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ASSESSMENT OF CARDIORESPIRATORY INTERACTIONS DURING LIFE THREATENING EVENTS IN PRETERM INFANTS USING POINT PROCESS AND BIVARIATE ALGORITHMS

by

MOHAMMED THANY ALENAZI

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science in Electrical Engineering
Department of Electrical Engineering

Premananda Indic, Ph.D., Committee Chair

College of Engineering

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May 2021

The University of Texas at Tyler
Tyler, Texas

This is to certify that the Master's Thesis of

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Dedication

I would like to primarily dedicate this page to my parents and my wife. I have been blessed with a beautiful family. My youngest son Hamad was born premature, hence my increased curiosity in premature births. As for my research, I would like to dedicate it to all premature infants who are experiencing life threatening events.

Acknowledgements

I would like to acknowledge everyone who played a role in my academic accomplishments. First of all, my parents, my wife, and all of my family members who supported me with love and understanding; without you, I could never have reached this current level of success.

Secondly, my committee members, each of whom have provided patient advice and guidance throughout the research process. Special thanks to Dr. Premananda Indic for his continued support, advise, encouragement, and professional supervision. Lastly, I would like to thank the Ministry of Education in Saudi Arabia and National Institute of Health Grant U01 HL133536, National Science Foundation and the Smart and Connected Health Grant IIS 166481 for their support.

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List of abbreviations

A	Apnea event
AB	Apnea and Bradycardia events
ABP	Arterial Blood Pressure
ANS	Autonomic nervous system
B	Bradycardia event
BPM	Beats per minute
CPAP	Continuous Positive Airway Pressure
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
EMA	Evolution Map Approach
GA	Gestational Age
HF	High Frequency
HR	Heart Rate
HRV	Heart Rate Variability
KS	Kolmogorov-Smirnov
LF	Low Frequency
NCRR	National Center for Research Resources
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICU	Neonatal Intensive Care Units
PI	Pulse Interval
PICS	Preterm Infants Cardio-Respiratory Signal

PPM	Point Process Model
QPC	Quadratic Phase Coupling
RP	Respiration Peak
RR	Peak to Peak Intervals
RSA	Respiratory Sinus Arrythmia
RWB	Real Wavelet Biphase
SIDS	Sudden Infant Death Syndrome
WFDB	WaveForm DataBase

Abstract

ASSESSMENT OF CARDIORESPIRATORY INTERACTIONS DURING LIFE THREATENING EVENTS IN PRETERM INFANTS USING POINT PROCESS AND BIVARIATE ALGORITHMS.

Mohammed Thany Alenazi

Thesis Chair: Premananda Indic, Ph.D.

The University of Texas at Tyler
May 2021

Infants who are born with less than 37 weeks gestational age have significant life threatening events such as apnea (pause in breathing), bradycardia (slowness of heart) and hypoxia (oxygen desaturation). These preterm infants need specialized care and treatment to overcome the adverse events. While several physiological signals are monitored during their care at Neonatal Intensive Care Units (NICU), there is no validated methods available to assess the development of infants. With the advent of high performance computers along with the development of advanced data analytics, engineers and clinicians have begun collaborating in developing methods for the assessment of neurodevelopment in infants.

Cardiorespiratory interactions considered as an important indicator of neurodevelopment of preterm infants. The strength of cardiorespiratory interactions are presumed to be weak and rapidly fluctuating. The current signal processing algorithms are insufficient to capture such time varying weak interactions. In addition, detection of these interactions becomes difficult during life threatening events due to lack of information available due to apnea (absence of output from respiratory system) and the transient temporal destabilization of cardiac system due to bradycardia.

To detect the cardiorespiratory interactions, we propose a point process algorithm of cardiac system with respiration as covariates. The bivariate model is embedded on the point process-

modeling framework to capture the time varying weak interactions between cardiac and respiratory system. The bivariate model helps to detect the interactions occurring in both directions, respiration to cardiac and vice versa. This integrated framework is employed to detect the cardiorespiratory interactions in preterm infants during their life threatening events. The standard method to assess the cardiorespiratory interactions is by defining Respiratory Sinus Arrhythmia (RSA) gain, which defines the ratio of cardiac output to respiratory output. The point process framework employed in this work provides a method to assess the instantaneous variation of RSA gain even in the absence of respiratory output or the transient destabilization of cardiac system.

The algorithm is applied to detect the interactions during 829 life threatening events (388 apnea only events, 236 bradycardia only events and 205 apnea as well as bradycardia occurring simultaneously) from 10 infants recorded for a duration of at least 48 hours for each infant. During apnea, cardiorespiratory interactions are significantly higher from respiration to cardiac system at the respiratory frequency compared to other events. Whereas, the interactions are significantly higher from cardiac to respiration during bradycardia as well as apnea-bradycardia at the cardiac frequency compared to apnea.

RSA gains are significantly higher during bradycardia compared to other events. Among the life threatening events, the presence of bradycardia events have a distinct classification in terms of cardiorespiratory interactions and gain compared to the regions in the data with no life threatening events. In addition, the bradycardia events differentiates significantly from apnea events. These observations suggests that the bradycardia is presumably a more adverse event than the apnea and its increased prevalent may be detrimental to the neurodevelopment of infants. The algorithm developed can be embedded in the existing monitoring system in the NICU and may potentially provide a useful tool to assess the neurodevelopment of preterm infants.

CHAPTER 1

INTRODUCTION

Cardiorespiratory interactions are considered as an important indicator of level of maturation in preterm infants, however the exact relationship between cardiac and respiratory systems are not known in infants [1-8].In healthy adults, such interactions are observed by the analysis of heart rate and respiration signals. Heart rate increases during inspiration and reduces during expiration resulting in a peak in the heart rate signal spectrum at the respiratory frequency ranges of adults [9-11]. Adults mean respiratory frequency is around 0.2Hz (12 breaths per minute) and a peak in the spectrum of heart rate variability signal observed at this frequency is the indication of interactions. Traditional coherence, which provides the relationship between cross spectral density of the two signals to its individual auto spectral density, are used to quantify the cardiorespiratory interactions [12]. Such cardiorespiratory interactions, where the unidirectional interactions occurring from respiration to heart rate is termed as ***Respiratory Sinus Arrhythmia*** (RSA).

Preterm infants have a mean respiratory rate of 60 breaths per minute (1Hz) and heart rate of 120 beats per minute (0.5Hz), however due to immaturity of the respiratory neurons in the brain, these infants have irregularity in breathing with pauses (apnea). These irregularities and the apneas can result in frequencies lower than 1Hz. *Hence, we hypothesize that the irregularities and the apneas in the respiration can result in RSA at frequencies lower than the 1Hz, resulting in interactions from respiration to heart rate occurring at range of frequencies*. In signal processing, RSA estimated as the gain of a transfer function defined by considering the respiration as the input and the heart rate as the output. The RSA gain is the absolute value of the transfer function at the respiratory frequency where the coherence is maximum [13].

The limitations of traditional RSA gain estimates is that the respiration as well as heart rate signals are assumed to be stationary, however in the case of preterm infants they are highly nonstationary in nature. In addition, heart rate fluctuations may exist at the respiratory frequencies even during apneas (absence of respiration) [14]. Furthermore, bradycardia (slow down of heart rate) can occur without any influence from respiration even in the absence of any instability or apnea [15]. Due to

neural reflexive baroreceptor influences on the neuronal respiratory neurons in the brain [16], there is a possibility of interactions occurring in the reverse direction occurring from cardiac to respiratory system. In addition, variability in breathing signals has been recorded that are correlated with the fluctuations in heart rate [17-19] suggesting influence of heart rate on respiration.

The current approaches do not account for any interactions occurring from heart rate to respiration.. Thus from a signal processing point of view, the interactions are not unidirectional and open loop, occurring from respiration to heart rate only, rather bi-directional and closed loop, occurring in both directions. In this work, an algorithm that captures the directional coherence (causal coherence) at range of frequencies 0.01Hz to 1.5Hz is proposed. The frequency range 0.01Hz to 0.45Hz are likely to capture all the interactions in the range of heart rate frequencies whereas the range 0.45Hz to 1.5Hz likely to capture the respiratory frequency range. The time varying nonstationary RSA gains were also estimated in the above frequency ranges.

One in ten infants are born premature with a gestational age less than 36 weeks resulting in one million deaths yearly [20]. The infants who survive have short-term adverse outcomes such as apnea, bradycardia and hypoxia (oxygen desaturation) and long term adverse outcomes such as cerebral palsy, learning disabilities, eye disorder (retinopathy of prematurity) and other complications [21, 22]. Preterm infants are treated in Neonatal Intensive Care Units (NICU), where they receive specialized treatments to overcome the short term outcomes, however the significance of long term outcomes with the adverse short term outcomes occurring at NICU are still unknown. The specialized units are expensive and results in over $26 billion in cost annually as per the Institute of Medicine Report [23].The factors leading to premature births are not known and may include low or high maternal age (usually below 18 or above 39), multiple miscarriages, carrying of multiple fetuses or even structural abnormalities of the womb [24]. In addition, these factors may also associate with premature births

- Smoking of cigarettes and use of illicit drugs.
- Giving birth in short intervals, an interval less than six months between pregnancies.
- Conditions such as high blood pressure and diabetes.
- Being underweight or obese before pregnancy [24].

The preterm infants are further divided as

- **Late preterm** (i.e. baby is born between 34 and 36 completed weeks of pregnancy),
- **Moderately preterm** (i.e. baby born between 32 and 34 of pregnancy),
- **Very preterm** (i.e. born at less than 32 of pregnancy),
- **Extremely preterm** (i.e. born at or before 25 weeks of pregnancy.

The complications occurring in Very and Extremely preterm infants are significantly different from other groups. Based on the condition of births, infants are admitted at different levels of NICU where they received uninterrupted specialized care under the supervision of specially trained neonatal physicians and nurses to observe and treat the complications due to prematurity. The NICU is made up of four levels according to required attention by a preterm infant [25].

- Level I gives basic care to newborns.
- Level II is a special care nursery to give care to preterm infants older than 32 weeks through CPAP (Continuous Positive Airway Pressure), mechanical ventilation for up to 24 hours.
- Level III comprises of a comprehensive care with high frequency ventilation and an on-site accessibility to pediatric subspecialists.
- Level IV is the regionalized neonatal intensive care unit that provides extracorporeal membrane oxygenation (ECMO) therapy that has been designed and equipped to treat complex cardiac abnormalities that may require cardiopulmonary bypass [25].

The symptoms considered as the evidence of prematurity in infants are

- Respiratory distress (labored breathing).
- Low body temperature, due to a lack of stored body fat.
- Small body size accompanied with a disproportionately huge head.
- No reflexes for sucking and swallowing which then makes it difficult to feed

The commonly understood short-term and long-term adverse outcomes of preterm births are:

Short-term Complications:

Apnea:

Apnea refers to pauses in breathing that occurs due to the immaturity of the infant's respiratory system and infant struggles to breathe. Apnea that last for more than 10 seconds considered as fatal

to infants. Apnea usually occur during sleep hence the name sleep apnea. The apnea that are caused by the respiratory neurons in the brain are called central apnea, however apnea can also occur due to the obstruction of the airway due to mechanical problems, and are called obstructive apnea. Sometimes infants experience both, called mixed apnea. Central apneas are more prevalent [22].

Bradycardia:

The condition in infants where the heart rate significantly slows down called bradycardia. The mean heart rate (HR) of premature infants is 120-180 beats per minute (bpm). A heart rate less than 100 bpm refers to as bradycardia which is further subdivided as mild bradycardia (100-80 bpm), moderate (80-60 bpm), and severe (<60 bpm)] [23]. Bradycardia results in lack of oxygen supply to the brain and the blood, resulting in the damage of brain and other vital organs.[24].

Hypoxia*:*

It is a condition where insufficient amount of oxygen reaches the body or a part of the body (tissue hypoxia). Hypoxia is known to be a common cause of brain damage in neonates [26].

These adverse events can occur simultaneously or individually or different combinations.

Long-term complications:

Cerebral Palsy:

The inadequate blood flow occurring at births can result in long term complications in infant's muscle tone, movement or posture as the infant survives and grows. These long term complications becomes permanent.

Vision impairments:

Lack of blood supply can damage the retina and results in vision impairment called Retinopathy of Prematurity (ROP). The blood vessels swells and overgrows in the light sensitive areas resulting in detachment of retina causing vison impairments. This can result in permanent vision impairments and blindness [24].

With the advent of continuous monitoring of physiological data along with the advanced data analytics approaches and the high performance computational capabilities, many of the precursors of adverse events in preterm infants can be detected. Such precursors along with advanced signal processing and machine learning algorithms can be employed to develop decision-making systems to assist clinicians in the effective management and treatment of these vulnerable infants. A better

understanding of cardiorespiratory interactions can provide a reliable marker of development and can help clinicians to better understand the maturation of preterm infants. While the physiological signals are continuously monitored and stored in NICU, no validated algorithms are available to assess the neurodevelopment of the infants. Physiological signals provide useful information about the instability as well as maturation. Understanding the interactions of respiration and cardiac systems can provide reliable marker of development that can assist clinicians to gain insights into neonatal health and subsequent development.

