f\left(\vartheta|H_\vartheta, \widehat{\theta_\vartheta}, \widehat{\sigma_\vartheta}\right) d\vartheta\right]^{-1} \tag{4}$$

The conditional intensity is the history dependent rate function for a point process that generalizes the rate function for a Poisson process. The τ_k values are independent, exponential random variables with a unit rate. With a transformation $Z_k = 1 - \exp\left(-\tau_k\right)$, the Z_k values become independent, uniform random variables on the interval (0,1]. Thus we can employ a KS test to assess the agreement between transformed Z_k values and a uniform probability density. If there is close agreement between the point process model and the IBI data series, then the transformed Z_k values plotted against the uniform density will have close agreement if the plot is closer to the 45 degrees diagonal (KS plot) The KS distance measures the largest distance between the cumulative distribution function of the IBI transformed in the interval (0,1] and the cumulative distribution function of a uniform distribution on (0,1]. The smaller the KS distance, the better the model in terms of goodness-of-fit.

E. Experimental Data

Animal Data—Neonatal rats exhibit respiratory patterns and chemo-responses analogous to preterm infants, including sporadic apneas with bradycardia and hypoxemia, as well as periodically occurring apnea episodes. One to two day old rats were placed in a sealed chamber and breathed through a face mask and pneumotachogram, allowing recordings of respiratory airflow through the mask. Measurement of pressure within the plethysmographically sealed chamber was an index of respiratory effort. These previously published studies have documented the occurrence of unstable breathing patterns of central origin [6].

Human Data—The preterm infant data considered in our analysis is from a study to understand the instability of breathing [7]. The study was conducted at the Newborn Intensive Care Unit, University of Massachusetts Memorial Healthcare and approved by the Committee for the Protection of Human Subjects in Research at the University of Massachusetts Medical School. The infants have a gestational age <36 wks and post-conceptional age (PCA) >30 wks at the time of study. These infants were spontaneously breathing room air or receiving supplemental oxygen through nasal cannulae at a fixed flow

rate. Respiratory signal was recorded using respiratory inductance plethysmography of abdominal movements during spontaneous breathing (Somnostar PT; Viasys Healthcare, Yorbalinda, CA) at a sampling rate of 100 Hz.

III. RESULTS

A. Analysis of Simulated IBI with Time Varying Parameters

We first tested the model using simulated data sets. We simulated data series from a lognormal distribution with specific mean and variance (σ^2) values. The instantaneous variation of the parameters is calculated along with the goodness-of-fit of the model using the point process model. It has been found that for a fixed mean and variance values, the model accurately estimates the mean as well as variance and also provides better fit in terms of KS plots.

To understand the ability of the model to capture the time varying parameters, we simulated the data in which the variance was kept at a fixed value for a specific duration of time and then randomly varied for a fixed time interval prior to setting to the initial variance value. The mean value was kept at a constant level. We found that the model accurately captured the time varying nature of the variance and also provided excellent goodness-of-fit in terms of KS plot. The simulated data with time varying variance during the interval 500 to 800 along with the estimated variance is shown in Fig 1.

The KS plot showing the goodness-of-fit measure is represented in Fig 2.

B. Analysis of Respiratory Data from Newborn Rats

We report only the estimated variance as an indicator of stability of breathing. In newborn rats, an IBI greater than 1 second indicates apnea. As the apnea occurs, the variance increases. Fig 3 provides an example from one continuous recording (R1), whereas Fig 4 represents the KS plots along with the autocorrelation from two data sets considered.

C. Analysis of Respiratory Data from Preterm Infants

Our estimation of variance captures the irregularity of breathing in preterm infants. The normal IBI is around 1 second, however due to irregularity in breathing, the IBI can vary from 1 second to 20 seconds. The change in IBI is reflected as the variance. An example of IBI from an infant along with the estimated variance is given in Fig 5. Fig 6 provides the KS plots from four infants considered for the analysis

IV. CONCLUSION

We have proposed a novel point process model for assessing the dynamics of breathing. The model was based on the observation that the IBIs follow a lognormal distribution. The instantaneous parameters of the distribution provide a novel measure for tracking the instabilities of breathing in real time. The new algorithm was applied to newborn rat data as well as preterm infant data and was found to capture the underlying nonstationary IBI variations. The dynamic statistical measures computed by the point process model, validated here at early stages of physiological development, could potentially be further refined to be employed in the neonatal intensive care unit for real time assessment of breathing, as well as obtaining information about the stage of maturation in preterm infants. Although we present an application to subjects at an early development stage, the model is expected to be effective also in the assessment of respiratory dynamics in the presence of a fully developed respiratory system.

