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ASSESSMENT OF RISK IN PRETERM INFANTS USING POINT PROCESS AND MACHINE LEARNING APPROACHES

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USING POINT PROCESS AND MACHINE LEARNING APPROACHES

by

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Dedication

I would like to primarily dedicate this dissertation to my grandparents. Having, unfortunately, lost two children due to premature birth, to my surprise, I arrived at a juncture where I have had an opportunity to perform my research on premature children. I also dedicate this to my friends and family for the love, support, and kindness they have shared.

I further dedicate this work to all mothers who deliver prematurely and to the mothers who had premature deliveries. Having had the opportunity to work with premature children, I can understand the anxiety of mothers waiting for their newborns health to improve and eagerly wait for the day to take them home. The analysis conducted and the results documented in this report could help predict a fatality and give sufficient time to perform treatment to save your child.

Finally, I would like to dedicate this thesis to all the nurses who strive day and night to save infants' lives. The algorithm proposed, when combined with an effective management strategy, could help identify infants needing care and supervision.

Acknowledgements

Multiple contributions towards my circuitous endeavors helped guide me on the path towards this dissertation. Its completion is part and parcel with the guidance and mentorship I received from many people. I am fortunate to have had an opportunity to work closely with Dr. Premananda Indic. His patience, suggestions, support, encouragement and expert tutelage had constantly motivated me to strive further into developing my thesis. I would like to thank Dr. Mukul Shirvaikar and Dr. Jimi Francis for being a part of my committee, reviewing my work, and providing thoughtful feedback aimed at moving me forward. I would also further like to thank Dr. Namasivayan Ambavalanam, Dr. Colm Travers, Dr. David Paydarfar and Dr. Riccardo Barbieri for their valuable inputs.

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List of Abbreviations

NICU	Neonatal Intensive Care Units
LTE	Life Threatening Event
GA	Gestational Age
LPT	Late Preterm
EPT	Extremely Preterm
AOP	Apnea Of Prematurity
OSA	Obstructive Sleep Apnea
HR	Heart Rate
ABD	Apnea Bradycardia and Desaturation
EOS	Early Onset Sepsis
LOS	Late Onset Sepsis
PDA	Patent Ductus Arteriosus
SIDS	Sudden Infant Death Syndrome
ROP	Retinopathy Of Prematurity
ASD	Autism Spectrum Disorder
HRC	Heart Rate Characteristics
ANN	Artificial Neural Networks
SVM	Support Vector Machine
NBC	Naive Bayesian Classifier
BDT	Boosted Decision Trees

MLR	Multivariable Logistic Regression
SMOTE	Synthesized Minority Oversampling Technique
AUC	Area Under Curve
ROC	Region Of Characteristics
ECG	Electrocardiogram
IBI	InterBreath Interval
PPG	Photo Plethysmography
QSVM	Quadratic Support Vector Machine

Abstract

ASSESSMENT OF RISK IN PRETERM INFANTS
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Preemies, infants who are born too soon, have a higher incidence of Life-Threatening Events (LTE's) such as apnea (cessation of breathing), bradycardia (slowing of heart rate) and hypoxemia (oxygen desaturation) also termed as ABD (Apnea, Bradycardia, and Desaturation) events. Clinicians at Neonatal Intensive Care Units (NICU) are facing the demanding task of assessing the risk of infants based on their physiological signals.

The aim of this thesis is to develop a risk stratification algorithm using a machine-learning framework with the features related to pathological fluctuations derived from point process model that will be embedded into the current physiological recording system to assess the risk of life-threatening events well in advance of occurrence in individual infants in the NICU.

We initially propose a point process algorithm of heart rate dynamics for risk stratification of preterm infants. Based on this analysis, point process indices were tested to determine whether they were useful as precursors for life-threatening events. Finally, a machine-learning framework using point process indices as precursors were designed and tested to classify the risk of preterm infants. This work helps to predict the number of

bradycardia events, N, in the subsequent hours measuring point process indices for the current hour. The model proposed uses Quadratic Support Vector Machine (QSVM), a machine learning classifier, which can solve class optimization problems and execute data at an exponential speed with higher accuracy for risk assessment that might facilitate effective management and treatment for preterm infants in NICU. The findings are relevant to risk assessment by analyzing the fluctuations in physiological signals that can act as precursors for the future life-threatening events.

CHAPTER 1
INTRODUCTION

An infant born prior to 37 weeks of pregnancy is classified as a prematurely born infant and is referred to as a preterm infant. As of today, premature births are the leading cause of infant mortality around the world. Every year 15 million premature babies are born around the globe. One million preterm infants die immediately after birth [1]. Brazil, China, India, Nigeria and the United States of America (US) are five countries where premature births are prominent [1]. In the US, 1 in every 10 babies born accounts for the 9.8 percent rate of preterm births annually [2]. To date, early birth remains a major cause of infant mortality, making it an unsolved clinical challenge.

Few of the causes for premature birth identified include pregnancy complications, low or high maternal age (woman over the age of 35 or under 19), multiple miscarriages, structural abnormality of the uterus, or carrying multiple fetuses [3]. Preventive measures such as progesterone supplements and cervical cerclage (where the cervix stitched with strong sutures to provide extra support to the uterus and are removed at the time of delivery) are employed to reduce high-risk pregnancies [3].

Despite having measures in place, premature births still occur. Premature infants are prone to health issues compared to infants born full-term. Due to underdeveloped organs, these infants risk facing short-term and often long-term health problems, which may affect the brain, lungs, hearing or vision. In order to survive, care and support are required and most often administered in neonatal intensive care units (NICUs). A 24/7

support is mandated at all NICU facilities, the resulting cost amounts to a $26 billion annually to care for preterm infants [4].

As per an article by Medscape “Revelation of busy NICU nurses” a survey was done focusing on the nurses who work at NICU’s [5]. From the survey conducted, more than 90% of nurses reported caring for two or more infants, while 5.6% reported caring for more than four infants. Their job functions entail attending daily rounds, parent education, feeding, vital data communication and signs assessment, oxygen administration, developmental care, infection control precautions, timely alarm response and more. Hence, keeping an eye on each patient within the facility could be incredibly cumbersome.

In NICUs clinicians are faced with the demanding task of assessing the risk of infants based on their physiological signals. Research conducted by engineers enabled them to derive different techniques for identifying outcomes before they can occur so preventative measures can be introduced in order save an infant’s life. Currently, a technological system that can assist clinicians to assess risk in preterm infants is not available. In order to effectively manage and treat preterm infants in NICU, a risk stratification algorithm is needed. Thus, we aim to develop a risk stratification algorithm using a machine-learning framework along with features derived from point process approach that be embedded into the current physiological recording system to assess risk as well as predict life-threatening events in infants.

1.1 Defining prematurity

Prematurely born infants are also termed as “Neonates” or “Preemies.” They are prone to severe medical problems, as their organs have not had sufficient time to develop. An inverse relationship exists between gestational age (GA) (which is a measure used to describe the duration of pregnancy) and infant mortality rate.

Depending on prematurity, these infants would be classified as late preterm (LPT) when born between 34 and 36 weeks of GA, moderately preterm when born between 32 and 34 weeks, very preterm when birth takes place before 32 weeks and extremely preterm (ET) if born by 25 weeks of GA [3] as shown in Figure 1.1. One in ten births in the United States are preterm [6]. According to American College of Obstetricians and Gynecologist, preterm births, late preterm and early term, accounts for 36% [7] of the live births. A notable mention of individuals who came into this world earlier than anticipated and lived to tell the tale would be: Mark Twain, Napoleon Bonaparte, Stevie Wonder, Sir Winston Churchill and Albert Einstein [8].