Therefore, in this work, we propose an algorithm using the point process nature of electrocardiogram from which the heart rate is derived along with a respiration as covariates to define the time varying nature of RSA gain at different range of frequencies (0.01Hz to 1.5 Hz). The bidirectional interactions are estimated using a bivariate autoregressive model that are embedded in the point process-modeling framework to estimate the causal coherence. These two modeling framework provides the instantaneous time varying nonstationary estimate of RSA gain as well as causal coherence in real time. The algorithm developed can be incorporated in the existing system for the real time assessment of maturation in preterm infants. The thesis is organized as follows, next chapter provides the background and the current state of art, followed by the methods employed and then the results and discussion. At the end, conclusions and future directions are presented.

CHAPTER 2
BACKGROUND

Oscillations are observed in most biological systems. A couple of prominent ones in human beings are related to the heart/cardiac cycle and to respiration. Cardio-respiratory coupling is a term encompassing the *reciprocal* interaction between these two rhythms or between the autonomic and respiratory control systems [27]. The cardiorespiratory system exhibits oscillations from many sources such as heart contraction, breathing and arterial blood pressure. These activities occur at widely varying frequencies and their interactions lead to heart rate variability, variability in breathing patterns and other cardio-vascular measurements [28].

Three main types of cardiorespiratory interactions have been widely studied: (1) Respiratory sinus arrhythmia (RSA) which is the variability in heart rate at the frequency of breathing, (2) cardioventilatory coupling which refers to the synchronization between the heartbeat and the onset of inspiration and (3) respiratory stroke volume synchronization which is the constant phase difference between the right and left stroke volumes over one respiratory cycle. The mechanisms and physiological significance of these interactions, especially the RSA have been studied in humans and other species and established to be a product of the central and involuntary nervous system processes [29]. RSA generation has been linked to direct brainstem control of the cardiac vagal preganglionic neurons and by restriction of cardiac vagal efferent activity by lung inflation. In addition, RSA is also believed to improve pulmonary gas exchange [30]. An impaired cardio respiratory coupling has been found in association with many diseases including hypertension, heart failure and depression [1]. Hence, an understanding of the interactions and their physiological implications can be beneficial in the prevention, diagnosis and treatment of cardiovascular diseases.

Premature infants exhibit a host of adverse outcomes such as respiratory distress syndrome, frequent apneas, diminished autonomic control of heart rate because of their lack of growth and maturation. The fragile nature of their immature cardiac and respiratory systems causes imbalances that lead to impaired cardio-respiratory interaction. The heart rate typically rises with inspiration and falls with expiration, in a healthy state. Adults have a mean respiratory rate of roughly 12

breaths per minute (0.2 Hz) and, assuming a linear pattern, these oscillations directly reflect the variability of the heartbeat. The influence of breathing on heart rate or RSA is detected as a peak in the normal respiratory frequency range in the HRV spectrum. Such a well-defined peak representing RSA is the HRV spectrum is the hallmark of cardio-respiratory coupling in adults. Even though the exact relationship between HRV and respiration in preterm infants remains incomplete, the regular respiratory rate of infants is approximately 60 breathes per minute (1Hz).

Most preterm infants experience irregular breathing patterns with recurrent breathing and brief breaks in breathing (apnea) that results in frequencies lower than the normal range. Hence, the respiratory influence on the heart rate, should there be any, exists at different ranges of frequencies, below 1 Hz. Due to this, in preterm infants, the normal RSA peak in HRV power spectrum at the normal breathing frequency of ~ 1Hz may not be prominent or noticeable due to the inconsistency in breathing. In addition, heart rate fluctuations may occur at respiratory frequencies even during the absence of respiration posing yet another problem in relying on traditional spectral methods for analysis of the dynamics of these physiological signals [31].

This chapter provides a comprehensive picture of the study of cardiorespiratory interactions in human subjects, with special reference to newborn infants, using methods from spectral analysis, coupled oscillator dynamics, information theory and others. Besides the strength of such interactions, the nature of causality, directionality of couplings or the driver-response behavior of the sub-systems is also important to under their physiological role and deduce how these are affected in health and disease. The next section provides a brief overview of these methods available in the literature.

2.1 METHODS TO ASSESS CARDIORESPIRATORY INTERACTIONS

An important methodology underlying the study and analysis of cardiorespiratory interaction from physiological signals follows that of weakly coupled oscillators. According to this, physiological systems or units interact with each other and this information is embedded within measured signals. When two systems are weakly connected, the amplitude of their oscillations may remain non correlated while their phases entrain with each other. The interactions can be

linear or non-linear in nature exhibiting a multi-stable system swapping between numerous phase attractive maps, accompanied by a precedence for a certain type of phase relations, which may be thought of as attracting frequency correlations. These various means of interactions are not independent of each other, rather they may concurrently exist side-by-side, depicting numerous characteristics of neural setting and acting on varying time intervals [30].

The pioneering work applying coupled oscillator theory to understanding cardiorespiratory interactions was that of Rosenblum and group in the early 2000s when they demonstrated synchronous epochs between the RR time series and respiration signals in adult subjects [32]. In a group of 22 healthy newborn infants spanning time from birth to 6 months, Mrowka and others showed age related changes to the coupling direction between respiration and cardiovascular rhythms. Applying principles of phase synchronization to phases derived from the RR series and respiration signal, they quantified the strength of relation between the interacting systems. The directionality of coupling was deduced and showed an evolution from bi-directional within a few days of birth to the uni-directional coupling from respiration to heart rhythm at 6 months of age [33].

More recently, Lucchini et. al. [30] extended this idea to study the effect of gestational age on the phase coupling and directionality of cardiorespiratory interactions in late premature and full-term infants. They analyzed RR time series derived from the ECG signal using the Pan Tompkins algorithm and respiration signal recorded simultaneously in 273 newborns with gestational ages (GA) ranging from 35 to 40 weeks. Instantaneous phases were estimated using the Poincare method and Hilbert transform respectively from the RR and respiration signals. They quantified the strength of interaction with the synchronization index, which reliably estimate synchronization at a particular locking ratio n:m, where n and m are integers. Using the Evolution Map Approach (EMA), the directionality index between the signals was also determined. It was observed that the time spent in specific (n:m) synchronized states did not change with gestational age while the directionality indices in both sleep states exhibited GA-related shift towards a stronger driving influence of respiration on HR. The major conclusion of this paper was that infants born even 1-4 weeks early showed irregular cardio-respiratory characteristics with respect to full-term. This suggests a crucial role for last weeks of pregnancy

in the maturation of the interaction between the cardiovascular and the respiratory systems. Their proposed cardiorespiratory coupling measures may provide a tool to assess maturity of cardiorespiratory regulation, thus serving as a potential biomarker for risk stratification of babies with respect to potential life-threatening apneic events or Sudden Infant Death Syndrome (SIDS).

A spectral analysis approach to studying cardio-respiratory interactions in preterm babies was adopted by Indic and colleagues [31] who used bivariate autoregressive modeling and surrogate data analysis. They studied signals from 11 preterm infants recorded during an experimental protocol designed to assess the aftereffects of mild vibrotactile stimulation in preterm infants. The electrocardiogram signals were sampled at a rate of 200 Hz while abdominal respiratory movements were sampled at a rate of 100 Hz using a respiratory Inductance plethysmograph. The R-waves were identified by employing a derivative and threshold algorithm and to get a better recognition of the signals, they used a fourth order band-pass zero-phase Butter-worth filter. The RR series then interpolated and re-sampled at 3 Hz with their corresponding respiratory signals.

Standard time domain measures were estimated first. Frequency domain measures were determined considering the RR and respiration as output variables of a multivariate autoregressive model. The coefficients of the model were calculated by solving the extended Yule-Walker equations and auto-spectra. The gain and coherence were obtained in the frequency domain from the calculated coefficients. This approach ultimately gave a measure of linear interdependence between RR and respiration series along the range of frequencies of interest. The estimated measures were validated by a surrogate analysis to rule out the possibility of obtaining these values just by chance. The multivariate assessment unveiled greater coherence in the frequency range related with eupneic breathing in comparison to the other ranges. Their analyses confirmed the models backing their approach, and the results indicated the presence of cardiorespiratory coupling in early stages of maturity [6].

Real wavelet Biphase (RWB), is a newly proposed method to detect quadratic phase coupling (QPC) between the cardiac and respiratory systems especially to assess alternations of nonlinear cardiorespiratory interactions related to ANS dysfunction and physiological regulation

of HRV in cardiovascular diseases. [34]. A simulation study tested the reliability of the method in QPC identification even when there were delays between interacting oscillations. These were then used to study cardiorespiratory couplings in 17 healthy young subjects during a tilt-table test. The application of this method in the context of pre-term infant research is yet to be explored.

Joshi, Kommers and others studied cardiorespiratory coupling in 20 preterm infants to help improve caregiving by tracking of maturational changes and subclinical disease signatures [35]. The RR series and chest impedance signal, post-processed to remove cardiac component and retain only respiration were analyzed using methods of PRSA and BPRSA, which detected and quantified quasi-periodic oscillations masked by the nonstationarities in composite signals, artifacts and noise. These methods together provided information on the strength and direction of coupling between the two interacting oscillatory signals. By selectively analyzing coupling from accelerations and decelerations in heart rate to respiratory oscillations and coupling from peaks and troughs of respiration to changes in heart rate using the BPRSA method they established that preterm infants exhibited cardiorespiratory coupling, and this coupling was nonsymmetric with regard to the direction of coupling.

An information theory approach, the lagged transfer entropy was applied by Luccchini et al. to study the cardiorespiratory information transfer mechanisms in infants as a function of gestational age (GA). On the same data set described in [30], these authors carried out a detailed pre-processing step to minimize the effect of signal nonstationarities on the computed entropy measure. Their study showed a fast, quickly decaying information transfer from Respiration to RR and a slower, more stable transfer from RR to respiration. They suggested that their results might reflect that information transfer directionalities are driven by different autonomic branches of the ANS. They also observed significant decrease of information flow in late preterm infants with respect to RSA component in quiet sleep. These methods can be applied to assess the cardiorespiratory interaction which is an important marker of health and can provide risk stratification in the high-risk population of preterm infants [36]

2.2 POINT PROCESS MODELS

In this thesis, a point process model (PPM) is employed to analyze the cardio-respiratory variables in preterm infants. This method is a statistical representation of a set of mathematical points randomly distributed in a mathematical space such the Cartesian plane and has found application in a wide range of discipline such as economics, astronomy and others. For the rest of this chapter, we discuss previous research focused on the use of the point process model analysis of data.

A bivariate point process investigation of heart rate and respiration was conducted by Gee and co. [37] to improve the estimation of heart rate in premature babies. Readings were taken by randomly selecting 10 preterm infants with mean post conceptual age of 31.14 weeks, average weight of 1468grams, and breathing room air. The ECG signals were collected for approximately 20-70 hours at a rate of 500Hz. The respiration signal was recorded at 50Hz by a respiratory inductance plethysmography during abdominal inspiration and exhalation movements. The study analyzed sections of the data with normal heart rates and clinical bradycardias from which 30 severe bradycardias were randomly selected. They analyzed cardiorespiratory interactions during the 3-minute window just before the occurrence of bradycardia events. By including respiration as a state variable, they enhanced the estimation of heart rate by improving the approximation precision by a mean of 11% over bradycardia severity and lessened the maximum error by 8%. The study also reported that cardio-respiratory coherence was more significant in the low frequency range just before the occurrence of severe bradycardia. This supported the hypothesis that including respiratory signal information could enhance models of heart rate dynamics while finding relevant features for predicting bradycardia [9].

Barbieri and co. [10] used time-variant bivariate spectral analysis for continuous quantification of respiratory and baroreflex control of heart rate. Despite the significant progress made in developing signal processing methods, a precise and continuous quantitative assessment of the cardiovascular system is yet to be established. The models in this paper, considered the closed-loop style of the interactivity between system inputs and outputs. Bi-variate autoregressive modeling of the interdependence between arterial blood pressure (ABP), heart rate and respiration

were carried out over low(LF) and high(HF) frequency ranges which were further widened. Cross variables of LF and HF gain for ABP-HR, coherent power and RSA gain were calculated. Similar outcomes were attained using a previous batch implementation algorithm, but the time-varying approach provided continuous parameters that made monitoring changes to circulatory control possible [38].

A point-process time-frequency assessment of RSA under altered respiration dynamics was undertaken by Kodituwakku and co. [10]. An algorithm to quantify instantaneous RPA during heartbeat intervals and respiratory recording was proposed in this study and applied to meditative states and contrasted with control resting conditions. An inverse gaussian point process modeled pulse intervals (PI) while a bivariate regression modeled instantaneous PI incorporating both past PI and respiration values at the beats. A point process maximum likelihood algorithm estimated the model parameters, and instantaneous RSA was determined by frequency domain transfer function approach. Kolmogorov-Smirnov (KS) goodness-of-fit analysis were employed to validate the models, as well as for independence tests. The algorithm tracked well the cardiorespiratory interaction changes occurring in meditation while not observed in the control state.

CHAPTER 3

METHODS

This chapter presents the data employed along with the methods implemented to detect the time varying nonstationary nature of cardiorespiratory interactions in preterm infants. The immaturity of the cardiorespiratory system results in weak interactions between the cardiac and respiratory systems. Unlike in adults where the interactions are significant and in the direction of respiration to cardiac, in preterm infants the interactions are bi-directional in nature. In addition, it is difficult to detect such interactions during life threatening events in preterm infants using traditional approaches, as apnea can results in lack of information flowing from respiration to cardiac system. To overcome the limitations, a point process model of peak events of ECG signal along with the respiration as covariates was implemented to capture the instantaneous bi-directional interactions between cardiac and respiratory system. Machine learning approaches were employed to study the significant differences in the features during different life threatening events (apnea, bradycardia and apnea-bradycardia) as well as in the absence of adverse events.