Acknowledgments

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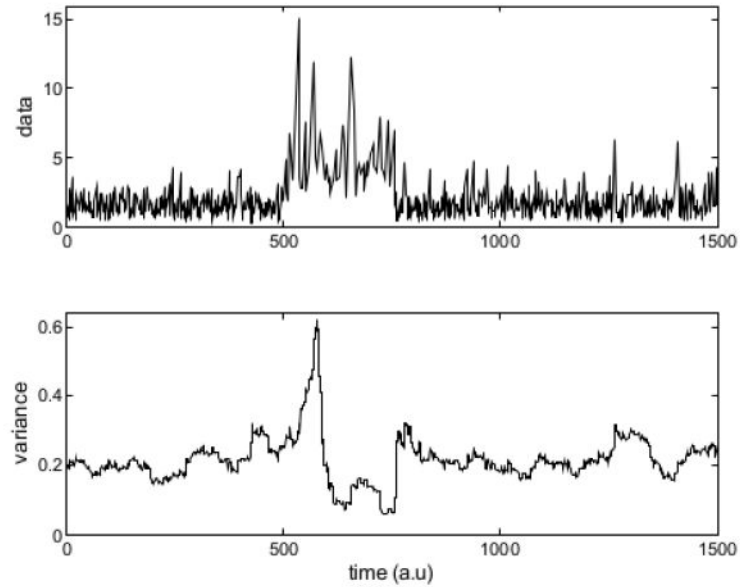
Fig 1.
(a) Simulated data with mean $\mu = 1$ and variance $\sigma = 0.2$ obtained from a lognormal distribution. The variance is varied randomly during the interval 500 to 800. (b) The instantaneous variance estimated by the point process model of order $p = 4$, with local likelihood window $I = 100$ and weighting time constant $\alpha = 0.01$ along with a time resolution $S = 0.01$.
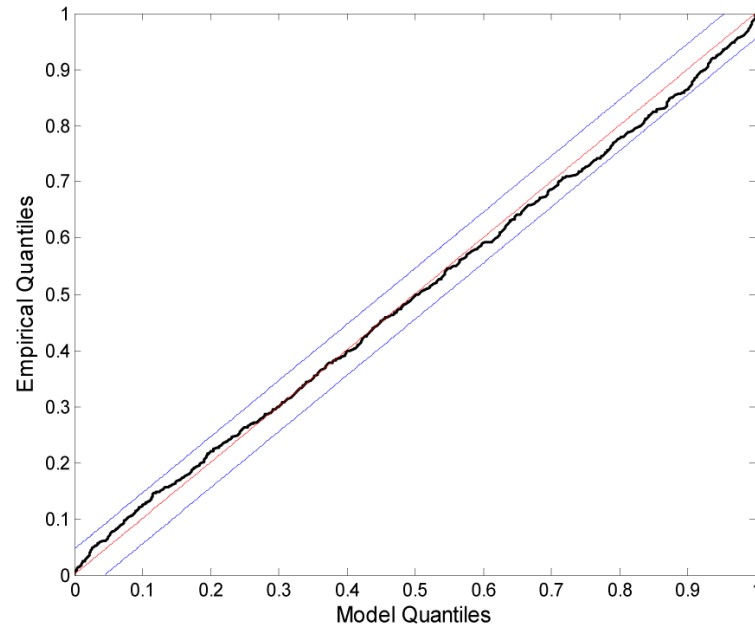
Fig 2.
KS plot of time-rescaled quantiles derived for the simulated data (black line). The blue lines are the 95% confidence intervals. The model is considered to be perfect, if the black line coincides with the theoretical values (red line).
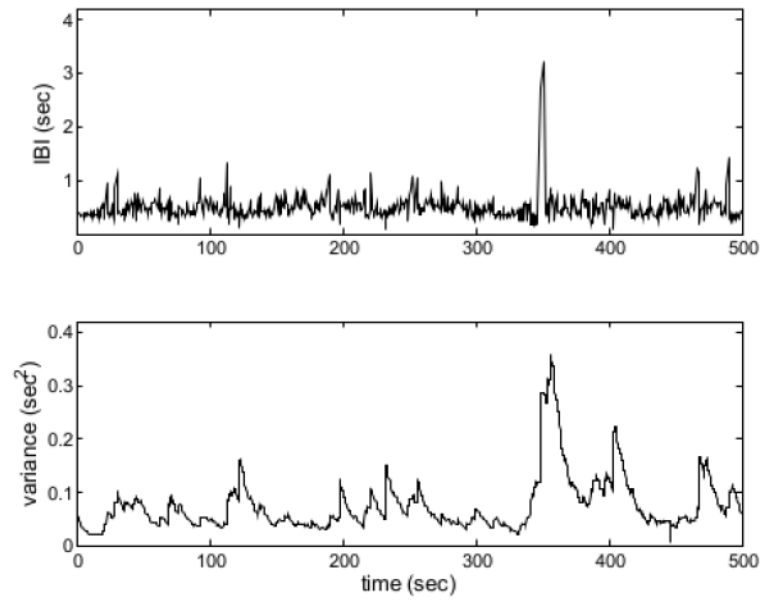
Fig 3.
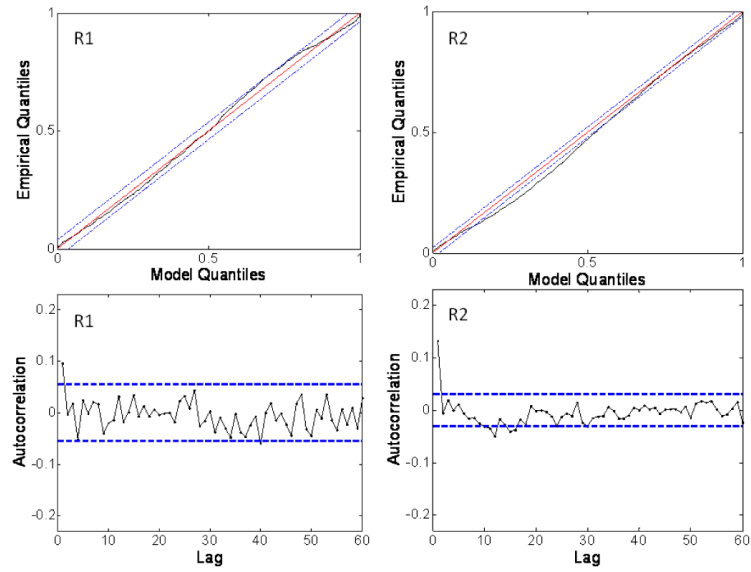IBI in seconds along with estimated variance from a rat data (R1)

