33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

A Point Process Model of Respiratory Dynamics in Early Physiological Development

Premananda Indic, *Member, IEEE*, David Paydarfar, and Riccardo Barbieri, *Senior Member, IEEE*

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

Infantswith 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.

Manuscript received March 15, 2011. This work was supported in part by the the Hansjörg Wyss Institute for Biologically Inspired Engineering at Harvard University and by National Institutes of Health (NIH) Grants R01-HL084502 , R01-HL49848 , R01-HL071884.

Premananda Indic is with the Department of Neurology, University of Massachusetts Medical School, MA 01655, USA (e-mail: Premananda.Indic @ umassmed.edu). David Paydarfar is with Department of Neurology, University of Massachusetts Medical School, MA 01655, USA and also with Wyss Institute, Harvard University, Boston, MA 02115, USA. (e-mail: David. Paydarfar@umassmed.edu). Riccardo Barbieri is with the 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. (e-mail: barbieri@neurostat.mit.edu).

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 $0 < u_1 < u_2 < , \dots \dots \dots , < u_k <, \dots \dots \dots , < u_K \leq T$. Then, we assume that at any given respiratory event u_k, the waiting time until the next event obeys a history dependent lognormal probability density $f(t|H_k, \theta)$ as

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

where t is any time, $t > u_k$, H_k is the history of IBI up to u_k represented as $H_k = \{u_k, w_k, w_{k-1}, \dots . , w_{k-p+1}\}$ with $w_k = u_k - u_{k-1}$is the k^{th} IBI and θ is a vector of model parameters. The instantaneous mean is modeled as a p-order autoregressive process as $\mu(H_k, \theta) = \theta_o + \sum_{j=1}^{p} \theta_j w_{k-j+1}$. 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 $u_{t-l}: u_t$ l being the length of the local likelihood observation interval. If we observe n_t peaks within this interval as $u_1 < u_2 <, \ldots \ldots \ldots, < u_{n_t} \leq t$ and if θ as well as σ are time varying, then at time t, we estimate the maximum likelihood estimate of $\hat{\theta}_t$ and $\hat{\sigma}_t$ to be the estimate of θ and σ in the interval l. Considering the right censoring, the local log likelihood is obtained as

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

where $w(t)$ is a weighting function to account for faster updates to local likelihood estimation and we selected as $w(t) = e^{-\alpha(t-u)}$ with α 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

$$\tau_k = \int_{u_{k-1}}^{u_k} \lambda\left(t\middle|H_t, \hat{\theta}_t\right) dt \quad (3)$$

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

$$\lambda\left(t\middle|H_t, \hat{\theta}_t\right) = f\left(t\middle|H_t, \hat{\theta}_t, \hat{\sigma}_t\right)\left[1 - \int_{u_{n_t}}^{t} f\left(\vartheta\middle|H_\vartheta, \hat{\theta}_\vartheta, \hat{\sigma}_\vartheta\right) d\vartheta\right]^{-1} \quad (4)$$

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 $z_k = 1 - \exp(-\tau_k)$, 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 the 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.

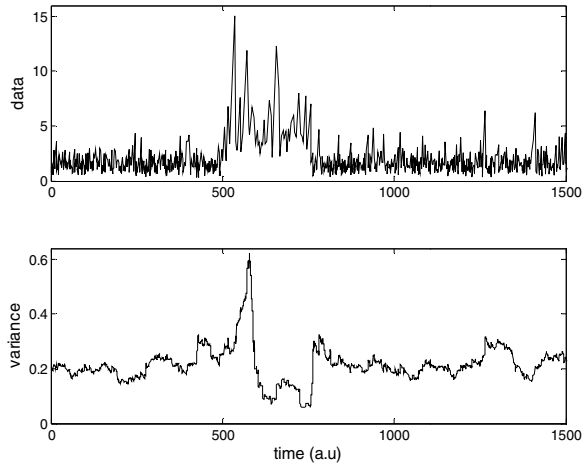

Fig 1. (a) Simulated data with mean $\mu = 1$ and variance $\sigma^2 = 0.2$ obtained from a lognormal distribution. The variance is varied randomly during the interval 500 to 800. (b) The instantaneous variance estimated by the point process model of order $p = 4$, with local likelihood window $l = 100$ and weighting time constant $\alpha = 0.01$ along with a time resolution $S = 0.01$.