3.1 DESCRIPTION OF PRETERM INFANT DATA

The preterm infant data downloaded from Preterm Infant Cardio-Respiratory Signals (PICS) database of Physionet (https://physionet.org/content/picsdb/1.0.0/) were employed in this work. Physionet, a ***Research Resource for Complex Physiologic Signals***, established in September 1999, is a unique national resource originally sponsored by the National Center for Research Resources (NCRR), and is subsequently funded

The overall mission of this resource is to promote, catalyze and perform basic-to-bedside research in complex biomedical systems by:

1. Making physiologic data available in open, Internet accessible, archives;
2. Providing open source software for the analysis of physiologic data;
3. Creating a multidisciplinary forum to facilitate the discovery of “hidden information” in complex physiologic signals.

The original data, used in this project, were collected from ten infants at the Neonatal Intensive Care Units of the University of Massachusetts Memorial Healthcare [39] as part of a larger study to understand the instability of breathing in preterm infants and develop technologies to provide interventions to reduce the life threatening events [40]. The description of the data provided in the database is summarized below.

Ten preterm infants with a post-conceptional age of 29 3/7 to 34 2/7 weeks (mean: 31 1/7 weeks) and study weights of 843 to 2100 grams (mean: 1468 grams) participated in this study. The ECG signal was collected using a single channel with a 3-lead electrode system with a sampling rate of 500 Hz (when available) from bedside patient monitors (Intellivue MP70, Philips Medical Systems) for ~20-70 hours per infant. In the absence of an ECG channel, a compound ECG signal was as an integrated signal of the three ECG lead channels at a frequency of 250Hz. Thus, ECG recordings were available at 500Hz for all infants except for Infant 1 and Infant 5, both at 250Hz. The respiratory signals were collected using external inductance bands placed around the chest wall and abdomen of the preterm infants and were recorded at a sampling rate of 50 Hz using a VueLoggerTM , a data acquisition system developed at the Wyss Institute, Harvard University [41]. All infants had respiratory recordings at 50Hz except Infant 1 whose signal was sampled at 500Hz. Physionet stores the data in a specific format called WaveForm DataBase (WFDB) which enables easy download and processing of the data [42]. The WFDB toolbox can be incorporated into MATLAB for data analysis.

To understand cardiorespiratory interactions, it is important to obtain the peak of ECG called R-event and peak-to-peak intervals called RR events along with the corresponding respiration values at the time of R event. The database provided the time of R events along with bradycardia onset. The bradycardia onset was defined as the time at which the heart rate ($HR = 60/RR$) goes below 100bpm and remains below this level for at least 1.2 sec.

The apnea was defined as the pause in breathing for at least 10 seconds, and these pauses were derived from the peak-to-peak duration of respiratory signals. From the signal, apnea and bradycardia events were noted. Thus there were 829 life threatening events (388 apnea only events, 236 bradycardia only events and 205 apnea as well as bradycardia occurring simultaneously) from

10 infants The given R events along with the respiration were further divided into 20-minute segments by considering intervals 10 minutes before and after of each of the life threatening events. Cardio-respiratory interactions were estimated using a point process model of R events with respiration as covariates. The instability of the system was accounted for by instantaneously estimating the mean as well as variance of RR and HR. The bi-directional interactions were determined by embedding a bivariate autoregressive model on the point process algorithm to give instantaneous estimates of bi-directional coherence. The details of the algorithm are presented below.

3.2 POINT PROCESS ALGORITHM WITH EMBEDDED BIVARIATE MODEL

A point process is a random process in which events occur at a specific discrete moment in continuous time [43]. The underlying probability distribution of these random events need not always be Gaussian but can be a non-Gaussian distribution. Many traditional deterministic signal processing algorithms require uniformly sampled data and stochastic signal processing algorithms assume the inherent randomness in such uniformly sampled data as Gaussian. Point process algorithms were designed for non-uniform point events that follow non-Gaussian distributions [44].

Brown and colleagues pioneered the point process algorithms to understand the neural spike trains from the brain. They formulated a paradigm for decoding information in neural spikes which resulted in a state space model of the underlying system generating the point process [45, 46]. Subsequently, using the point process framework, Barbieri and colleague [47, 48] developed an algorithm for the assessment of cardiac dynamics in adults with the underlying distribution of R events as the inverse Gaussian. They also incorporated the respiration as covariates in the model to study the interactions between cardiac and respiratory system [49].

Since preterm infants have higher heart (HR) and respiration rates, the point process modeling framework developed for adults was modified to include the higher rates. In addition, preterm infants have instability in both heart rate and respiration signal. The parameters of the underlying model describing the interactions were tuned to reflect these instabilities. Furthermore, RR events of preterm infants were shown to have a lognormal distribution [37, 39, 50] and this distribution

was incorporated in the modeling framework. The accuracy of the model was determined using the Kolmogorov-Smirnov (KS) statistics with the time rescaling theorem [51].

Thus, given a specific R peak at u_k, the waiting time until the next event u_{k+1} was assumed to follow a lognormal distribution described as

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

The instantaneous variation of μ can be represented as

$$\mu(t) = a_0(t) + \sum_{k=1}^{p} a_k(t)\, RR_{t-k} + \sum_{k=1}^{q} b_k(t) RP_{t-k} \quad (2)$$

where a_k and $b_k$are the parameters of the model. Where a= $\{a_0, \ldots., a_k, \ldots, a_p\}$ represents the estimation vector for the RR series, and RR_{t-k} is the previous RR events b=$\{b_0, \ldots., b_k \ldots b_q\}$ represents the estimation vector for the respiration, whereas RP_{t-k} denotes previous respiration signal at the same time as RR_{t-k}. The parameters as well as σ^2 were estimated using the local maximum likelihood approach. The $\mu(t)$ estimated in Eq. (1) determines the instantaneous nonstationary dynamics of RR.

The transfer function from RP to RR gives the continuous RSA gain as,

$$RSA(\omega,t) = \frac{\sum_{k=1}^{q} b_k(t) z^{-k}}{1-\sum_{k=1}^{p} a_k(t) z^{-k}} \quad (3)$$

This RSA gain was computed at the frequency where there was maximum coherence between RR and RP. This was achieved by employing a bivariate autoregressive model represented as,

$$X(n) = -\sum_{k=1}^{M} A(k) \cdot X(n-k) + w(n) \quad (4)$$

n= 1,2,3,… N.

M is the order and N is the total number of data points.

X(n) = [RR(n) RP(n)], $A(k) = \begin{bmatrix} a_{11}(k) & a_{12}(k) \\ a_{21}(k) & a_{22}(k) \end{bmatrix}$

and $[\, w(n) = \, [w_{RR}(n) \quad w_{RP}(n)]$.

w(n) denotes white noise and a_{ij} the autoregressive coefficients. These coefficients were determined using a recursive algorithm and the spectral components were in turn estimated from these coefficients.

In the frequency domain, the model takes the form,

$$\begin{pmatrix} RR(f) \\ RP(f) \end{pmatrix} = \begin{pmatrix} A_{11}(f) & A_{12}(f) \\ A_{21}(f) & A_{22}(f) \end{pmatrix} \cdot \begin{pmatrix} RR(f) \\ RP(f) \end{pmatrix} + \begin{pmatrix} W_{RR}(f) \\ W_{RP}(f) \end{pmatrix} \tag{5}$$

Where $A_{ij}(f) = \sum_{k=1}^{M} a_{ij}(k) e^{-12}$ with i, j = 1,2 and l=$\sqrt{-1}$ which is a complex quantity. Eq. (4) can then be expressed as,

$$\begin{pmatrix} RR(f) \\ RP(f) \end{pmatrix} = \begin{pmatrix} H_{11}(f) & H_{12}(f) \\ H_{21}(f) & H_{22}(f) \end{pmatrix} \cdot \begin{pmatrix} W_{RR}(f) \\ W_{RP}(f) \end{pmatrix} \tag{6}$$

where

$$H_{11}(f) = \frac{1 - A_{22}(f)}{\big(1 - A_{11}(f)\big)\big(1 - A_{22}(f)\big) - A_{21}(f)A_{12}(f)}$$

$$H_{12}(f) = \frac{1 - A_{12}(f)}{\big(1 - A_{11}(f)\big)\big(1 - A_{22}(f)\big) - A_{21}(f)A_{12}(f)}$$

$$H_{21}(f) = \frac{1 - A_{21}(f)}{\big(1 - A_{11}(f)\big)\big(1 - A_{22}(f)\big) - A_{21}(f)A_{12}(f)}$$

$$H_{22}(f) = \frac{1 - A_{11}(f)}{\big(1 - A_{11}(f)\big)\big(1 - A_{22}(f)\big) - A_{21}(f)A_{12}(f)}$$

The coherence γ^2 at a specific frequency according to the traditional definition is:

$$\gamma^2(f) = \frac{|P_{CROSS}(f)|^2}{P_{RR}(f)P_{RP}(f)} \tag{7}$$

where $P_{RR}(f)$ and $P_{RP}(f)$ are the auto-spectral density functions of RR and RP respectively. $P_{CROSS}(f)$ represents the cross spectral density between RP and RR.

The auto-and cross-spectral density functions were estimated as:

$$\begin{bmatrix} P_{RR}(f) & P_{CROSS}(f) \\ P_{CROSS}(f) & P_{RP}(f) \end{bmatrix} = \begin{bmatrix} |H_{11}|^2\sigma_{RR}^2 + |H_{12}|^2\sigma_{RP}^2 & H_{11}^*H_{21}\sigma_{RR}^2 + H_{12}^*H_{22}\sigma_{RP}^2 \\ H_{21}^*H_{21}\sigma_{RR}^2 + H_{22}^*H_{12}\sigma_{RP}^2 & |H_{21}|^2\sigma_{RR}^2 + |H_{22}|^2\sigma_{RP}^2 \end{bmatrix} \tag{8}$$

Using Eq. (6) the causal coherence was evaluated with the matching loop regarded as zero. Hence in the case of causal coherence of respiration influencing RR ($RP \rightarrow RR$), $H_{21}$is set to zero and termed as $Cohx$. In the opposite case of the causal coherence of RR acting on respiration ($RR \rightarrow RP$), H_{12} was then set as zero and termed as $Cohy$. The traditional coherence evaluated using Eq. (7) is termed as Coh.

Coherence (Coh) were first evaluated over the complete frequency range up to the Nyquist frequency. Then the maximum coherences were calculated in the frequency ranges of interest as outlined in [31].

These were: one Low Frequency 0.01-0.15Hz (LF) range and 3 high frequency ranges – High Frequency-1 0.15-0.45Hz (HF1), High Frequency-2 0.45-0.7Hz (HF2) and High Frequency-3 0.7-1.5Hz (HF3). In general, normal respiration of preterm infants falls in the HF3 range whereas RR fluctuations occur in HF1. These interactions may however occur in the other ranges as well, due to apneic and bradycardic events.

Thus, corresponding to obtained maximum coherence at each of the frequency ranges, RSA gains were estimated as

$$GainLF(t) = |RSA(LF, t)| \quad (9a)$$

$$GainHF1(t) = |RSA(HF1, t)| \quad (9b)$$

$$GainHF2(t) = |RSA(HF2, t)| \quad (9c)$$

$$GainHF3(t) = |RSA(HF3, t)| \quad (9d)$$

Furthermore, to capture the instability of RR and respiration dynamics, four statistical features were estimated in addition to $\mu(t)$ and $\sigma^2(t)$ of RR, as instantaneous mean $M_{RR}(t)$ and instantaneous variance$V_{RR}(t)$ of RR as

$$M_{RR}(t) = e^{\mu(t)+\sigma(t)^2/2} \quad (10a)$$

$$V_{RR}(t) = \left(e^{\sigma(t)^2} - 1\right)e^{2\mu(t)+\sigma(t)^2} \quad (10b)$$

Although HR is the inverse of RR, the instantaneous mean $M_{HR}(t)$ in the point process modeling framework is not the inverse of $M_{RR}(t)$ rather it is a distinct measure obtained by setting $\mu(t) = -\mu(t)$ [52].

The same is applicable for instantaneous variance $V_{HR}(t)$ of heart rate.

Thus

$$M_{HR}(t) = e^{-\mu(t)+\sigma(t)^2/2} \quad (11a)$$

$$V_{HR}(t) = \left(e^{\sigma(t)^2} - 1\right)e^{-2\mu(t)+\sigma(t)^2} \quad (11b)$$

In summary, there were sixteen spectral features that include four traditional coherences, eight bi-directional coherences and four RSA gain measures along with six point process features were employed to understand the interactions as well as instability in cardiorespiratory system in preterm infants during life threatening events.

3.3 MACHINE LEARNING CLASSIFIERS

MATLAB classification Learner app was used to test the binary classification. The test include to compare whether the estimates during an event significantly different from prior or post event and to compare between events, This test was used to determine if any of the 25 supported classification models could accurately classify the data. These models included multiple variants of decision tree, discriminant analysis, logistic regression, naïve Bayes, support vector machine, nearest neighbor, and ensemble classifiers. Since there are sixteen spectral estimates and six point process estimates, traditional statistical models will be difficult to build that can consider with multiple comparisons. In this work, the primary goals are to explore whether the cardiorespiratory synamics during life threatening events differ before or after and to explore whether the cardiorespiratory dynamics differ during different types of life threatening evernts. Hence, the problem becomes a classification problems, in which given different features attributed to a specific class differs from other classes of interest. Machine learning methods are the natural choice of analysis for such classification problems [53]. While the statistical models focuses on assoctaion of features to a desired outcome, the machine learning methods purpose is for classification.