Fig 4.
KS plot of time-rescaled quantiles derived for two newborn rat data labeled R1-R2 along with the autocorrelation function. The blue line indicates 95% confidence intervals.
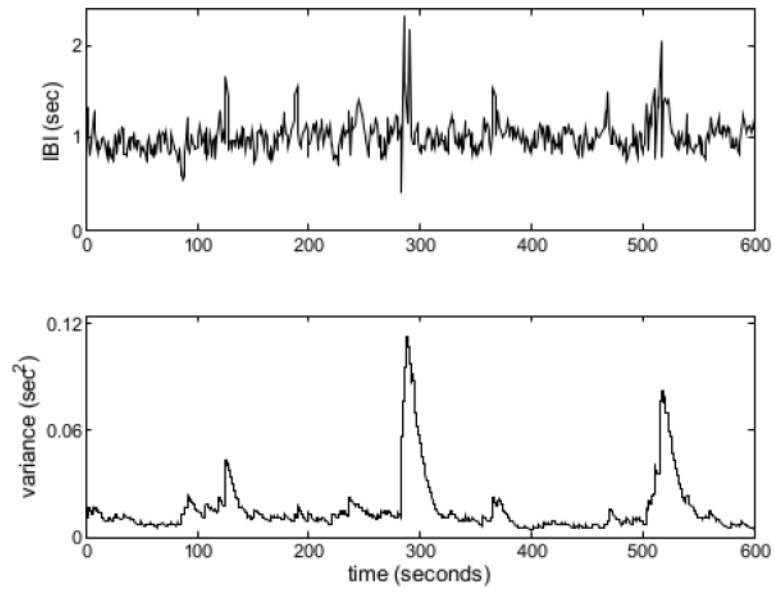
Fig 5.
IBI in seconds along with estimated variance from a preterm infant data (I1). The instantaneous variance increases during the apnea, suggesting larger varibility.
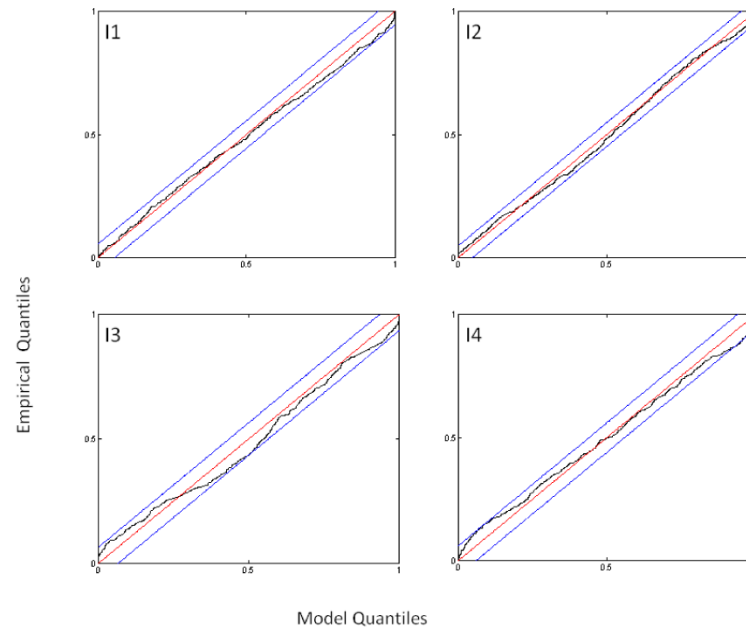
Fig 6.
KS plot of time-rescaled quantiles derived for four preterm infants labeled I1-I4. The blue lines are the 95% confidence intervals. All infant data fits the model well in terms of KS statistics.