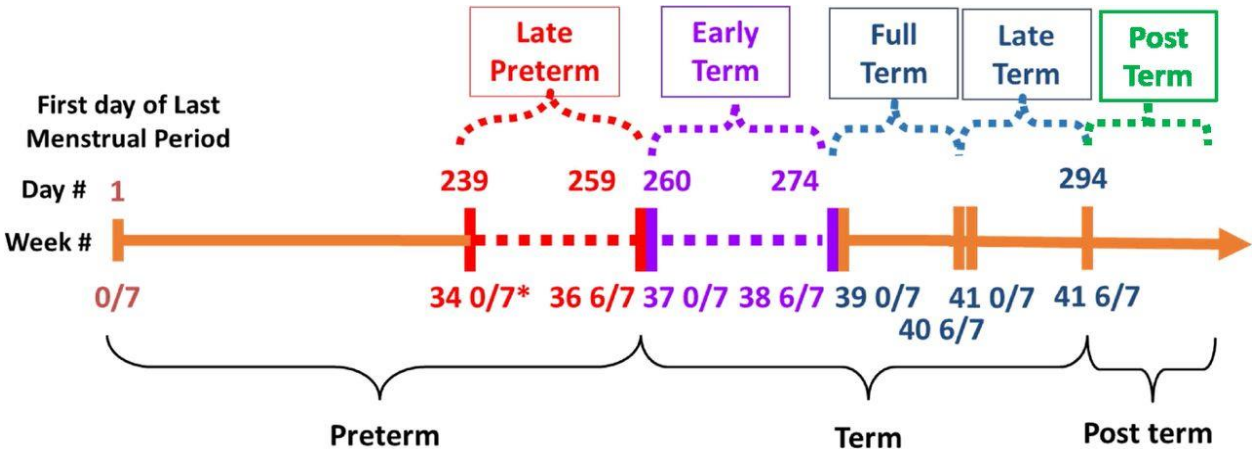

Figure 1.1 Definitions of gestational age periods for premature infants [7]

1.2 Signs of prematurity

The premature infant is typically small in size with a disproportionately large head having less rounded features when compared to a full-term infant. They often experience distressed respiration, lower body temperatures and lack reflexes resulting in difficulties for feeding [3]. Table 1.1 shows the median birth weight and length of an infant as per GA. Any GA less than 37 weeks is designated as a preterm infant. The earliest preemie to ever survive was born at 21 weeks, 6 days' gestation and smallest preemie to ever survive was born weighing 9.1 oz [9].

Table 1.1 Weight and length by gestational age

GA (weeks)	**Weight** (lbs)	**Length** (inches)
24	1	12.2
28	2	14.4
32	3	16.5
35	5	18.1
40	7	20

Figure 1.2, below, represents a comparison of size of a preterm infant with the hand size of a typical adult measuring around 17 inches. It is evident that premature infants are tiny and vulnerable. Furthermore, these infants require specialized monitoring and care.

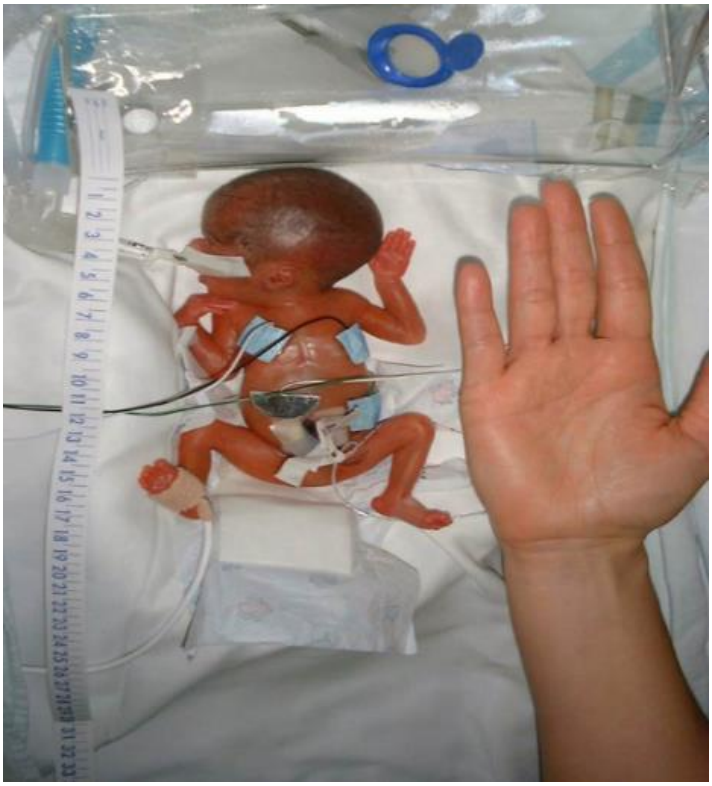

Figure 1.2 Premature infant under specialized care at University of Alabama NICU [44]

1.3 Premature care and support

Most of the premature infants are moved to the neonatal intensive care unit (NICU) right after their birth, as shown in Figure 1.3, where specialized supportive care is provided by the neonatal nurse around the clock to examine and treat the conditions due to prematurity with medical interventions as needed.

There are four levels of NICU's: Level I provides primary care to newborns; Level II has Special Care Nursery providing care to neonates > 32 weeks' gestational age through continuous airway pressure (CPAP), mechanical ventilation for up to 24 hours; Level III Neonatal Intensive Care has comprehensive care with high-frequency ventilation and onsite accessibility to pediatric subspecialists; and Level IV Regionalized Neonatal

Intensive Care Unit provides level III care, Extracorporeal Membrane Oxygenation ECMO therapy and has the capability to treat complex cardiac abnormalities requiring cardiopulmonary bypass [10].

Figure 1.3 Neonatal Intensive Care Unit setup [11]

Extremely preterm infants are commonly treated for 71 days in the NICU prior to discharge. Very preterm infants are taken care for 39 days in NICU. Moderately preterm infants and late preterm infants spend on an average of 12 days and 4 days, respectively, in the NICU prior to discharge.

1.4 Organization of Thesis

Chapter 2 addresses the premature infant's risks, diagnosis, and treatment. Chapter 3 provides information of previous research papers relating to the current research strategy. Chapter 4 explains point process model and machine learning techniques used in the study methodology. The results are presented in Chapter 5 and Chapter 6 has conclusions, limitations and discusses on future directions of the study conducted.

CHAPTER 2
NEONATAL RISK, DIAGNOSIS AND TREATMENT

Premature infants need care as well as support for surviving and are often admitted to NICU immediately after birth for observation and treatment. These premature infants commonly have several short term and long-term adverse complications that can lead to negative health outcomes. Complications due to premature birth are the underlying reasons for the infant death. With increasing prematurity, the risk of complications increases. Even after surviving birth, these infants are at the greatest risk of developmental challenges in the future. In this chapter, we briefly discuss examples of short term and long term adverse outcomes.

2.1 Short-term adverse outcomes

During the neonatal period, a premature infant may have adverse outcomes that include any or all of the following: apnea (pauses in breathing), bradycardia (slowness of heart rate), hypoxia (oxygen de-saturation), sepsis (an infection in blood), and Patent ductus arteriosus (an opening between two main arteries of heart. Not all adverse outcomes are listed here.

2.1.1. Apnea

A lung disorder (bronchopulmonary dysplasia) which develops due to the infant's immature respiratory system which can inhibit breathing. This leads to apnea where infants experience a typically short-term cessation of breathing [12]. Apnea or Apnea of prematurity (AOP) is defined as an episode of a sudden pause in breathing that can last

for 10 seconds or longer followed by oxygen desaturation and/or bradycardia. This occurs commonly during sleep and generally is called sleep apnea [13]. Hypopneas are partial reductions in breathing. The normal range of respiratory rate for newborns is 30–60 breaths per minute (bpm). Three types of apnea observed in preterm infants are central, obstructive and mixed.

Central apneas occur due to lack of diaphragmatic activity resulting from a problem in brain or heart. Obstructive Sleep Apnea (OSA) is an obstruction of airflow occurring from collapse of soft tissue in the back of throat. Mixed apnea is a combination of central apnea followed by an obstructive apnea episode [14].