Two types of approaches are used, (i) supervised learning and (ii) unsupervised learning. In supervised learning, the machine is trained with a set of training data and the trained model us used to test the classification of groups. Many of the models in the classification learner app belongs to supervised learning category. Unsupervised learning in general are used for finding clusters where the underlying classes are unknown. In this work, since the features associated with each of the class are known, for example features associated with apnea nad bradycardia, supervised learning algorithms are employed for classification.

The models employed for classifications include: (a) Decision Tress and Rules, in which each features associated with a class are identified and the corresponding decision rules are calculated. (b) Bayseian Classifiers, in which the conditional probabilities of each of the classes are determined (c) k – Nearest Neighbor, in which learning rules are determined based on all the data based on nearest points in the space defined by the feature vector space. (d) Linear Discriminant, in which a discriminat function is estimated that seperates the class and (e) finally

Support Vector Machines, the advanced method to discriminate by using hyperplanes to classify the data.

The Artificial Neural Networks and also Deep Learning Methods, perhaps would have been better choice for differentiating the different types of life threatening events, however for such models the interpretability is very less. The standard approaches described above can provide insights into the the underlying physiological mechnisms and potentially provide intrepretaion of results.

In addition, when dealing with features derived from physiological data that are highly non staitionary and rapidly fluctuating, machine learning approaches are found to be effective in identifying abnormal patterns in the data associated with clinical problems [54]. Many of the features are used not only to classify but also to use as precursors for predicting adverse events. Some of the examples include sepsis and cardiac arrest [55].

CHAPTER 4

RESULTS AND DISCUSSIONS

This chapter describes the results of cardiorespiratory interactions and instability of the system obtained using point process and bivariate models. The first section represents the data parsing performed on the total of 829 life threatening events. These events were further categorized as those in which only apneas occur (388), or those in which only bradycardia events are present (236), or those in which both apnea and bradycardia occur together within 3 minutes of each other (205). This is followed by a presentation of the results from the point process modeling of the bidirectional interactions and the RSA gain at different predefined frequency ranges. Finally, we discuss the implications of each of these findings along with their clinical significance and potential use of the approach for real time assessment of cardiorespiratory interactions during life threatening events in preterm infants.

4.1 DATA PREPROCESSING

The obtained 40-44 hours of physiological data from preterm infants are divided into segments based on each of the life threatening events. The bradycardia onset information obtained from Physionet was tagged on the given physiological data (RR and RP). Respiration peaks were detected using a custom code in MATLAB and peak-to-peak intervals were calculated to identify the apneas, which is defined as the pause in breathing greater than 10 seconds. Each of the apnea onsets thus obtained were also tagged into the physiological data. Using these tags, the events with only apnea, only bradycardia and apnea as well as The apnea-bradycardia events are those events where apneas and bradycardias occur within three minutes apart, irrespective of the order in which they occur. The point process model with bivariate algorithm was applied to all these segments and the time varying results are stored for further analysis.

Figure 1 provides an example of apnea-bradycardia event showing heart rate slowing down to below 100bpm resulting in an increase in RR at that instant followed by apnea. It has to be noted that these infants have many life threatening events in which either apnea or bradycardia appears.

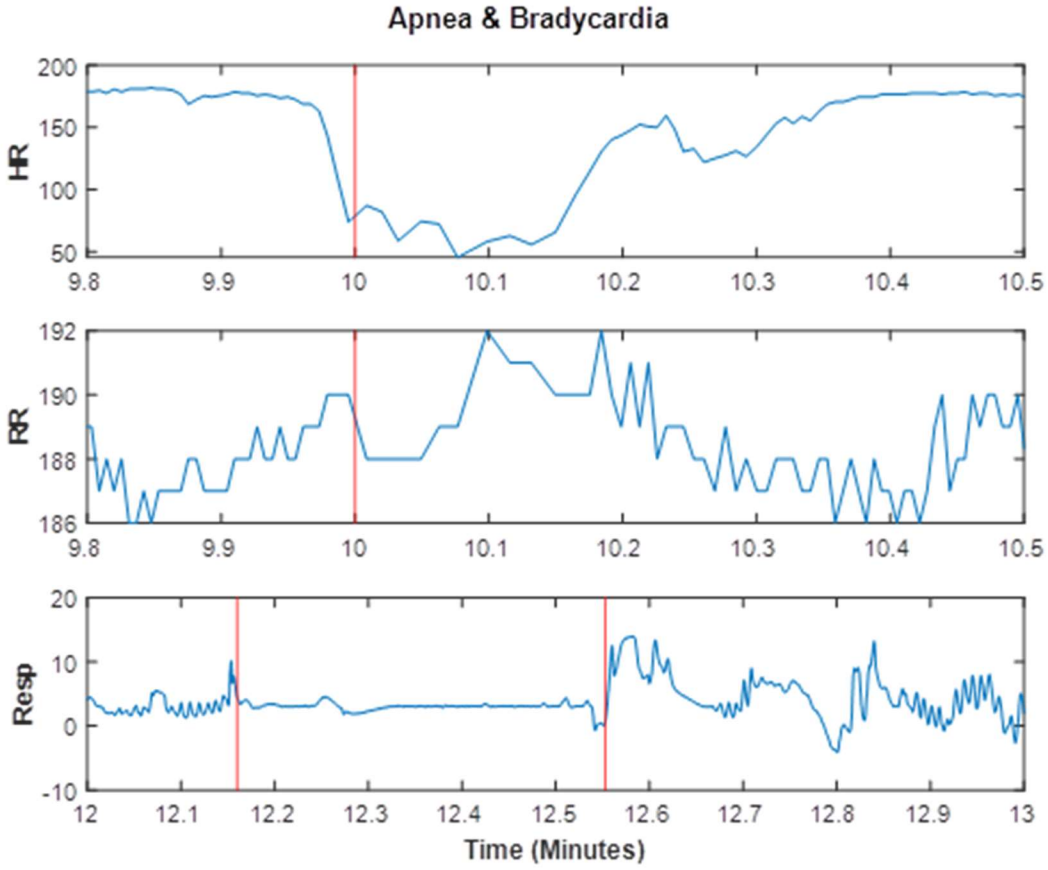


Figure 4. 1: Example of apnea-bradycardia event showing heart rate slowing down below 100 bpm for 10 seconds which is leading to be followed by apnea for 23.4 seconds

4.2 TIME VARYING POINT PROCESS AND SPECTRAL ESTIMATES

The primary estimates that capture the dynamics of cardiorespiratory system in a point process modeling framework are $\mu(t)$ and $\sigma^2(t)$. While $\mu(t)$ tracks the sinus node and autonomic influences, $\sigma^2(t)$ tracks the instability of cardiorespiratory system. The other estimates were derived from these two estimates. Figure 2 provides an example of six point process estimates obtained from a subject during an apnea event. These estimates capture the non-stationary nature of the data. However, it is not obvious from the time varying estimates whether the estimates during an event are significantly different from before or after an event. Similar estimates were obtained during bradycardia and apnea-bradycardia events as shown in Appendix A.

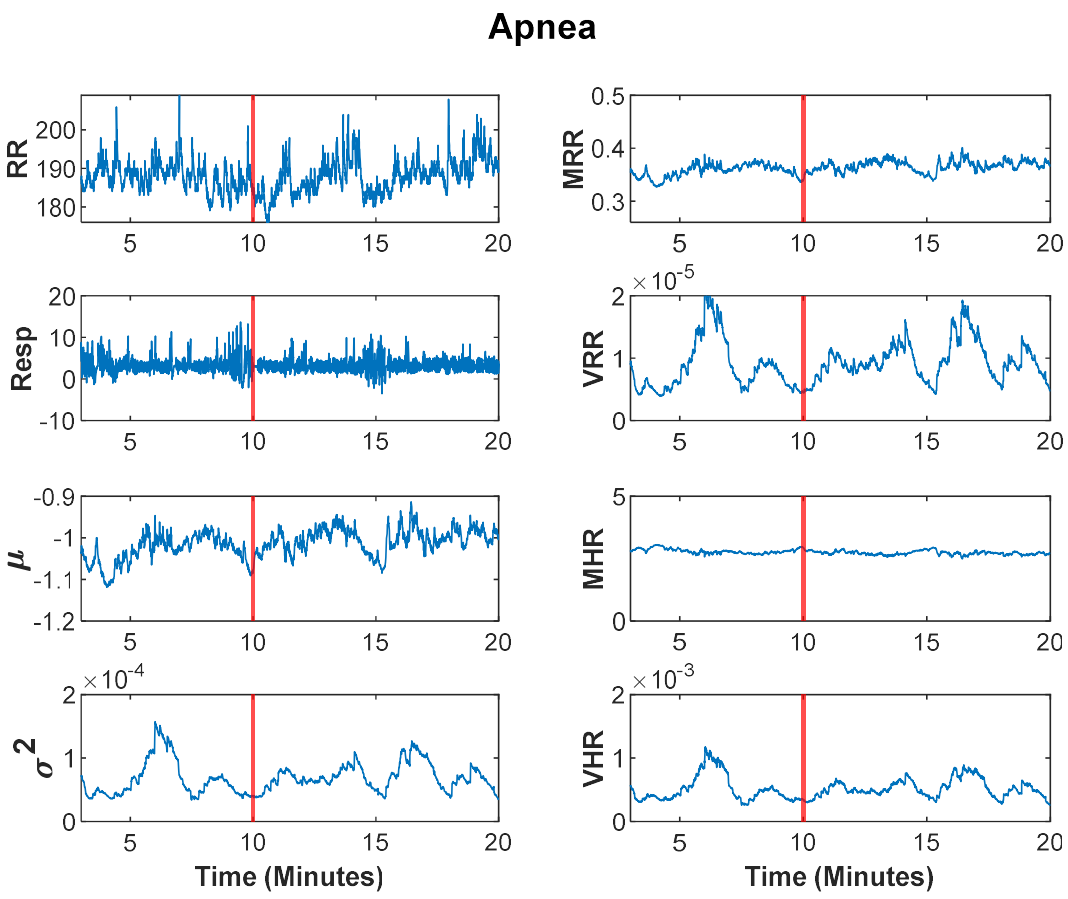


Figure 4. 2: Point Process Estimates during an apnea event. Six point process estimates evaluated ten minutes before and after of an apnea event (marked in red line). This segment has 360 seconds apnea with no bradycardia.

The Kolmogorov-Smirnov plot (***not shown***) were well within the 95% confidence interval of the estimated data of the point process model. Further confirmation is obtained with autocorrelation plot, again was within the 95% confidence interval. The history dependency of 120 seconds along with the regression order of four was sufficient to achieve the results with local maximum likelihood approach. For details see [37].

Time varying estimates of coherences (Figure 3) captures the bi-directional interactions. Traditional coherence at LF (CohLF) resembles interactions from RR to RP (CohyLF) whereas CohHF1 resembles RP to RR interactions at this frequency CohxHF1. Similarly, CohHF2 resembles CohxHF2 and CohHF3 resembles CohyHF3. An example from bradycardia and apnea-bradycardia are presented in Appendix A.

Thus, in the case of systems that exhibit bi-directional interactions, the traditional coherence might reflect one of the interactions that appears to be predominant. It must be noted that such resemblances were not consistent among other segments analyzed. Thus, depending on the immaturity of cardiac and respiratory systems, interactions in one of the directions may dominate reflecting in the traditional coherence. The RSA gain is traditionally defined as the relationship of heart rate to respiration that occurs at the respiratory frequency. However, in the case of preterm infants, RSA gain, although weak, is exhibited in all the frequency ranges with the same order of magnitude (Figure 4). Similar observations in other events are presented in Appendix A.

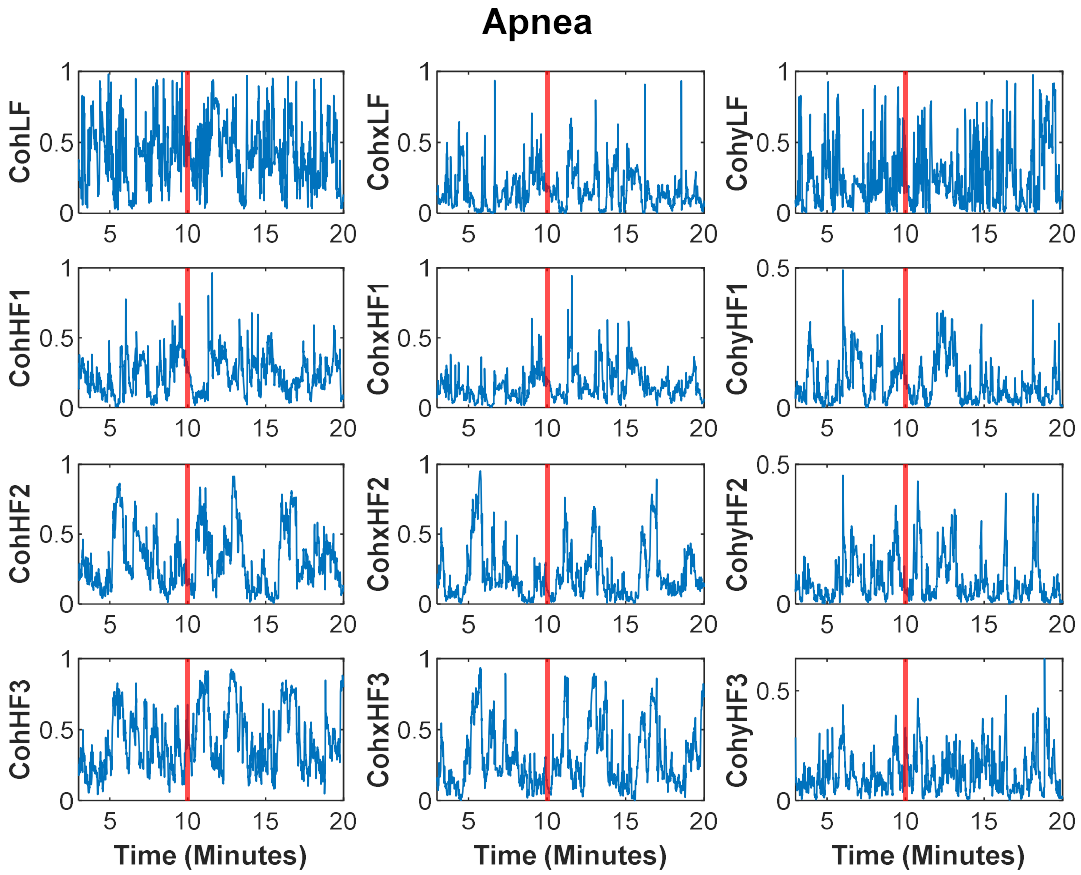


Figure 4. 3: Spectral Estimates during an apnea event. Spectral estimates evaluated ten minutes before and after an apnea event (marked in red line). This segment has 360 seconds apnea with no bradycardia.