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

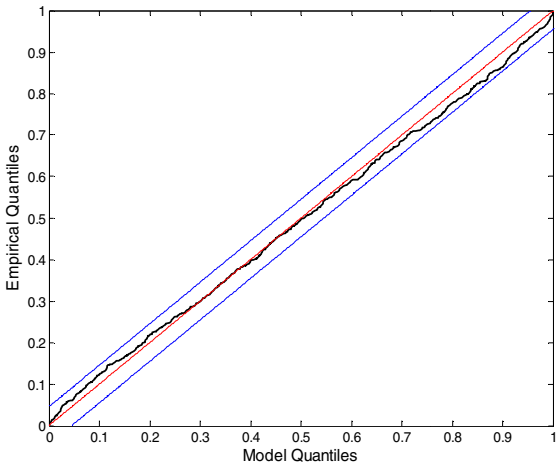

Fig 2. KS plot of time-rescaled quantiles derived for the simulated data (black line). The blue lines are the 95% confidence intervals. The model is considered to be perfect, if the black line coincides with the theoretical values (red line).

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.

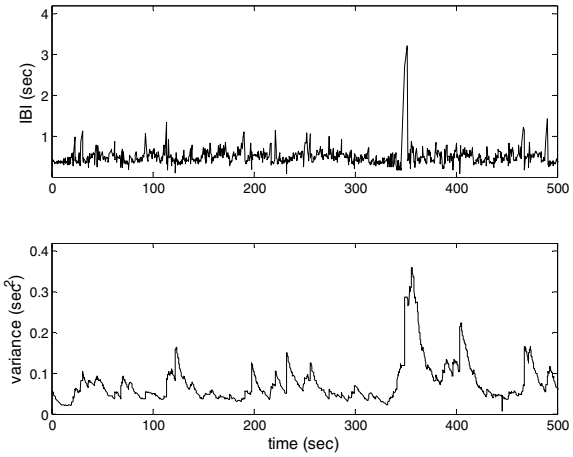

Fig 3. IBI in seconds along with estimated variance from a rat data (R1)

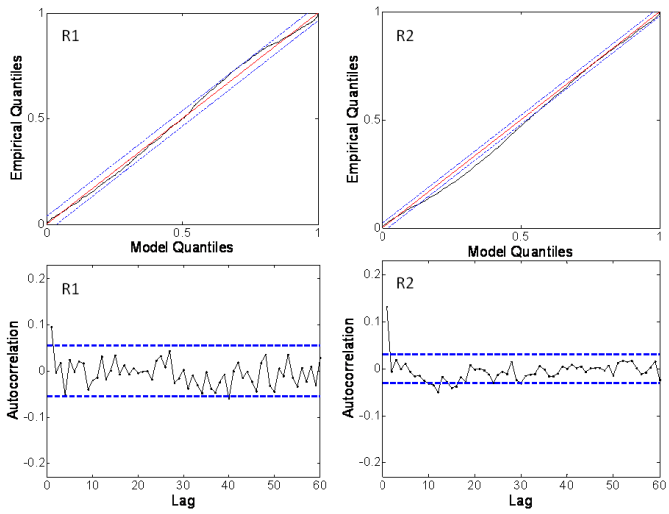

Fig 4. KS plot of time-rescaled quantiles derived for two newborn rat data labeled R1-R2 along with the autocorrelation function. The blue line indicates 95% confidence intervals.