2.1.2 Bradycardia

Bradycardia is the medical condition in preterm infant whose heart rate is slows significantly. The average heart rate (HR) of premature infants is 120-180 beats per minute (bpm). A heart rate less than 100 bpm would result in a 10-50% reduction of cerebral blood velocities from baseline [15], which may have adverse effects in preterm infants.

2.1.3 Hypoxemia (Oxygen de-saturation)

Oxygen saturation level is a measurement of blood oxygen; a below-normal blood oxygen level is called hypoxemia, which leads to complications in body tissue and organs. Hypoxemia is a below-normal level of oxygen in the blood, specifically in the arteries [16]. It is estimated by measuring the oxygen saturation level in blood using a pulse oximeter (a small device that clips to a finger or in the case of infants wraps around their foot).

Normal levels of pulse oximeter readings usually range from 95 to 100 percent and values under 90 percent are considered to be low.

Thus, Apnea Bradycardia and Desaturation (ABD)–events are defined as apnea duration greater than 10 seconds associated with bradycardia where HR is less than 100 bpm and desaturation (SpO2) is less than 85%. Figure 2.1 shows the infant physiological signals which are monitored at level 4 NICU showing apnea, bradycardia and hypoxemia events.

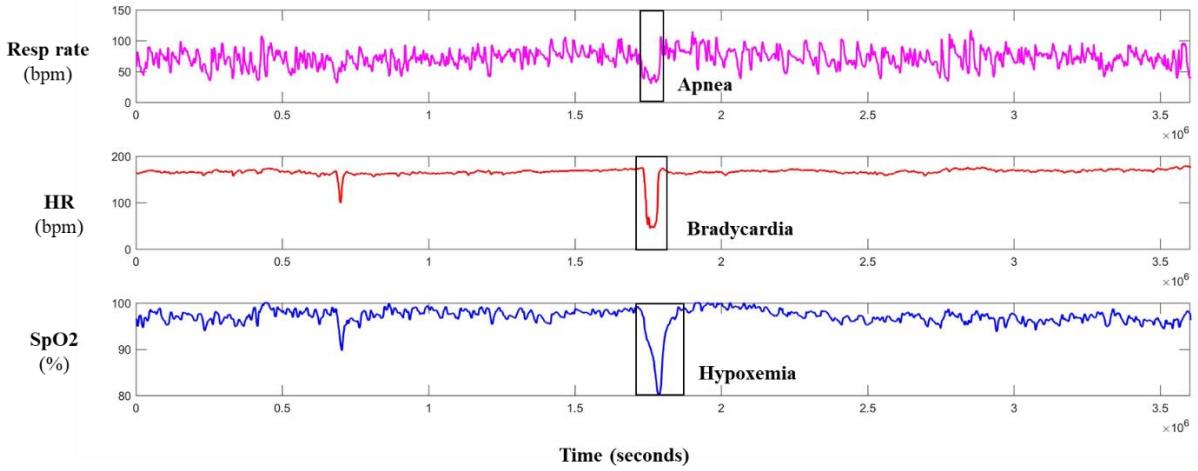

Figure 2.1 Preterm infant's Respiratory rate (Resp rate), Heart rate HR and SpO2 levels

2.1.4 Sepsis

Another complication for preterm infants who have premature immune systems is the development of sepsis. Sepsis is the overwhelming and life-threatening response of the infant’s body to infection that can lead to tissue damage, organ failure, and death [17]. Depending on the mode of infection, it is divided into: early onset sepsis (EOS) which is caused by maternal transmission of invasive organisms during the first 7 days of life and late-onset sepsis (LOS) when an infection is in blood.

2.1.5 Patent Ductus Arteriosus (PDA)

A common heart problem in premature infants in which abnormal blood flow occurs between the two main arteries of the heart and when untreated can lead to heart failure [18]. PDA is a congenital heart defect in which a vessel connecting the pulmonary artery to the aorta fails to close allowing the blood to bypass the lungs. While a small PDA may cause no symptoms, a large PDA may cause failure to thrive and/or breathlessness.

2.2 Long-term adverse outcomes

In premature infants, the frequency of the cardio-respiratory events has been associated with long-term neurodevelopmental impairment [19], some of which are cerebral palsy (injury to a newborn's developing brain), impaired vision, hearing limitations, having developmental delays, learning disabilities, and chronic health issues.

2.2.1 Cerebral Palsy (CP)

Cerebral Palsy (CP) is a non-progressive brain lesion that occur during early development resulting in disorders that impair the control of movement due to damage to the developing brain associated with immature lungs that provide insufficient oxygen to the brain.

2.2.2 Vision impairment

Vision impairment in premature infants include Retinopathy of Prematurity **(**ROP) which is an abnormal growth of blood vessels in the eye which can damage the eye’s retina resulting in loss of vision due to scarring and retinal detachment. Stevie Wonder, a world-renowned singer, is a victim of ROP that caused his blindness in infancy [3].

2.2.3 Neurodevelopmental impairment

Neurodevelopmental impairment includes Autism Spectrum Disorder (also called ASD) which is a developmental disability that can cause severe challenges with communicating, behavior, cognitive, and learning skills. While ASD can be detected in a child as early as 12 months of age, it is often not diagnosed until the child is older [20]. These older children may not get early intervention.

2.2.4 Other chronic health issues

Premature infants are more likely to have chronic health problems such as recurring infections, asthma, feeding challenges, and increased risk of sudden infant death syndrome (SIDS) [21].

2.3 Diagnosis

Ongoing observations that are performed to diagnose complications in the preterm infants include breathing and heart rate monitoring, fluid levels, blood biomarkers, ultrasound examinations, and eye examinations. Many sensors are often taped to infant's body to monitor blood pressure, heart rate, breathing and temperature as shown in Figure 2.2. Infants commonly have a negative reaction to the tape being removed.

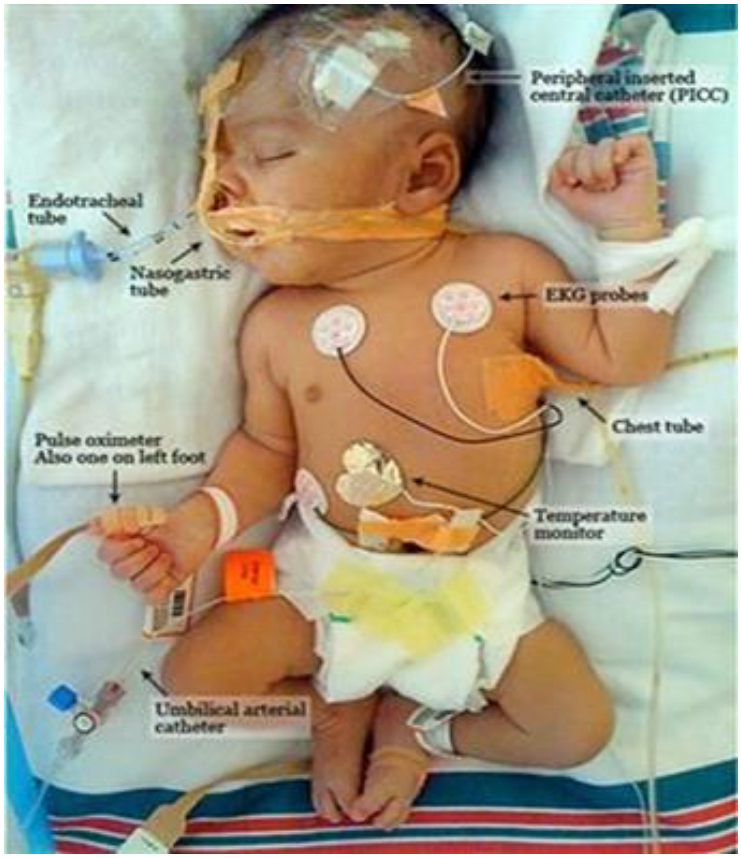

Figure 2.2 Different types of sensors attached to infant's body for monitoring vital signs [22]

2.3.1 Monitoring heart rate, breathing and ultra sound scans

While in the NICU, heart rate and breathing are monitored continuously along with blood pressure readings. An echocardiogram is used for displaying moving images on the monitor as shown in Figure 2.3. Ultrasound scans are conducted to diagnose brain tissue for any bleeding or fluid buildup, and to examine the gastrointestinal tract, liver and kidneys for any abnormalities.