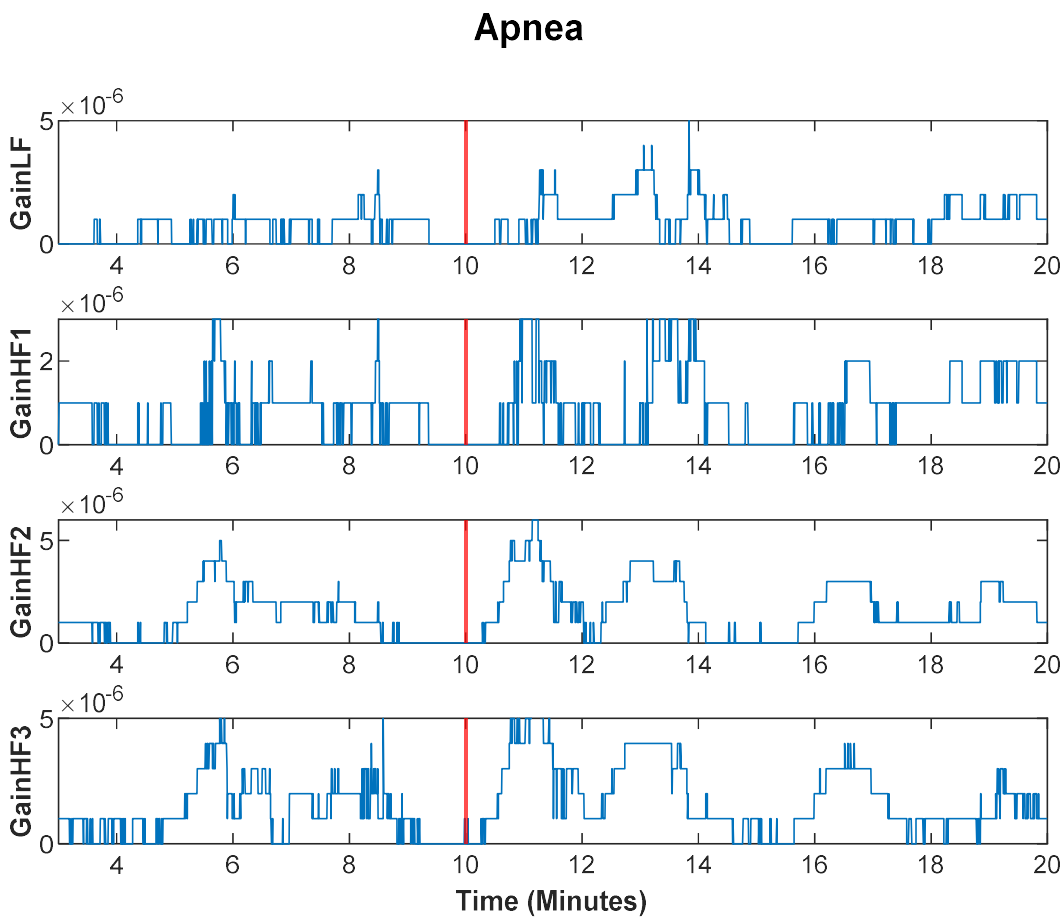


Figure 4. 4: RSA gain during an apnea event. RSA gain evaluated ten minutes before and after an apnea event (marked in red line). This segment has 360 seconds apnea with no bradycardia

4.3 AVERAGE POINT PROCESS AND SPECTRAL ESTIMATES

The point process and spectral estimates were compared between pre-, during and post- segments for the three types of life threatening events. These are shown in Figures 5, 6, and 7. The average of the point process estimates did not reveal much difference between segments from visual inspection of the standard errors, whereas σ^2 shows an apparent increase in all three events. The values during the event were much higher than before and after segments. Bradycardia events had the most difference in σ^2 values. This is apparent in the combined case as well. Interestingly, the post segment values are of higher magnitude than the before event segments in bradycardias and

combined events. While statistical inference tests still need to be done, these findings suggest that the influence of bradycardic events persists in the system even after the event itself has ended. On the other hand, variance of HR measure showed a much higher magnitude during compared to or before segments during bradycardias and combined events. This behavior was absent in apneas, where the event segment again had a slightly higher magnitude than the segments before and after it. The interaction behavior captured by point process estimates in the combined events seem to largely follow the bradycardic pattern and the effect of apnea has only a diminishing effect on the magnitudes of estimates. The behavior seems to mimic that of the bradycardias that occur in the event.

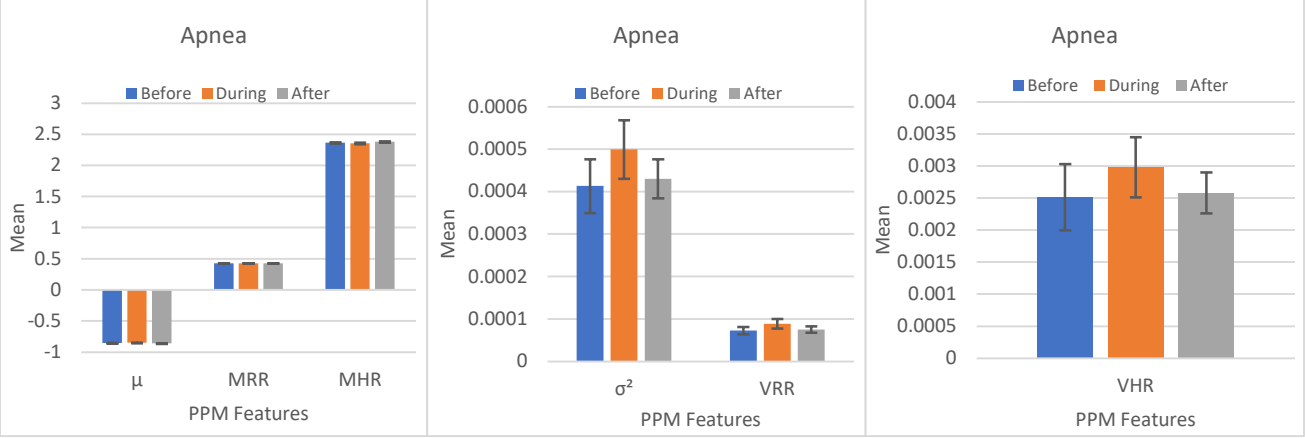


Figure 4. 5: Average of the point process estimates for Apnea only (before, during and after)

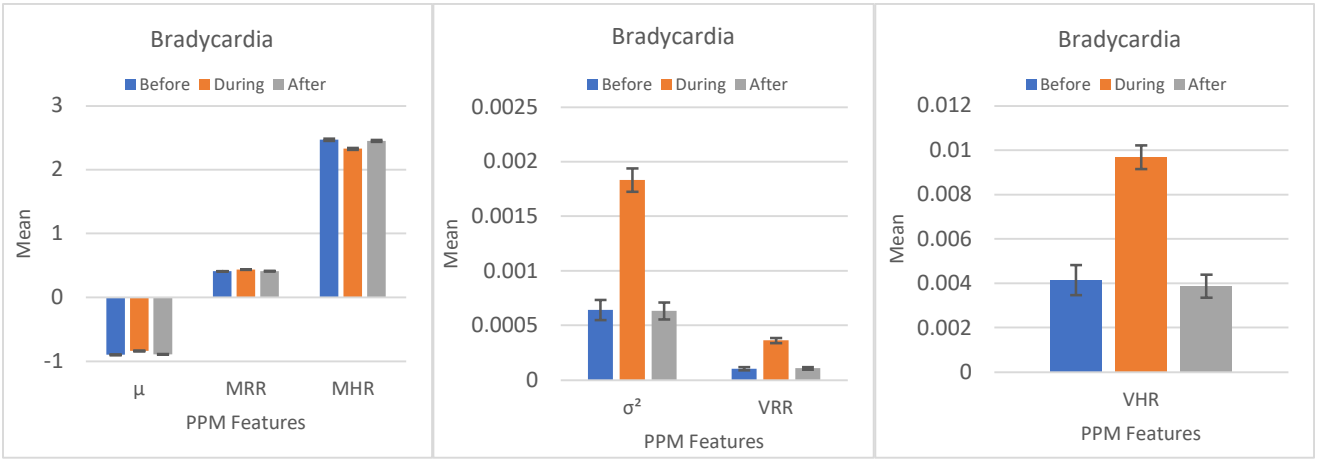


Figure 4. 6: Average of the point process estimates for Bradycardia only (before, during and after)

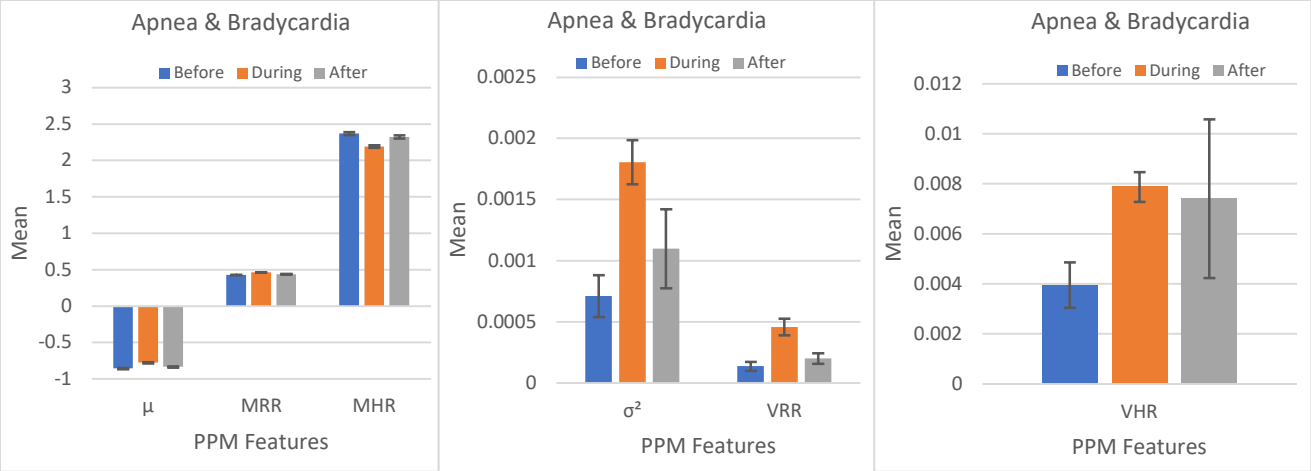


Figure 4. 7: Average of the point process estimates for Apnea & Bradycardia (before, during and after)

Coherence values for the three types of events are given in Figure 8, 9 and 10. For apneas, (Figure 8), Coh and Cohy show similar variations as we move from LF to HF3, with Coh (Cohy)LF showing the highest and Coh(Cohy)HF3 being the next higher in coherence magnitude, than the estimates for the HF1 and HF2 frequency ranges. Cohx exhibits a different behavior. In this case, LF, HF1 and HF2 are of comparable magnitudes while the maximum coherence is in the HF3 range.

In apnea only events, besides a strong coherence between the signals in the LF band, HF3 band also exhibits coherence in both Coh and Cohy. In the case of bradycardias, only Coh estimates had higher magnitudes in both LF and HF3, CohyHF3 was much smaller, compared to the apnea case. This implies that high frequency coherence is not exhibited by either Cohx or Cohy but is seen only in Coh for bradycardias. The most prominent coherence between RR and RP during bradycardias is in the LF band. Interestingly, the coherence during combined apnea-bradycardia events showed a behavior somewhat between these two. The Coh estimates had the same pattern of being highest in LF and then in HF3, but Cohx had more marked coherence in HF3 similar to the apnea alone events. However, Cohy estimates in the high frequency bands were closer to each other as in the bradycardia case.

These estimates had very close magnitudes between the segments (pre-, during and post-) in each band during apnea, thus making differences in coherence between segments non-significant.