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 4. Fig 5 provides the KS plots from four infants considered for the analysis

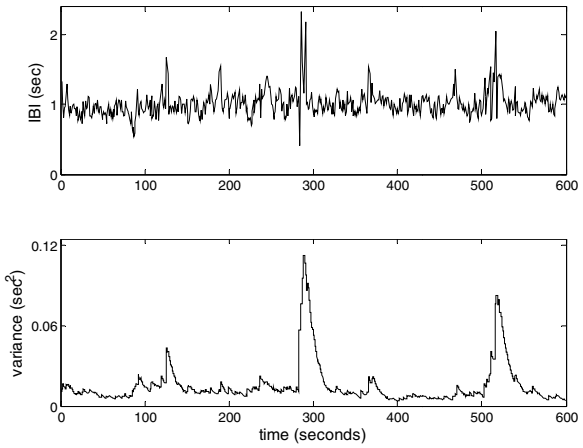

Fig 3. IBI in seconds along with estimated variance from a preterm infant data (I1)

The instantaneous variance increases during the apnea, suggesting larger varibility.

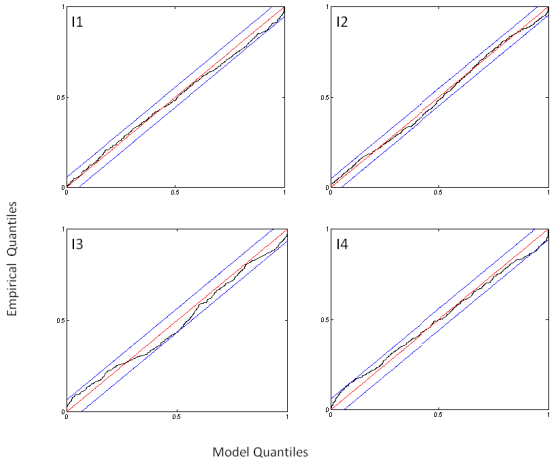

Fig 4. KS plot of time-rescaled quantiles derived for four preterm infants labeled I1-I4. The blue lines are the 95% confidence intervals. All infant data fits the model well in terms of KS statistics.

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.

ACKNOWLEDGMENT

The authors would like thank Elisabeth Salisbury, Frank Bednarek and Emery Brown for the stimulating discussions during the course of this work. Kevin Cummings kindly provided data of the newborn rat [6].

REFERENCES

[1] J. M. Abu-Shaweesh, and R. J. Martin, "Neonatal apnea: What's new?," *Pediatric Pulmonology,* vol. 43, no. 10, pp. 937-944, Oct, 2008.

[2] E. N. Brown, R. Barbieri, V. Ventura *et al.*, "The time-rescaling theorem and its application to neural spike train data analysis," *Neural Computation,* vol. 14, no. 2, pp. 325-346, Feb, 2002.

[3] J. L. Feldman, and C. A. Del Negro, "Looking for inspiration: new perspectives on respiratory rhythm," *Nature Reviews Neuroscience,* vol. 7, no. 3, pp. 232-242, Mar, 2006.

[4] U. Frey, M. Silverman, A. L. Barabasi *et al.*, "Irregularities and power law distributions in the breathing pattern in preterm and term infants," *Journal of Applied Physiology,* vol. 85, no. 3, pp. 789-797, Sep, 1998.

[5] R. Barbieri, E. C. Matten, A. A. Alabi *et al.*, "A point-process model of human heartbeat intervals: new definitions of heart rate and heart rate variability," *American Journal of Physiology-Heart and Circulatory Physiology,* vol. 288, no. 1, pp. H424-H435, Jan, 2005.

[6] K. J. Cummings, and P. B. Frappell, "Breath-to-breath hypercapnic response in neonatal rats: temperature dependency of the chemoreflexes and potential implications for breathing stability," *American Journal of Physiology-Regulatory Integrative and Comparative Physiology,* vol. 297, no. 1, pp. R124-R134, Jul, 2009.

[7] E. Bloch-Salisbury, P. Indic, F. Bednarek *et al.*, "Stabilizing immature breathing patterns of preterm infants using stochastic mechanosensory stimulation," *Journal of Applied Physiology,* vol. 107, no. 4, pp. 1017-1027, Oct, 2009.