Figure 2.3 Infants monitor displaying HR, RR, SpO2%, pulse and temperature [23]

2.3.2 Fluid levels, blood tests and eye examinations

The NICU team vigilantly tracks the amount of fluid level present in the baby. Blood samples are analyzed regularly to monitor critical nutrient levels, anemia, and any signs of infection. The infant's vision is also examined regularly to prevent damage to the retina.

2.4 Treatment

Depending on the condition of the baby, medicines such as caffeine are used to treat apnea. A ventilator may be used to help the infants breathe and continuous positive airway pressure (CPAP), which is oxygen under pressure may be given through a nasal cannula. Infants may be placed in an incubator to stabilize the infant's body temperature.

The ophthalmologist may perform laser therapy or cryotherapy to eliminate abnormal blood vessels and scars in an effort to protect the retina. Phototherapy is one of the treatments administered in the NICU to help the infant cope with jaundice.

CHAPTER 3
BACKGROUND

Premature infant mortality rate is relatively high due to cardio-respiratory events such as apnea, bradycardia and hypoxemia. Assessing the risk of occurrence of these events is a major challenge for the clinician caring for the preterm infant. Part of the challenge in caring for premature infants is the complication of multiple conditions. R. J. Martin, et al., provided an overview of apnea of prematurity, stating that afferent input to the brain stem correlates with the central pattern generation circuitry [24]. This paper discusses the interplay of apnea, bradycardia, and desaturation while providing a basis for therapeutic approaches to treating apnea of prematurity.

E. Bloch-Salisbury, et al., studied breathing patterns in 10 preterm infants consisting of highly variable inter-breath intervals. Studies were conducted by using a respiratory oscillator and a mattress with embedded actuators that delivered small stochastic displacements by causing arousal from sleep to wakefulness [25]. This study suggests that the incidence of apnea and hypoxia can be reduced using the nonlinear properties of respiratory control system by stabilizing normal breathing. Caffeine may also prevent hypoxemic episodes. J. R. Moorman, et al., conducted a two-group clinical trial of very low birth weight infants in NICU's [26]. Heart rate characteristics (HRC) monitoring was displayed in one group while being masked for the other group. This experimental study shows that HRC monitoring can reduce the mortality rate in very low birth weight infants. All the above works have analyzed the cause of apnea, hypoxia, and bradycardia

to provide strategies for reducing the occurrence. However, it is not sufficient for clinicians to protect infants. They are actually in need of a risk stratification model to predict events in very fragile infants well in advance for effective scheduling of staff as well as defining treatment plans.

Determining when to cease interventions with minimal infant risk is difficult, M. Mueller, et al., worked toward developing a tool for the prediction of appropriate timing for extubation (the final step in removing a patient from mechanical ventilation) in the premature infants with a help of Artificial Neural Networks (ANN), Support Vector Machine (SVM), Naive Bayesian Classifier (NBC), Boosted Decision Trees (BDT), and Multivariable Logistic Regression (MLR) machine learning algorithms [27]. This work also explains about the different extubation supports that are provided to these infants.

A. K. Singha, et al., reported their analysis of the cause for infants' mortality and created a model in the machine learning for a solution [28]. Logistic Regression (LR), Naive Base (NB), and Linear Support Vector Machine (LSVM) models were used to solve Binary classification problems. The performance of LR model is better with high precision score of 0.87 when compared with the NB and LSVM. R. D. Shirwaikar, et al., compared machine learning techniques such as decision tree (C5.0), Support Vector Machine (SVM) and ensemble approach including random forest to predict apnea in neonates [29]. The results obtained has the higher accuracy of 0.88 and kappa of 0.72 for random forest algorithm using mtry =3 than other techniques. This work has the class imbalance problem which is affecting machine learning because of disproportionate number of class instances. N. Mago, et al., used machine learning techniques like the

Support Vector Machine (SVM) and random forest for predicting Apnea of Prematurity (AOP) in neonates [30]. They overcame the class imbalance problem by using Principal Component Analysis for feature extraction and Synthesized Minority Oversampling Technique (SMOTE). They obtained AUC of 0.72 in Random Forests and AUC of 0.66 in Support Vector Machine. In all the above works, the prediction model is developed only for apnea in neonates.

C. F. Poets, et al., studied the downloaded data for oxygen saturation and pulse rate data of infants [31]. The mean percentages of hypoxemia and bradycardia were recorded and studied due to the severe detrimental impact these events have on infants. This work clearly explains how hypoxemic episodes were associated with an estimated increased risk of late death or disability at 18 months. The authors also suggest that caffeine therapy can decrease the risk of developmental coordination disorder of the child. Caffeine can reduce apnea and assist infants in case of respiratory support as well as possible prevention of hypoxemic episodes.

R. Barbieri, et al., stated that heart rate variability is an important quantitative measure of cardiovascular regulation by the autonomic nervous system [32]. He modeled the stochastic structure of heartbeat intervals as a history-dependent inverse Gaussian process and derived instantaneous R-R interval and heart rate standard deviations. Estimating the time-varying parameters of the inverse Gaussian model by local maximum likelihood and by Kolmogorov-Smirnov model, he illustrated an analysis of heartbeat intervals from 10 healthy subjects undergoing a tilt-table experiment. P. Indic, et al., analyzed Interbreath interval (IBI) for extracting breathing patterns from the neonates [33]. The discrete bursts

of neural activity generated during the IBI time series exhibits stochastic and deterministic dynamics. It uses a stochastic dynamic modeling with point process model of IBI to quantify the irregularity of breathing. This study validates a new class of algorithms based on the point process theory for defining instantaneous measures of breathing irregularity in neonates using Kolmogorov-Smirnov.

A. H. Gee, et al., examined bradycardia events by the use of a point process model for heart rate dynamics in preterm infants [34]. Due to the long-tail nature of distribution of R-R interval time series, a log normal distribution model is used. It also provides the statistical information of vulnerability measure of bradycardia in premature infants. M. B. Schmid, et al., reported on the influence of hypoxemia and bradycardia on cerebral oxygenation [35]. Data was recorded from 16 preterm infants with intermittent hypoxemia and/or bradycardia, cerebral tissue oxygen saturation (StO2), heart rate and pulse oximetric saturation (SpO2) for 16 hours. If combined events are compared with isolated bradycardias, the combined events usually have the highest impact on cerebral desaturation.

Studies show that the occurrences of bradycardia events have more impact on preterm infants and hence, we considered inter beat interval of electrocardiogram and employed a point process model to derive features for the machine learning framework for risk stratification.

CHAPTER 4
METHODS

This chapter explains the infant dataset acquisition and the use of point process model to extract features which can act as predictors for future life threatening events. It explains in detail how the life threatening events have been estimated and classified. An algorithm based on a point process model framework to capture heart rate fluctuations and machine learning classifier using Quadratic Support Vector Machine (QSVM) is employed to stratify risk in preterm infants as high or low risk for future events.

4.1 Infant Data Set

The data were collected from preterm infants at the Level 4 Regional Neonatal Intensive Care Unit (NICU) at the University of Alabama at Birmingham using the ixTrend and Philips MP70 systems. The electrocardiogram (ECG) data were obtained using a sampling rate of 500 Hz and the HR using a sampling rate of 1Hz.

Eighteen preterm infants whose parents/legal guardian provided informed consent at the time of enrollment were studied at a gestational age of 27 to 37 weeks recorded for 24 hours per infant in a servo-controlled oxygen environment.