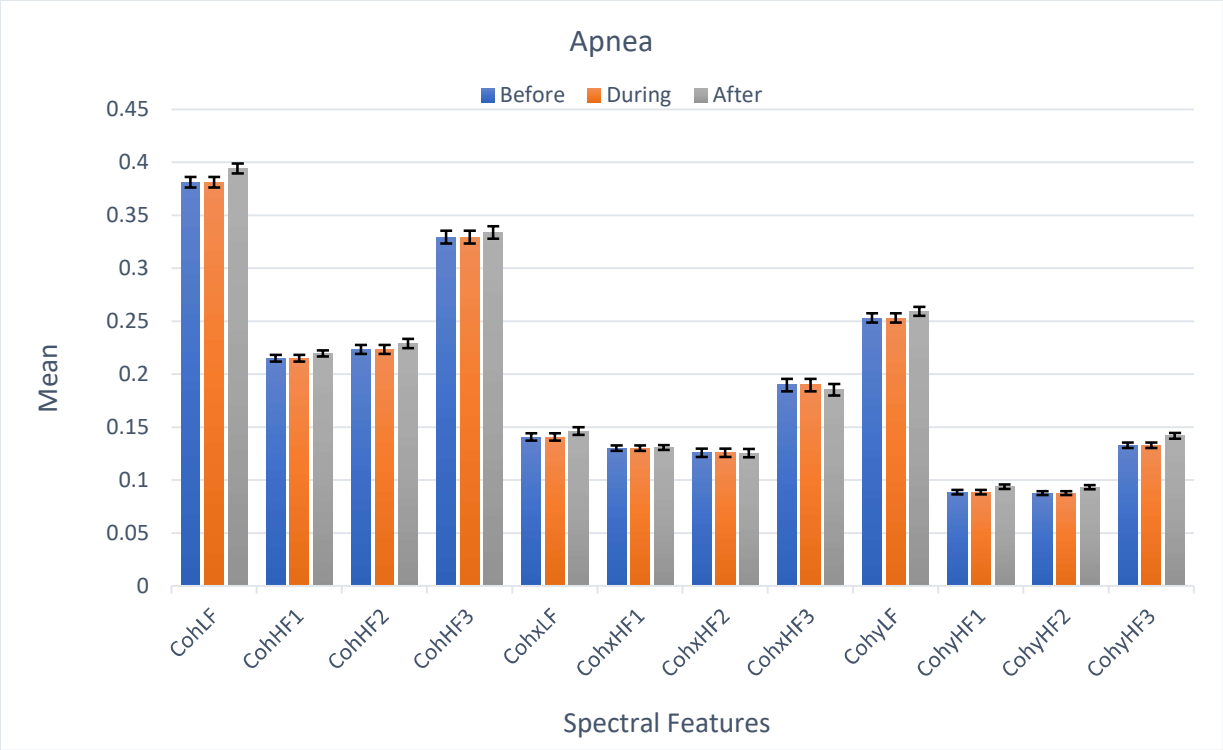


Figure 4. 8: Average Spectral estimates for apnea only (before, during and after)

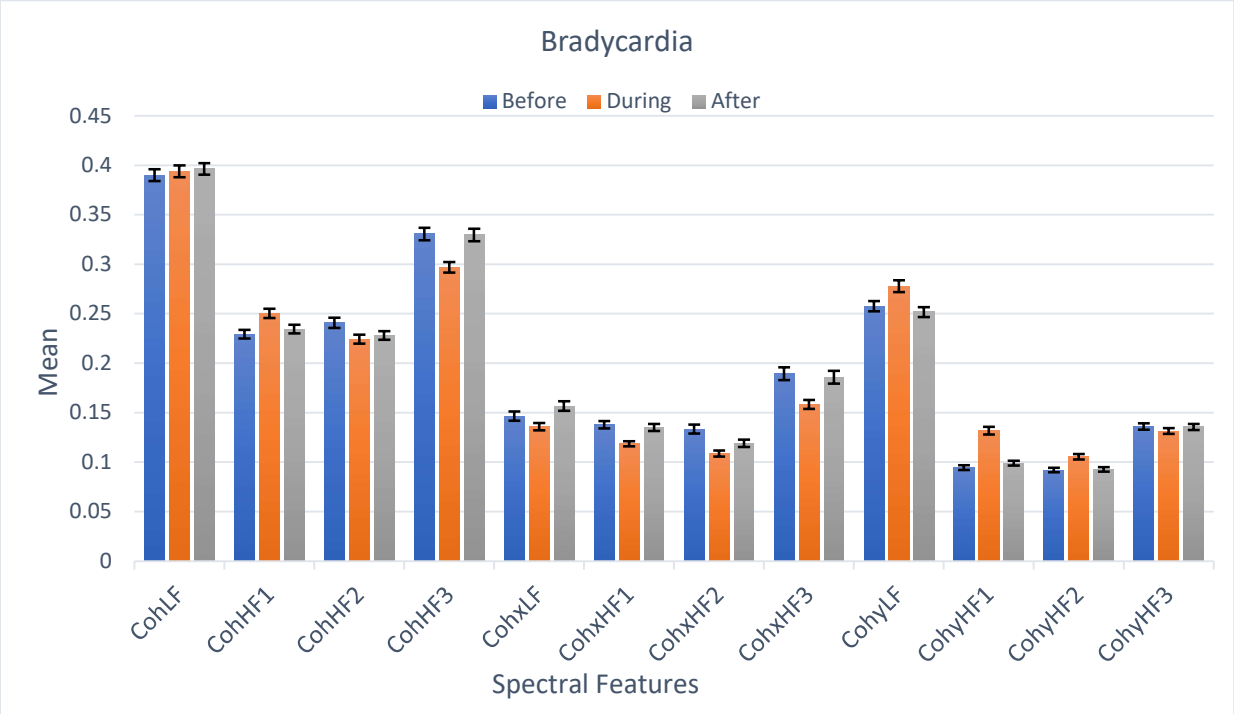


Figure 4. 9: Average Spectral estimates for Bradycardia only (before, during and after)

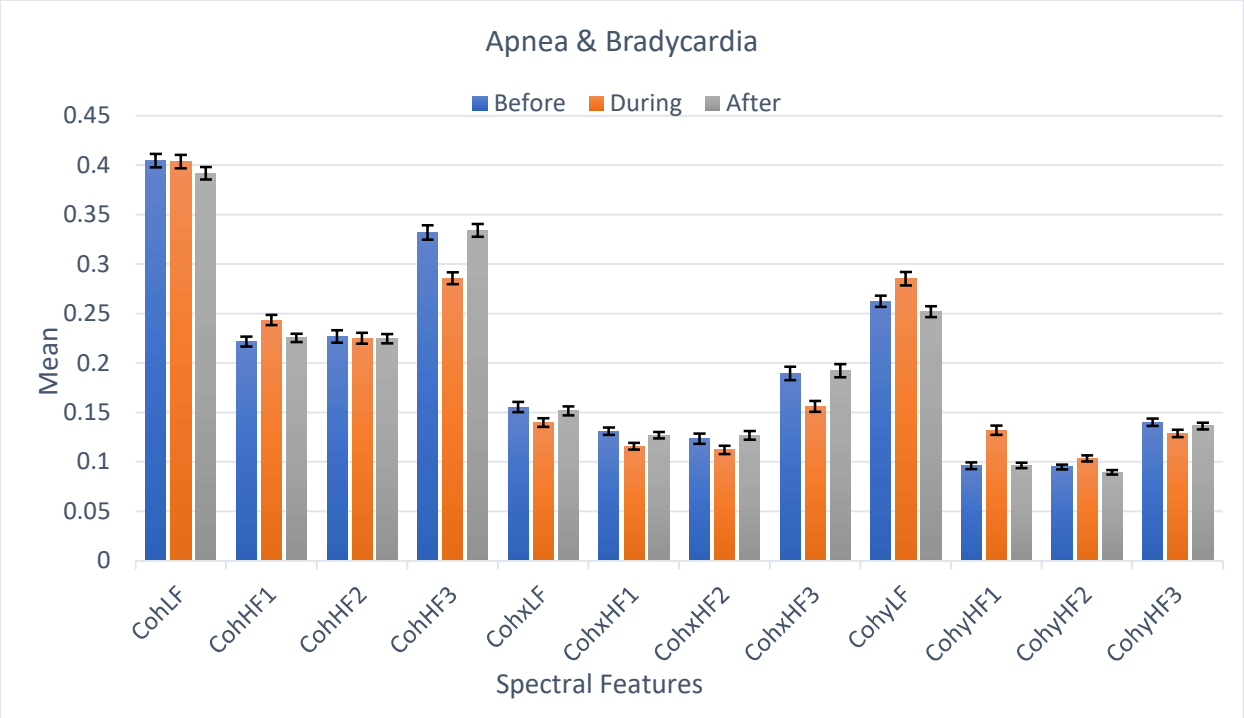
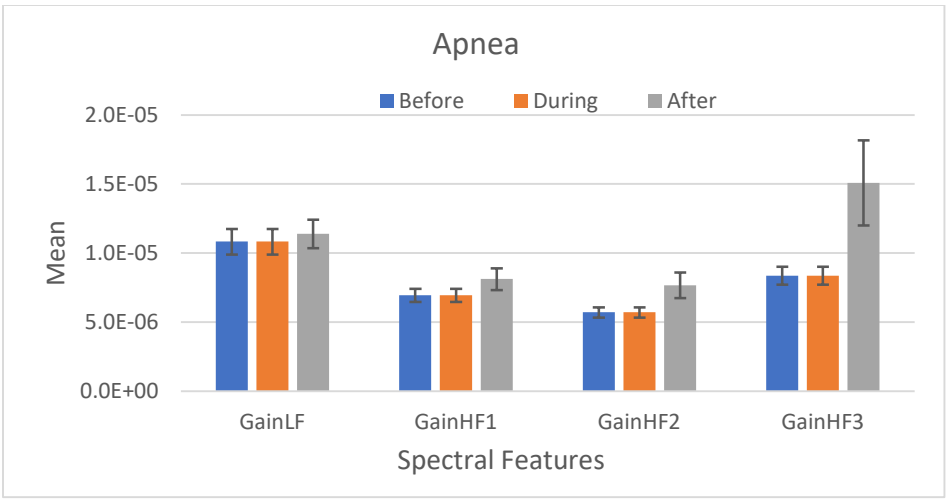
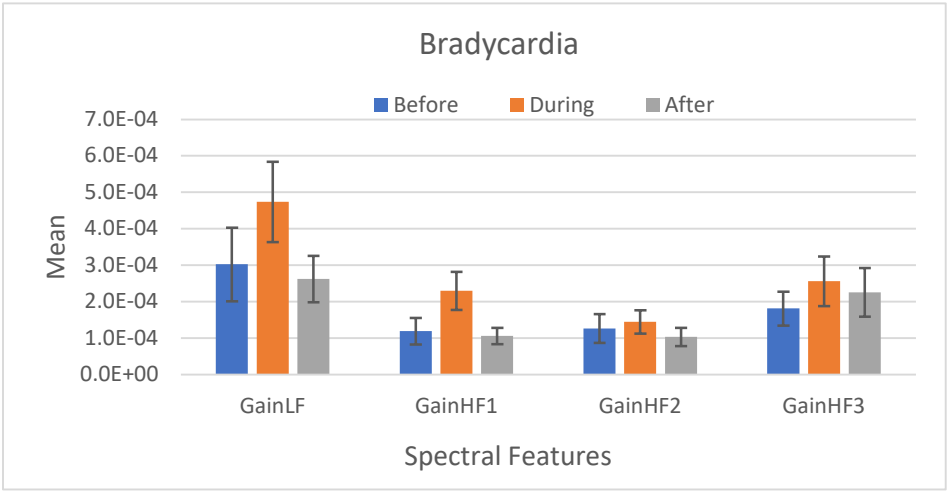


Figure 4. 10: Average Spectral estimates for Apnea and Bradycardia (before, during and after)

The RSA gains are significantly higher during the event compared to before and after during bradycardia and apnea-bradycardia events (Figure 11). This distinct increase is not seen in apneas at all. Increase in RSA gains can be attributed to the decrease in drive from respiration or increase in effort of the cardiac system to overcome the life threatening bradycardia events. In spectral analysis, CohyLF, CohyHF1 and CohyHF3 values, which are the interactions from RR to respiration, are significantly higher suggesting that the increase in gains observed are due to cardiac system struggling to recover from life threatening bradycardia events and not due to the influence of respiration to heart.





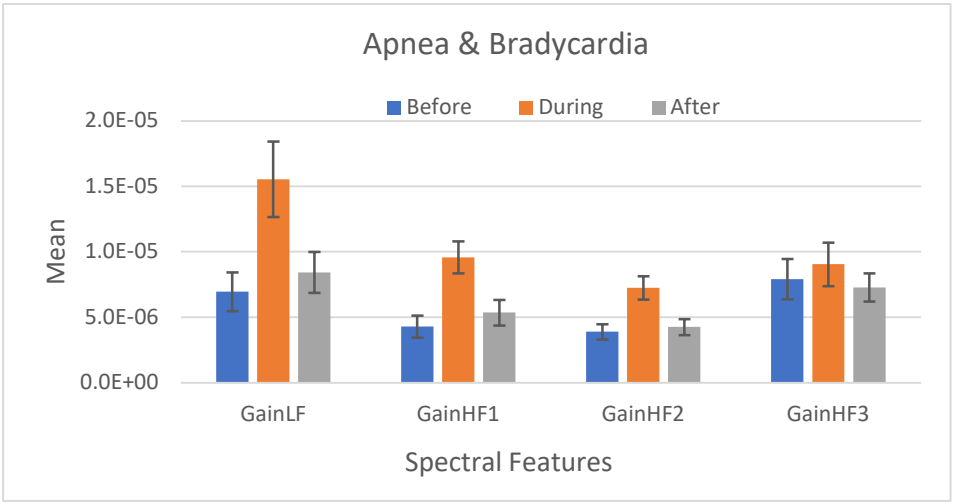


Figure 4. 11: Average RSA gains for Apnea, Bradycardia, Apnea and Bradycardia, respectively (before, during and after event)

We also compared these estimates for the segments during which the events occur (Figure 12 and 13). This analysis clearly shows the similarity between bradycardic and combined apnea-bradycardia events. The estimates values are quite close for these two types of events once again, establishing how a bradycardia event dominates the interactions of cardiac and respiratory systems. The apnea estimates are in comparison lower in magnitude, showing there is much greater disruption to the coherence/interaction strength during an apnea event. This is especially seen for the point process variance and VHR values. Coherence estimates show a slightly different behavior. The combined events and bradycardia only coherence Coh is higher than apneas in LF band. In HF3, apnea coherences, Coh and Cohy are more than the other events B and AB. In the case of RSA gains, B events have much higher values than either A or AB.