Table 4.1 Characteristics of 18 Preterm Infants data set

Parameter	Range
Sex	9 Males and 9 Females
GA at Enrollment (weeks)	27 – 37
Weight at Enrollment (grams)	920 – 2380

4.1.1 Data Acquisition

ixTrend Express is a professional software used for visualization and data acquisition of vital signals from Philips infant monitors [36]. The data acquired is stored by exporting it into different files formats like .csv for clinical research and long-term studies. Signals that are most commonly recorded are electrocardiogram (ECG), Arterial Blood Pressure (ABP), Plethysmograph (Pleth), Pulmonary Arterial Pressure (PAP), Pulse Rate, Heart Rate (HR), Respiration Rate (Resp rate) and Oxygen Saturation (SpO2).

4.2 Feature extraction using point process model

Point process model require inter beat interval of ECG called RR intervals. We considered heart rate data to obtain R-R intervals [37] as:

$$\text{RR (secs)} = 60/\text{HR (bpm)} \tag{4.1}$$

This data, RR in seconds, is given to the point process algorithm for obtaining the required features. According to statistics and probability theory, a point process is a mathematical model used to represent the randomly located events as points in some type of space such as the real line or the Cartesian plane. Point processes are powerful tools in

statistics for modeling and analyzing spatial data in different disciplines such as astronomy, computational neuroscience, economics, geography, seismology and others.

RR interval of preterm infant follows a lognormal distribution [22, 24]. An algorithm by representing RR as a lognormal distribution is employed to estimate the instantaneous mean $\mu(t)$ as well as instantaneous variance $\sigma^2(t)$. At the k^{th} interval given $RR_k = u_k - u_{k-1}$ and for a time $t > k$ before the next beat occurs, the probability distribution can be represented as

$$f_{k+1}(t \mid HD_k, \beta) = \left[\frac{1}{2\pi\sigma(t)^2(t-u_k)}\right]^{\frac{1}{2}} \exp\left\{-\frac{1}{2}\frac{(\ln(t-u_k)-\mu(t)^2)}{\sigma^2(t)}\right\} \quad (4.2)$$

where $f_{k+1}(t \mid HD_k, \beta)$ represents lognormal probability distribution and u_k time of k^{th} estimated *R*-wave peak. HD_k is the set $\{RR_k, RR_{k-1}, \ldots\ldots, RR_{k-n+1}\}$. The instantaneous mean is represented as a n^{th} order linear regression process as

$$\mu(RR_k, \beta(t)) = \beta_0 + \sum_{i=1}^{n} \beta_i RR_{k-n+1} \quad (4.3)$$

Whose estimation vector $\beta(t)$ is set $\{\beta_0, \ldots, \beta_i, \ldots, \beta_n\}$.

$\mu\ (t)$ and $\sigma\ (t)$ are the indices estimated using a local maximum-likelihood optimization to obtain a continuous estimation of mean as well as variance of the RR signal by using a history-dependent window of 120 seconds and 4th order linear regression process [33]. The average of $\mu(t)$ and $\sigma^2(t)$ as $\bar{\mu}$ and $\overline{\sigma^2}$ respectively for the first one hour were calculated. We also estimate instantaneous mean M(t) and variance V(t) for R-R interval and heart rate (HR) signal by following the below traditional transformation from a lognormal to normal distribution, thus obtaining point process derived indices mean of

RR (M_{RR}) variance of RR (V_{RR}) and mean of HR (M_{HR}) and variance of HR (V_{HR}) respectively.

$$M_{RR}(t) = e^{\mu(t)+\sigma(t)^2/2} \tag{4.4}$$

$$V_{RR}(t) = (e^{\sigma(t)^2} - 1)e^{2\mu(t)+\sigma(t)^2} \tag{4.5}$$

$$M_{HR}(t) = e^{-\mu(t)+\sigma(t)^2/2} \tag{4.6}$$

$$V_{HR}(t) = (e^{\sigma(t)^2} - 1)e^{-2\mu(t)+\sigma(t)^2} \tag{4.7}$$

The standard statistical mean m and variance v are also measured for comparing these with the mean and variances obtained from the point process. The averages of $\mu(t)$, $\sigma^2(t), M_{RR}(t), V_{RR}(t), M_{HR}(t), V_{HR}(t)$ are the six features that are generated using point process model (ppm) for one hour of data for 18 infants. To train a machine-learning model with these 6 features the number of observations obtained from these 18 infants is insufficient. Hence, these 6 ppm features are estimated for 2nd hour, 3rd hour and 4th hour so on up-to 10th hour of data thus making a total of 180 observations.

4.3 Estimation of Life Threatening Events and classification design

We estimated the number of bradycardia events (*N),* defined as a heart rate below 100 bpm. For example, since the HR is sampled at 1 Hz, a bradycardia of 10-seconds duration was estimated as $N = 10$.

We considered all events below predefined thresholds (HR < 100 bpm to define life threatening events because there is insufficient evidence in the literature to indicate that a specific threshold for a certain duration has greater association with worse outcome. The

total number of events experienced by infants is predictive of worse outcomes [29]. An observation window of 3 hours, 6 hours and 9 hours is considered to classify risk based on LTE's (which is number of times N<100bpm) in that particular risk assessment window. We have arbitrarily determined high risk as N>3 per hour and low risk as N <=3 per hour. Which means high risk is considered as N>27 for 9 hours, N>18 for 6 hours and N>12 for 3 hrs whereas low risk is considered as N<=27 for 9 hours, <=18 for 6 hours and N<=12 for 3 hrs.

4.4 Machine learning using Quadratic Support Vector Machine (QSVM)

Machine learning can help to analyze the life-threatening events in neonates. A specialized model based on machine learning is trained using the past data records of preterm infants, which helps to predict the classification of risk in cardiorespiratory events. This thesis work presents an idea of using a Quadratic Support Vector Machine QSVM which may help clinicians to provide better treatment in Neonatal Intensive Care Unit (NICU). Through this model, risk stratification for each individual infant can be predicted in a short time period so that necessary intervention can be given to the infants to potentially prevent negative events.

Supervised Learning is a pair of vector and supervisory signals. Supervised learning algorithm is designed basing on linear and distance functions. The Support Vector Machines, linear regression, logistic regression, naive Bayes, linear discriminant analysis, decision trees, k-nearest neighbor and Neural Networks are a few supervised learning algorithms. In this work, a new quadratic kernel-free non-linear support vector machine which is also known as QSVM is used.

A new quadratic kernel-free non-linear support vector machine is called QSVM [29]. The QSVM is focused to find the locations of discriminative hyperplanes. QSVM is a novel discretized interpretable multilayer perceptron (DIMLP) network trained by an SVM algorithm. This special architecture makes it possible to apply the rule extraction algorithm. It will analyze and train the data in an exponential learning speed. Quadratic Machine learning QML is robust against decoherence and hence it can work in a real-time environment. In this thesis, to solve the optimization problem, a quadratic decision function is used. QSVM gives better performance than the SVM with polynomial kernel (PSVM). The optimization problem is the maximization of the geometrical margin to all sets of the training data with a functional margin which is always greater than a constant. QSVM solves the optimization problem into two parts: the linear part of the quadratic function and the non-linear term. In this work, the Matlab quadratic optimization function 'quadprog ()' is used with the default maximum number of iterations. The main advantage of QSVM is that it can separate the data linearly and non-linearly and the decision surfaces can be assumed at any of the general forms like hyper-planes, hyper-spheres, hyper-ellipsoids, hyper-paraboloids, hyper-hyperboloids whereas in kernel trick can classify only nonlinear data in hyper planes and also helps to solve a class imbalance problem. Hence, in this work QSVM is used. Figure 4.1 shows the block diagram for the proposed model using Point process model and QSVM machine learning technique for risk classification of preterm infants at the NICU