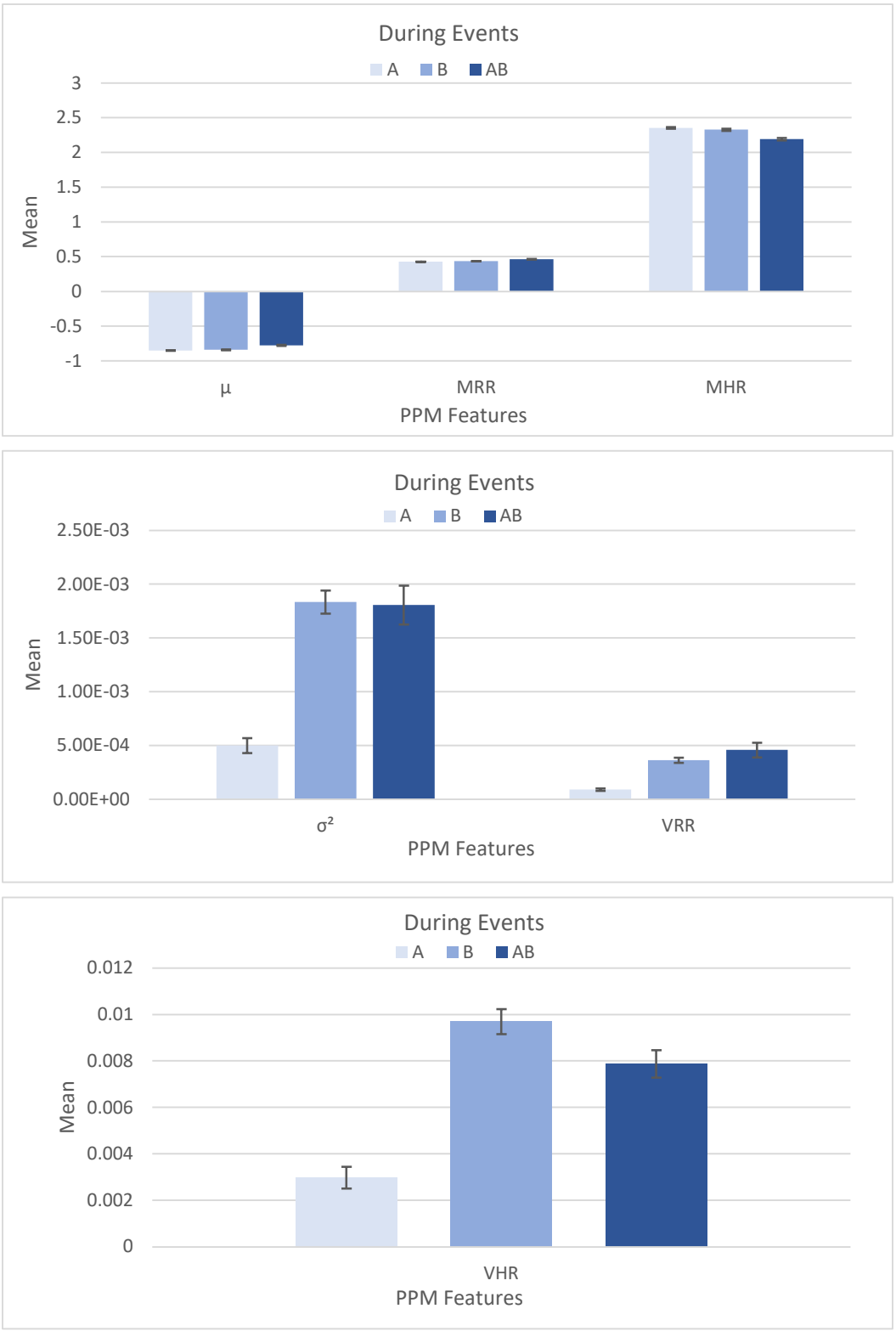


Figure 4. 12: Average point process estimates during event for **A** apnea, **B** bradycardia and **AB** apnea& bradycardia, respectively

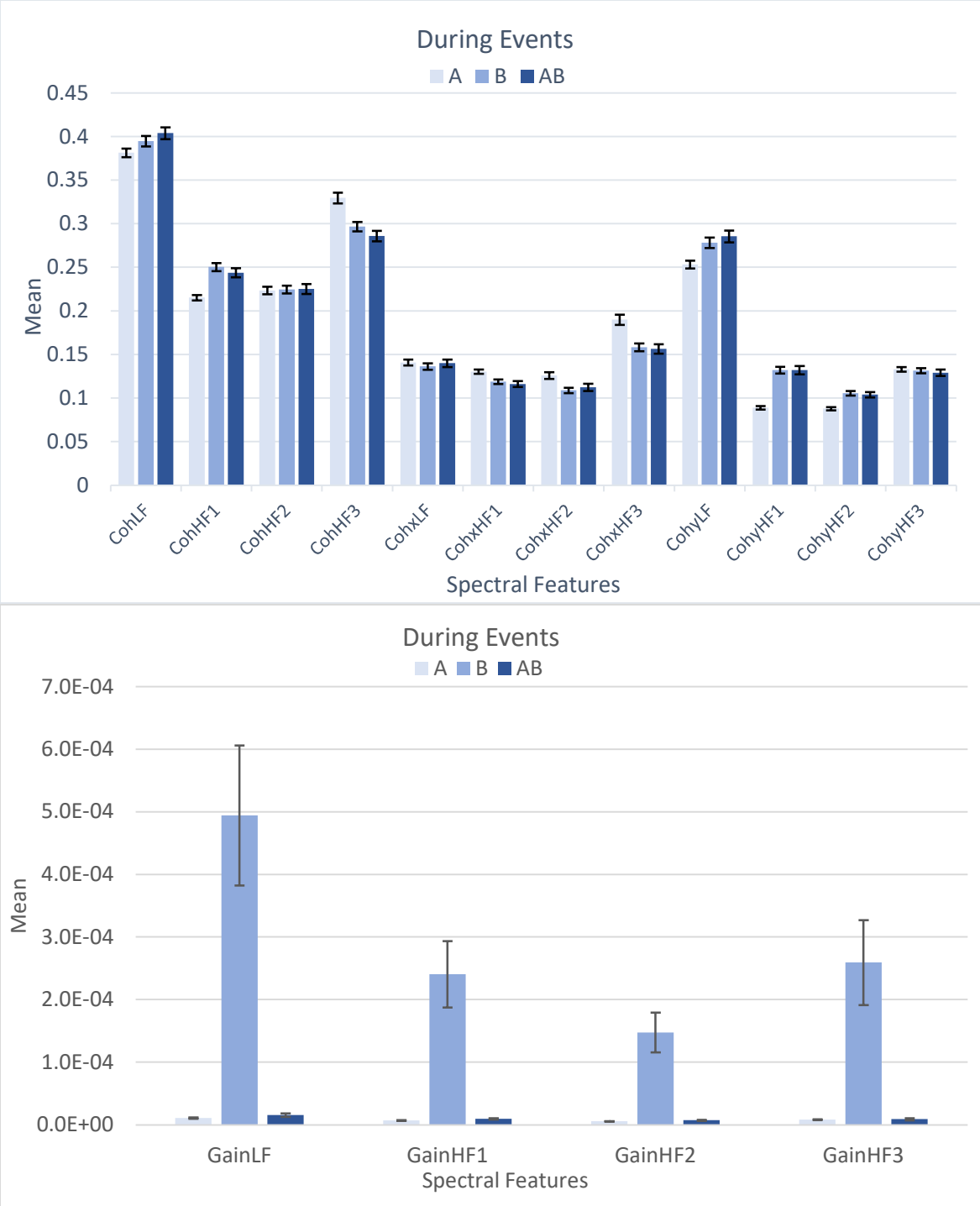


Figure 4. 13: Average Coherence (b) and RSA Gains(c) estimate during event for **A** apnea, **B** bradycardia and **AB** apnea& bradycardia, respectively

4.4 CLASSIFICATION BASED ON MACHINE LEARNING

Point process or spectral measures showed only minimal distinction between segments before or after following the segments with the events themselves. As a way to combine and use their distinguishing ability, machine-learning algorithms with these measures as features were employed to classify the different segments. In order to achieve this, the time varying estimates are divided into five segments each segment of duration three minutes. Thus window #3 has the adverse events and using the average features from these windows several machine learning algorithms were tested to explore whether any of these algorithms can (1) differentiate a life threatening event from a non-life threatening event and (2) differentiate between the type of life threatening events. We tested several machine-learning classifiers, which successfully differentiated segments of life threatening events from segments occurring before the events. Tables 4.1, 4.2 and 4.3 provide the performance of the machine learning models trained by including point process and spectral features, spectral alone and point process alone for the apnea, bradycardia and apnea-bradycardia.

Although the models incorporating all the estimates performs well, point process estimates alone provides a reasonably good performance. The spectral estimates performed poorly compared to other scenarios. Comparing between types of events (Tables 4.4, 4.5 and 4.6), apnea was best differentiated from either bradycardia only and combined apnea-bradycardia events with accuracy over 85% in each case. This suggests that during bradycardia, the overall dynamics is significantly different from an apnea event. The bradycardia event appears to have a dominating effect on the cardiorespiratory system even when apnea occurs along with it. This is perhaps why the classifiers have comparable accuracy in distinguishing apneas from combined bradycardia-apnea segments as those from bradycardias alone.

When estimates from all the events are combined into one class, the machine learning models perform poorly compared to other scenarios (Table 4.7), further confirming that these life-threatening events have differential effects on the cardiorespiratory system.

Table 4.1. Result of machine learning for all PPM and SPE features combined (before vs during the events)

PPM & SPE Features	Accuracy	AUC	Model Type
Apnea (Before vs During)	50.3%	0.50	Tree
Bradycardia (Before vs During)	85.6%	0.92	Ensemble
Apnea & Bradycardia (Before vs During)	81.5%	0.88	Ensemble

Table 4.2. Result of machine learning for SPE features (before vs during the events)

SPE Features	Accuracy	AUC	Model Type
Apnea (Before vs During)	47.3%	0.44	SVM
Bradycardia (Before vs During)	74.6	0.81	Ensemble
Apnea & Bradycardia (Before vs During)	74.9%	0.80	SVM

Table 4.3. Result of machine learning for PPM features (before vs during the events)

PPM Features	Accuracy	AUC	Model Type
Apnea (Before vs During)	54.9%	0.56	KNN
Bradycardia (Before vs During)	82.4%	0.85	Tree
Apnea & Bradycardia (Before vs During)	80.2%	0.84	Tree

Table 4.4. Result of machine learning for all PPM and SPE features combined (during events)

PPM & SPE Features	Accuracy	AUC	Model Type
Apnea vs Bradycardia (During events)	89.3%	0.94	Ensemble
Bradycardia vs (Apnea & Bradycardia) (During events)	64.2%	0.70	Ensemble
Apnea vs (Apnea & Bradycardia) (During events)	85.3%	0.93	Ensemble

Table 4.5. Result of machine learning for SPE features (during events)

SPE Features	Accuracy	AUC	Model Type
Apnea vs Bradycardia (During events)	77.6%	0.83	Ensemble
Bradycardia vs (Apnea & Bradycardia) (During events)	58.3%	0.62	Ensemble
Apnea vs (Apnea & Bradycardia) (During events)	76.2%	0.78	Ensemble

Table 4.6. Result of machine learning for PPM features (during events)

PPM Features	Accuracy	AUC	Model Type
Apnea vs Bradycardia (During events)	82.1%	0.88	SVM
Bradycardia vs (Apnea & Bradycardia) (During events)	58.3%	0.62	Ensemble
Apnea vs (Apnea & Bradycardia) (During events)	80.2%	0.84	Ensemble

Table 4.7. Result of machine learning for combined events (A, B&AB), (before vs during the events)

Combined Events (A, B&AB)	Accuracy	AUC	Model Type
PPM & SPE Features (Before vs During)	66.6%	0.68	Tree
SPE Features (Before vs During)	60.7%	0.64	Linear Discriminant
PPM Features (Before vs During)	66.8%	0.71	SVM

CHAPTER 5

CONCLUSIONS AND LIMITATIONS

A comprehensive analysis of cardiorespiratory interactions during life threatening events in preterm infants is performed using point process and bivariate modeling approaches. The RSA gain estimated at range of frequencies (0.15Hz to 1.5Hz) shows a significant gain at every range in preterm infants, which is quite different from adults where RSA gain observed only at the respiratory frequency (0.2Hz) of adults.