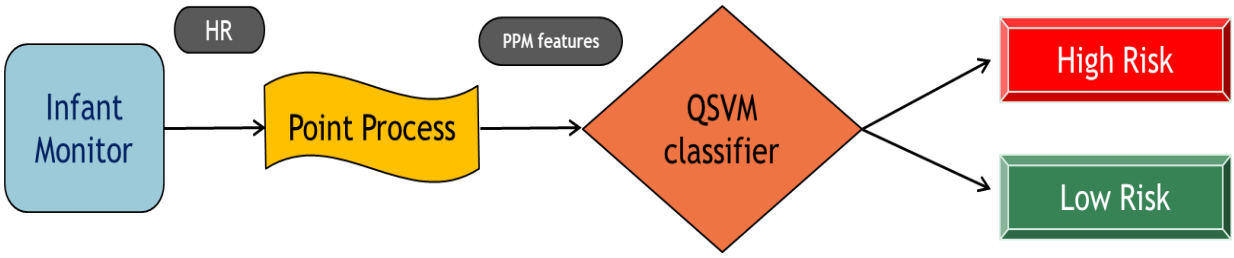

Figure 4.1 Block diagram representation of the proposed risk stratification algorithm

The parameters which can access the performance of classifiers are called performance metrics. In this work accuracy, Receiver Operating Characteristic ROC, and Area Under Curve AUC are the performance metrics that helped to determine the performance of the model designed using machine learning classifier QSVM.

4.5 Receiver Operating Characteristic (ROC) and Area Under Curve (AUC)

This metric was first used to detect the signal in radar in 1950's. ROC curve should be straight up to the Y axis and then along the X axis for the perfect classifier. A classifier which is in diagonal always shows that it has no power, whereas most classifiers will fall somewhere in between. Hence, ROC curve is plotted between Sensitivity on the Y-axis and Specificity on the X axis [10]. The sensitivity is called the True Positive Rate and specificity called the False Positive rate. This curve can able to access the performance of a built model using Area Under Curve AUC. ROC curve can be used to be a threshold value for a classifier which maximizes true positives and minimizes the false positives as shown in Figure 4.2.

The Area Under Curve AUC will compare the performance of two or more classifiers. This curve helps to interpret the classifier. The perfect machine learning model has AUC

of 1.0. A good model should have at least 0.7. If AUC is 0.5, it has 50% of chance to predict correctly.

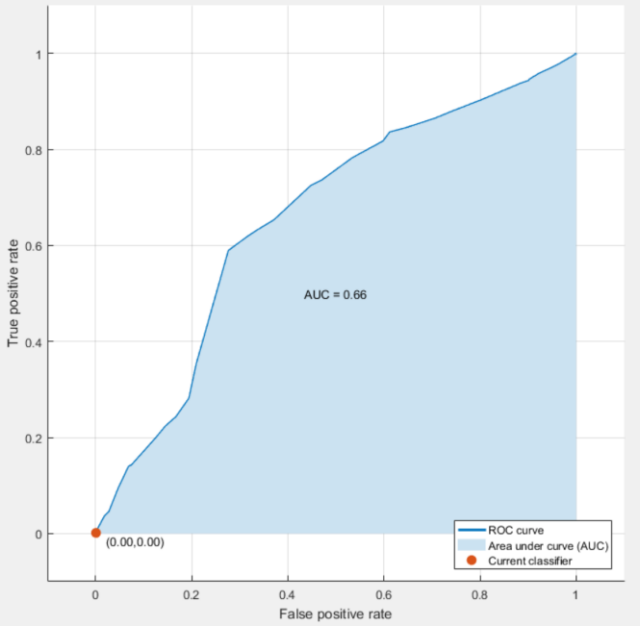

Figure 4.2 Sample ROC curve [40]

4.6 Accuracy

$$Accuracy = \frac{TP+TN}{TP+FP+FN+TN} \tag{4.4}$$

Accuracy helps to predict the performance level of the model. Lower accuracy indicates poor prediction. Accuracy is the number of correct predictions to the overall prediction made by the created model. The numerator shows all the correct predictions and the denominator shows all the correct and false predictions.

When we assign the event row as ‘positive’, the no-event row as ‘negative’, the event column of predictions as ‘true’ and the no-event as ‘false’ we get confusion matrix [41] with true positive (TP) which gives the correctly predicted events, false positive (FP)

shows the incorrectly predicted events, true negative (TN) gives the correctly predicted no-events and false negative (FN) shows the incorrectly predicted no-events as shown in Table 4.2.

Table 4.2 Confusion matrix for events classification

	Predicted	
Actual	event	no-event
event	TP	FN
no-event	FP	TN

CHAPTER 5
RESULTS AND DISCUSSIONS

The results from our analysis are presented below, divided into two main sections. First, we investigated whether the life-threatening events were associated with growth characteristics of the infants and studied the correlation between the point process indices (as well as the traditional statistical measures) with the life threatening events. Finally, we developed a risk stratification model using QSVM to classify high and low risk infants using point process indices obtained from one hour of data.

5.1 Infant Characteristics and Heart rate measures

The gestational age (GA) and weight of the18 preterm infants at enrollment is shown in the following Figure 5.1 along with the features obtained from point process model for first one hour of heart rate data which are the averages of instantaneous mean $\mu(t)$ and instantaneous variance $\sigma^2(t)$ represented as $\bar{\mu}$, $\overline{\sigma^2}$ respectively. We calculated the standard mean *m* and variance *v* of the logarithm of the original RR interval data for the first one hour and the number of life threatening events N for the remaining 23 hours of data is presented.

Figure 5.1 $\bar{\mu}$, $\overline{\sigma^2}$, m, v for first one hour and N for next 23 hours of data of 18 preterm infants

Infant ID	GA at Enrollment (weeks)	Weight at Enrollment (grams)	$\bar{\mu}$	$\overline{\sigma^2}$ ($x10^{-3}$)	m	v ($x10^{-3}$)	Events N
E2	34.42	1310	-1.01	0.059	-1.01	4.29	112
E4	30	1250	-0.98	0.033	-0.98	1.69	84
E5	31.28	1330	-1.02	0.03	-1.02	2.53	33
E7	31.85	1130	-0.98	0.025	-0.98	2.71	148
E9	31.57	1170	-1.05	0.023	-1.06	3.72	3
E10	32.42	920	-1.11	0.013	-1.11	1.07	58
E12	37.57	2380	-0.9	0.041	-0.91	3.17	23
E13	29	1080	-1.05	0.023	-1.05	0.73	108
E14	31.28	1150	-1.05	0.028	-1.05	0.86	61
E17	33.85	1270	-0.93	0.106	-0.93	5.31	194
E18	35.42	1600	-1.02	0.03	-1.02	3.68	9
E20	27.42	1010	-1.06	0.031	-1.06	1.69	129
E22	32.57	1240	-0.89	0.136	-0.89	2.84	399
E23	31.14	1190	-1.01	0.091	-1.02	2.16	246
E24	31.57	1310	-1.01	0.173	-1.02	7.03	299
E25	31.57	1220	-1.06	0.081	-1.07	9.66	93
E26	37.57	1350	-0.73	0.021	-0.74	11.31	68
E27	36	1730	-1.12	0.039	-1.12	1.88	72

The point process indices that are obtained using point process model mentioned in section 4.3 are M_{RR}, V_{RR} and M_{HR} and V_{HR} mentioned earlier in section 4.2. Figure 5.2 shows the heart rate of infant E25 along with the point process indices of estimated HR for the first one-hour. As the heart rate goes below 100 bpm, the $\mu(t)$ as well as $\sigma^2(t)$ shows a significant increase. While $\mu(t)$ follows the RR interval, $\sigma^2(t)$ captures the variability in the fluctuations of RR during bradycardia events.

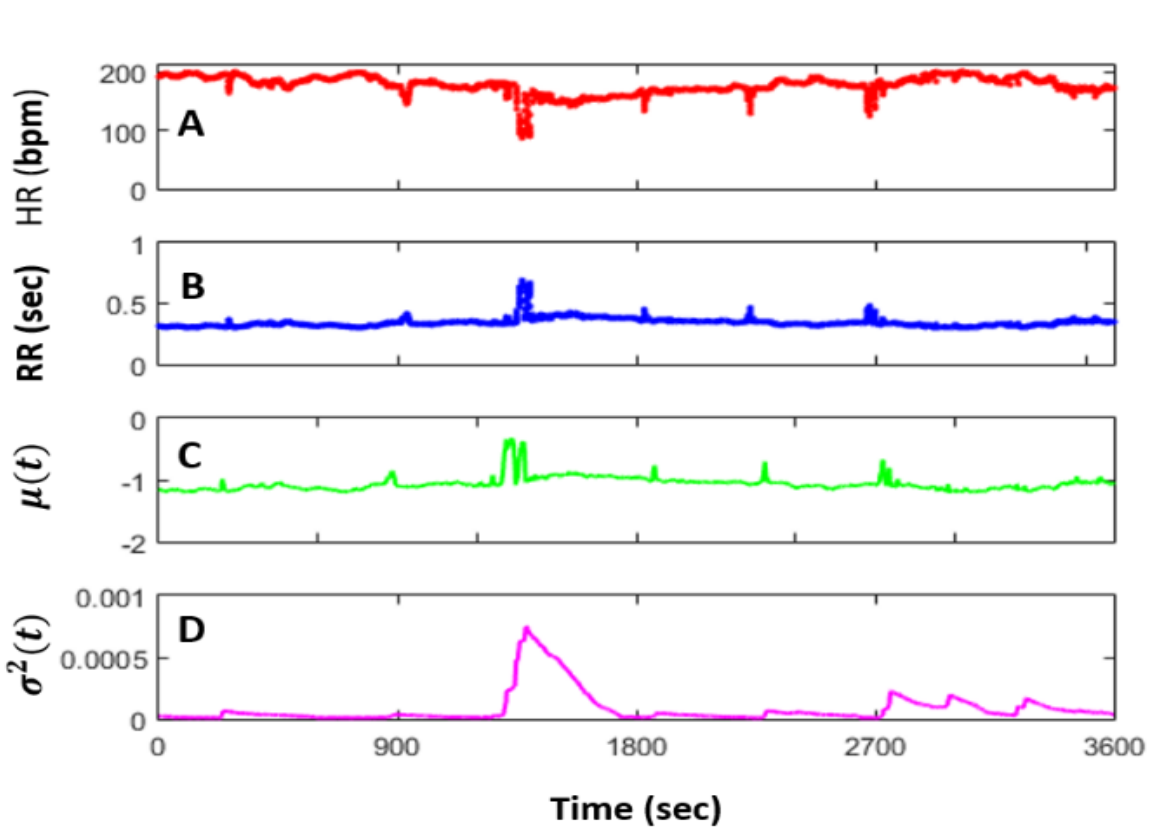

Figure 5.2 Point Process Indices from Infant E25 in the first one-hour data (A) HR in bpm, (B) RR in seconds, (C) instantaneous mean $\mu(t)$, and (D) instantaneous variance $\sigma^2(t)$

5.1.1 Relationship of Life Threatening Events with Growth Characteristics

We investigated whether infant growth characteristics were associated with life threatening events as shown in Table 5.1. This was undertaken to ensure that the infants' vulnerability to events was independent of age and weight, and that each infant requires special attention regardless of growth characteristics. We found that GA and Weight at the time of enrolment do not correlate with N. Here, we calculated Pearson correlation coefficient r and probability p value where $p < 0.05$ is considered to be statistically significant [42].

Table 5.1 Growth Characteristics vs. Life Threatening Events

Growth	***N***	
	r	***p***
GA	-0.22	0.38
Weight	-0.25	0.31

5.1.2 Relationship of Point Process Indices with Traditional Statistical Measures

We investigated whether the point process indices $\bar{\mu}$ and $\overline{\sigma^2}$ correlate with the standard statistical estimates mean *m* and variance *v*. We found that the $\bar{\mu}$ correlates strongly with *m* (***r*** = 0.99 and ***p*** = < 0.0001), suggesting that no additional information is gained by employing the point process framework for estimating the first order statistics. On the other hand, $\overline{\sigma^2}$ shows no correlation with *v* (**r** = 0.32 and ***p*** = 0.2), suggesting that the point process model captures the fluctuations in RR differently than the traditional statistical variance. This lack of correlation would point to a possible improvement in risk stratification by using the point process algorithm.

5.1.3 Relationship of Life Threatening Events with Point Process Indices

We investigated whether the point process indices can act as precursors for the life-threatening events. Hence, we studied the correlation between the point process indices instantaneous mean $\mu(t)$, instantaneous variance $\sigma^2(t)$ and these LTE's for 18 preterm infants. We found that the $\overline{\sigma^2}$ correlates strongly with the bradycardia events *N*. None of

the standard statistical measures as well as $\bar{\mu}$ correlated with life threatening events [43] as shown in Table 5.2.

Table 5.2 Point Process Indices vs. Statistical Measures

Measures	*N*	
	r	***p***
$\bar{\mu}$	0.22	0.37
$\overline{\sigma^2}$	0.84*	<0.001
m	0.22	0.37
v	0.07	0.80

*represents significance

5.2 Risk Classification using Point process indices as predictors for machine learning classifier QSVM

Life threatening events (LTE's) calculated in each hour of 24 hours' data for 18 preterm infants is calculated. Figure 5.3 shows the number of bradycardia events N in each hour for 24 hours' data in infant E2. Similarly, these events are calculated for all other 17 preterm infants.

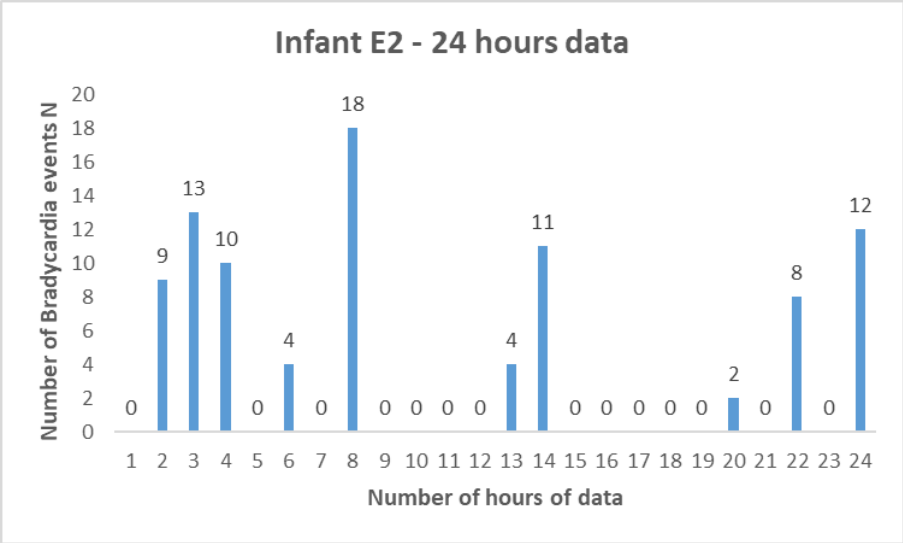

Figure 5.3 Number of N when HR<100 bpm in each hour for Infant E2

Since, features obtained from 18 preterm infants is insufficient to train a machine learning model, we have increased the number of observations by taking point process features (PPM) for 1st hour of data as observation window and calculating bradycardia events for next 3 hours, 6 hours and 9 hours as risk assessment windows. Similarly, we repeat the same process for 2nd hour, 3rd hour so on up to 10th hour obtaining a total of 180 observations.

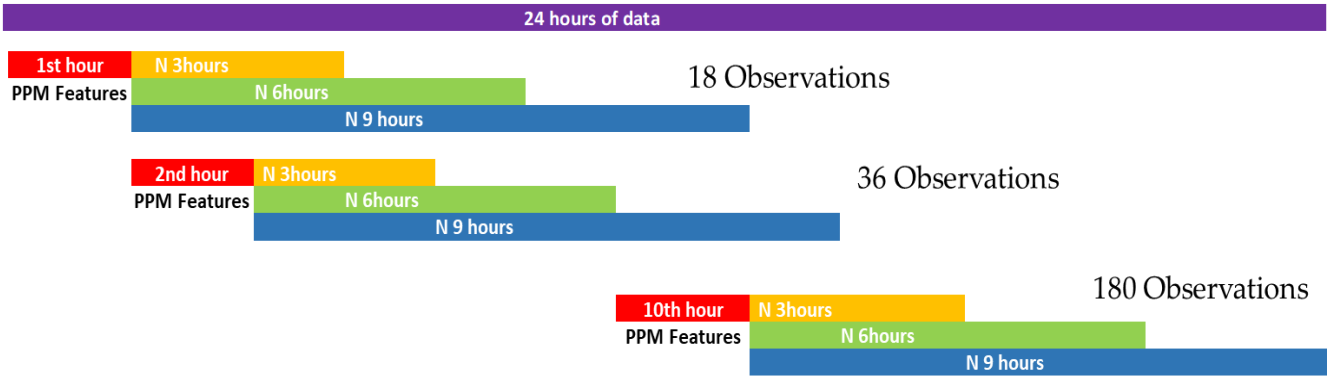

Figure 5.4 Demonstration for obtaining 180 observations

Number of high and low risk infants in each risk assessment window for 180 observations is listed as follows in Table 5.3 to estimate the total number of bradycardia events (N) for 3, 6, and 9 hours' period of time. The six features that are generated using point process model for one hour of data act as predictors for estimating risk in infants after 3hours, 6 hours, and 9 hours.

Table 5.3 Number of infants with high risk and low risk

	N 3 hours	N 6hours	N 9hours
High risk	69	91	102
Low risk	111	89	78

5.2.1 Outcomes for 9 hours' risk assessment window

We employed QSVM to classify high risk and low risk infants. We obtained an Accuracy of 76.4%, an AUC of 0.80 using 5-fold cross validation and 40% hold out for 180 observations in 9hours prediction window. We were able to classify 22 low risk infants out of 31 infants and 33 high risk infants out of 41 infants as mentioned in Table 5.4. The TPR obtained is 80% and FNR obtained is 20% for high risk classification whereas TPR and FNR for low risk classification is 71% and 29% respectively.

Table 5.4 Confusion matrix for classifying high risk and low risk of infants using QSVM

	Predicted	
Actual	Low Risk	High Risk
Low Risk	22	9
High Risk	8	33

We obtained an Accuracy of 70.2 %, an AUC of 0.77 using 5-fold cross validation and 30% hold out for 180 observations in 9 hours' prediction window. We were able to classify 16 low risk infants out of 23 infants and 23 high risk infants out of 31 infants as mentioned in Table 5.5. The TPR obtained is 74% and FNR obtained is 26% for high risk classification whereas TPR and FNR for low risk classification is 70% and 30% respectively.

Table 5.5 Confusion matrix for classifying high risk and low risk of infants using QSVM

	Predicted	
Actual	Low Risk	High Risk
Low Risk	16	7
High Risk	8	23

5.2.2 Outcomes for 6 hours' risk assessment window

We obtained an Accuracy of 63.9%, an AUC of 0.65 using 5-fold cross validation and 40% hold out for 180 observations in 6 hours' prediction window. We were able to classify 25 low risk infants out of 36 infants and 21 high risk infants out of 36 infants as mentioned in Table 5.6.

Table 5.6 Confusion matrix for classifying high risk and low risk of infants using QSVM

	Predicted	
Actual	Low Risk	High Risk
Low Risk	25	11
High Risk	15	21

We obtained an Accuracy of 68.5 %, an AUC of 0.71 using 5-fold cross validation and 30% hold out for 180 observations in 6hours prediction window. We were able to classify 19 low risk infants out of 27 infants and 18 high risk infants out of 29 infants as mentioned in Table 5.7.

Table 5.7 Confusion matrix for classifying high risk and low risk of infants using QSVM

	Predicted	
Actual	Low Risk	High Risk
Low Risk	19	8
High Risk	9	18

5.2.3 Outcomes for 3 hours' risk assessment window

We obtained an Accuracy of 68.9%, an AUC of 0.67 using 5-fold cross validation and 40% hold out for 180 observations in 3 hours' prediction window. We were able to classify 21 low risk infants out of 27 infants and 10 high risk infants out of 18 infants as mentioned in Table 5.8.

Table 5.8 Confusion matrix for classifying high risk and low risk of infants using QSVM

	Predicted	
Actual	Low Risk	High Risk
Low Risk	21	6
High Risk	8	10

We obtained an Accuracy of 64.8 %, an AUC of 0.68 using 5-fold cross validation and 30% hold out for 180 observations in the 3-hours prediction window. We were able to classify 24 low risk infants out of 33 infants and 11 high risk infants out of 21 infants as mentioned in Table 5.9.

Table 5.9 Confusion matrix for classifying high risk and low risk of infants using QSVM

	Predicted	
Actual	Low Risk	High Risk
Low Risk	24	9
High Risk	10	11

CHAPTER 6
CONCLUSION, LIMITATIONS and FUTURE DIRECTIONS

There are several algorithms available to predict the bradycardia events or apnea occurrences for a shorter interval of time. But, there is no model that is currently available to assess the risk in preterm infants. The model developed in this research can classify the risk for a longer period of time up to 9 hours, so that the clinicians will have enough time to provide necessary interventions for preterm infants to overcome risks.

The time taken for assessment of risk after 9 hours using one-hour heart rate data is around 14mins including extracting point process features and applying machine learning technique. The advantage of this model is that it can continuously assess the risk every one hour and 14 minutes after the initial start time period of 9 hours if applied in real time and infant's risk assessment can be updated every hour thereafter.

The model designed can assess high risk and low risk in preterm infants for 9 hours by observing the infant heart rate dynamics collected for an hour. The overall accuracies and AUC's obtained for risk assessment window of 9, 6, and 3 hours for 108 observations with 40% and 30% holdout are shown below in Tables 6.1 and 6.2 using 5-fold cross validation.

Table 6.1 Accuracy and AUC with 40% holdout

	N 9 hours	**N 6 hours**	**N 3hours**
Accuracy	76.4%	63.9%	68.9%
AUC	0.80	0.65	0.67

Table 6.2 Accuracy and AUC with 30% holdout

	N 9 hours	**N 6 hours**	**N 3hours**
Accuracy	70.4%	68.5%	64.8%
AUC	0.77	0.71	0.68

We conclude that the estimation of life threatening events for 9 hours is more effective because of obtained higher accuracies and AUC's when compared to their estimation for 6 hours or 3 hours. The results obtained show an Accuracy of 76.4% and AUC of 0.80 for 9-hour risk assessment window using point process model features and quadratic support vector machine classifier with 5-fold cross validation and 40% holdout. Thus, this study designed a model for classification of high risk infants and low risk infants after 9 hours which can assist clinicians for risk assessment to effectively manage and treat preterm infants in NICU's.

6.1 Limitations and future directions

In this work, only heart rate HR data is considered and is focused only on slowness of heart (bradycardia events). The data examined to design the algorithm is using less number of infants which is data from eighteen preterm infants. The model is developed by considering statistical features derived from point process model only.

Consideration of respiratory rate for apnea events and oxygen desaturation for hypoxemic events can further improve the model. Exploring additional features including non-linear features like entropy, detrended fluctuations, etc., along with statistical features will help to improve the model. The algorithm must be designed using more preterm infant data sets to test and to implement this model in real time for assessment of risk in preterm infants at the NICU.

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