While the literature suggests that the cardiorespiratory interactions are unidirectional with interactions from respiration to cardiac system in adults, in preterm infants although weak, the interactions are bidirectional. The point process framework provided a method to capture the time varying instantaneous estimation of both the gain and the causal coherences. In addition, this framework enabled the estimation of these estimated at wide range of frequencies. The advantage of point process framework is that it can give estimates at any desired time resolution from RR interval of electrocardiogram with respiration as covariates. This capability enables to estimate the gain and the coherences even during the absence of breathing as well as transient destabilization during bradycardia.

The point process model incorporates the underlying probabilistic distribution of RR intervals thereby providing reliable estimates of statistical fluctuations in the data and the autoregressive structure of the estimated mean of the distribution provides the reliable estimate of the deterministic dynamics of the cardiorespiratory system. Thus spectral as well as point process estimates at the fine time resolution helps to classify apnea and bradycardia events.

Contrary to the traditional spectral approaches in which coherence between two signals are estimated without knowing the direction of interactions, the bivariate structure of RR and respiration in a single modeling framework enables to estimate the bidirectional coherence. Furthermore, incorporation of bivariate model on a point process-modeling framework enables to

estimate the bidirectional coherence instantaneously. The bivariate algorithm estimates separately the causal interaction between the respiration and RR.

The *Significance* of this work is that a point process and bivariate regressive modeling framework is applied to detect the bi-directional cardio-respiratory interactions. The algorithm developed could be employed to detect weak interactions from RR and respiration in real time. In addition to the interactions from respiration to RR, the RR to respiration interactions are also obtained, thus, providing additional measures to understand the maturation of preterm infants. In the clinical literature, the term apnea of prematurity [56] is defined as the apnea with pauses greater than 20 seconds and often associated with bradycardia and hypoxia. Thus, the primary focus has always been on apnea, and other life threatening events are considered as the results of apnea.

In this work, it was found that the point process and spectral features associated with bradycardia classifies differentially from apnea with an AUC of 0.88 and the apnea-bradycardia evenst from apnea with an AUC of 0.84. The PPM features by itself classifies with AUC of 0.88 in comparison to spectral features, which has an AUC of 0.83. Interestingly, the features associated with cardiorespiratory interactions before and during apnea were not much different with an AUC of 0.50 whereas for the same scenario the features associated with bradycardia provided an AUC of 0.92 and apnea-bradycardia 0.88. Bradycardia is found to be providing significant impact on cardiorespiratory interactions than apnea.

The *Broader Impact* is *t*he proposed framework could be adapted and employed in the analysis of other systems even in adults. The method of analysis employed in this framework could be used to understand interactions between any physiological systems.

The *Intellectual Merits* of this study is that it integrates advanced signal processing methods to solve an important clinical issue. A better understanding of cardio-respiratory interactions gives a better understanding of the physiology of cardiovascular system in preterm infants. The proposed method can be used as a clinical tool in the NICU to assist physicians to make a better judgment on the neurodevelopment of preterm infants.

The *Limitations* of the proposed method is that the bivariate model used is applicable to stationary and quasi-stationary data. This assumption needs further validation. A more advanced wavelet based bi-variate model rather than the currently used autoregressive model can provide better estimation of coherence for nonlinear nonstationary segments of data. An additional limitation is that hypoxia episodes, which is also a life threatening events in preterm infants not considered. The oxygen desaturation signals were not available in the database. Once available, this signal become available, it can also be incorporated in the point process-modeling framework as one of the covariates similar to respiration. The dataset is small with only 10 preterm infants and further validation with more preterm infants can confirm the findings. In addition, it can also provide precursors of life threatening events that can be employed in advanced machine learning approaches to predict the life threatening events in preterm infants.

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Appendix A PPM Results

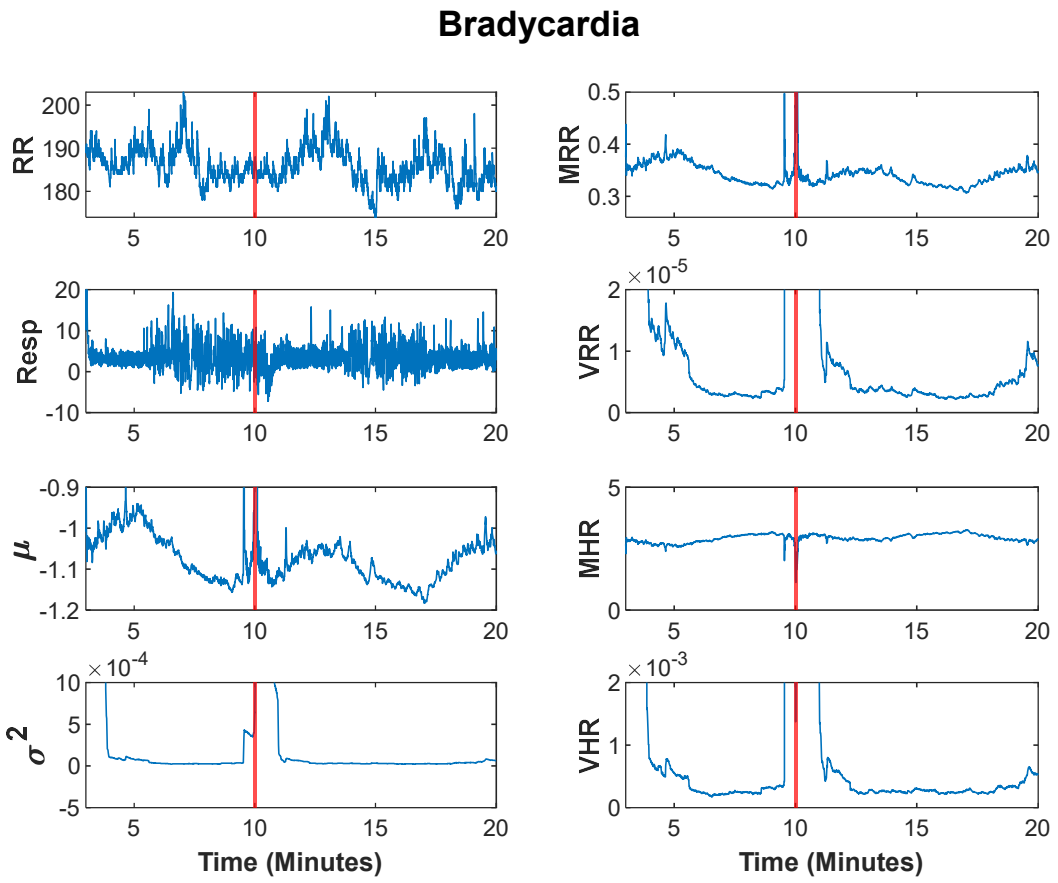

Figure A 1: Point Process Estimates during a bradycardia event. Six point process estimates evaluated ten minutes before and after of a bradycardia event (marked in red line). This segment has 12 seconds bradycardia with no apnea

Appendix A (continue)

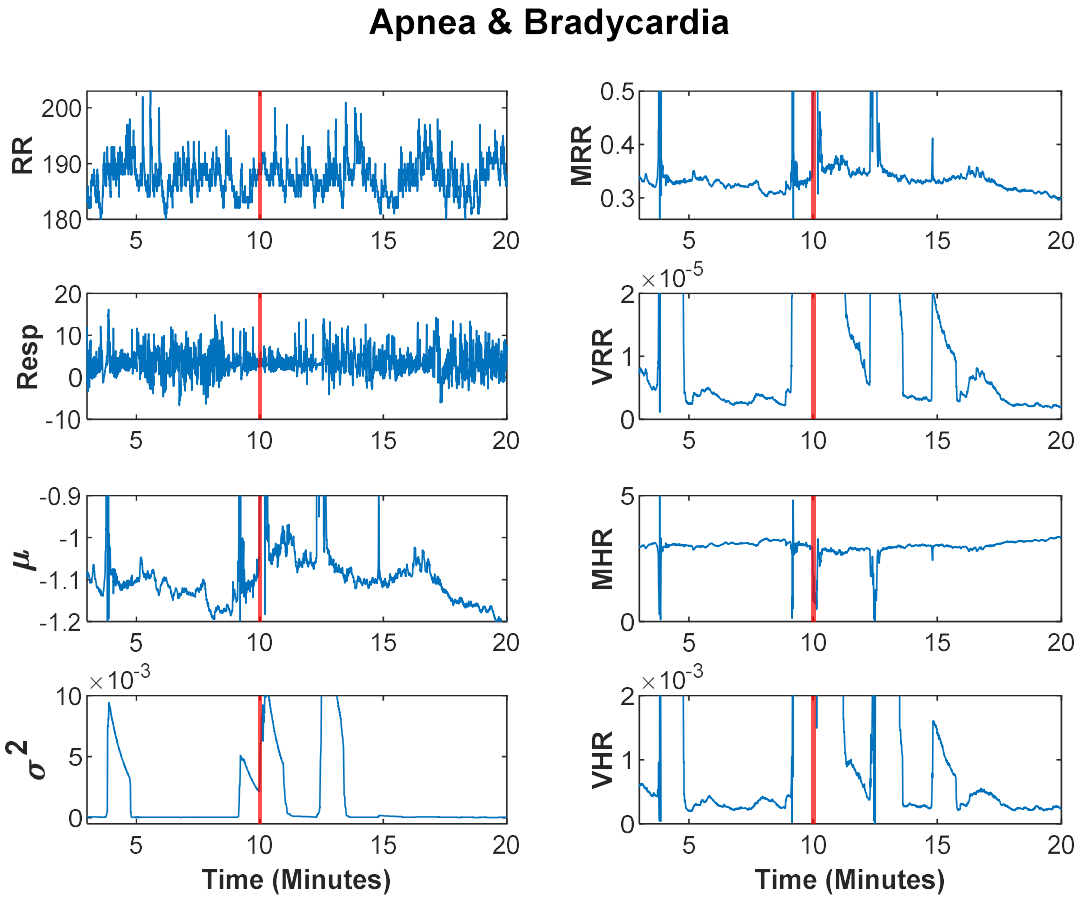

Figure A 2: Point Process Estimates during apnea- bradycardia event. Six point process estimates evaluated ten minutes before and after of apnea-bradycardia event (marked in red line). This segment has 10 seconds bradycardia and 10 seconds apnea

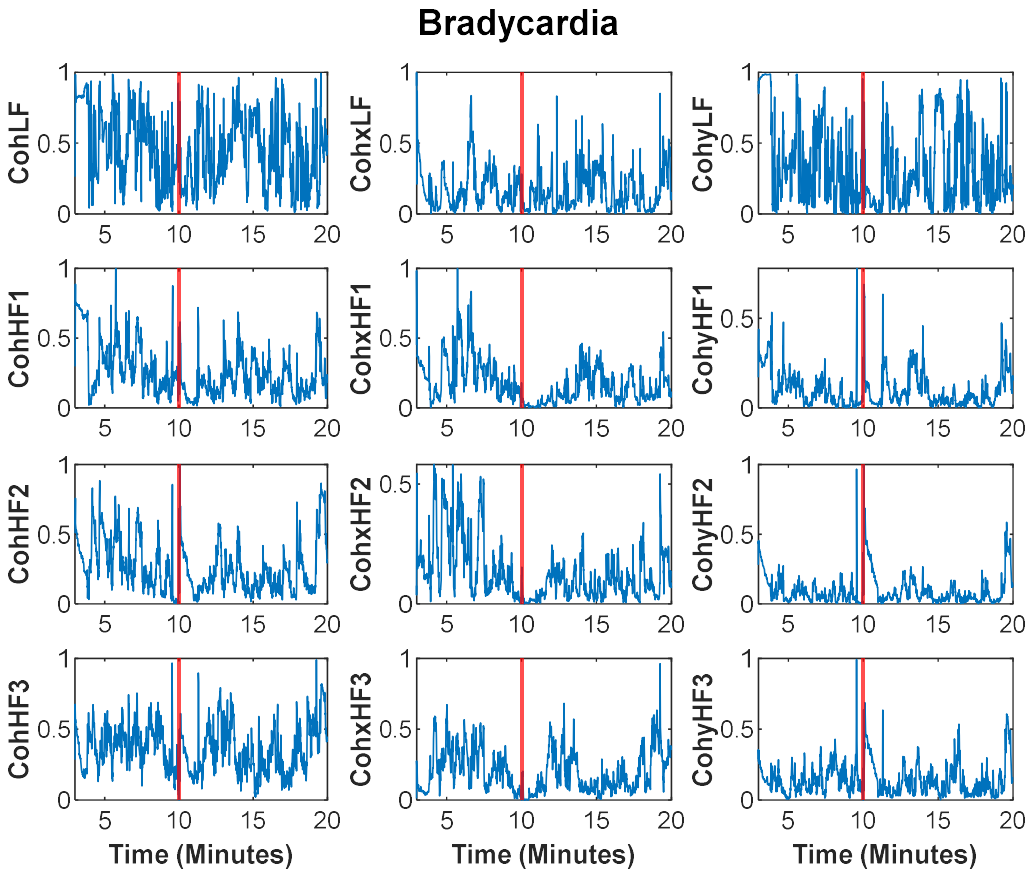

Figure A 3: Point Process Estimates during a bradycardia event. Six point process estimates evaluated ten minutes before and after of a bradycardia event (marked in red line). This segment has 12 seconds bradycardia with no apnea

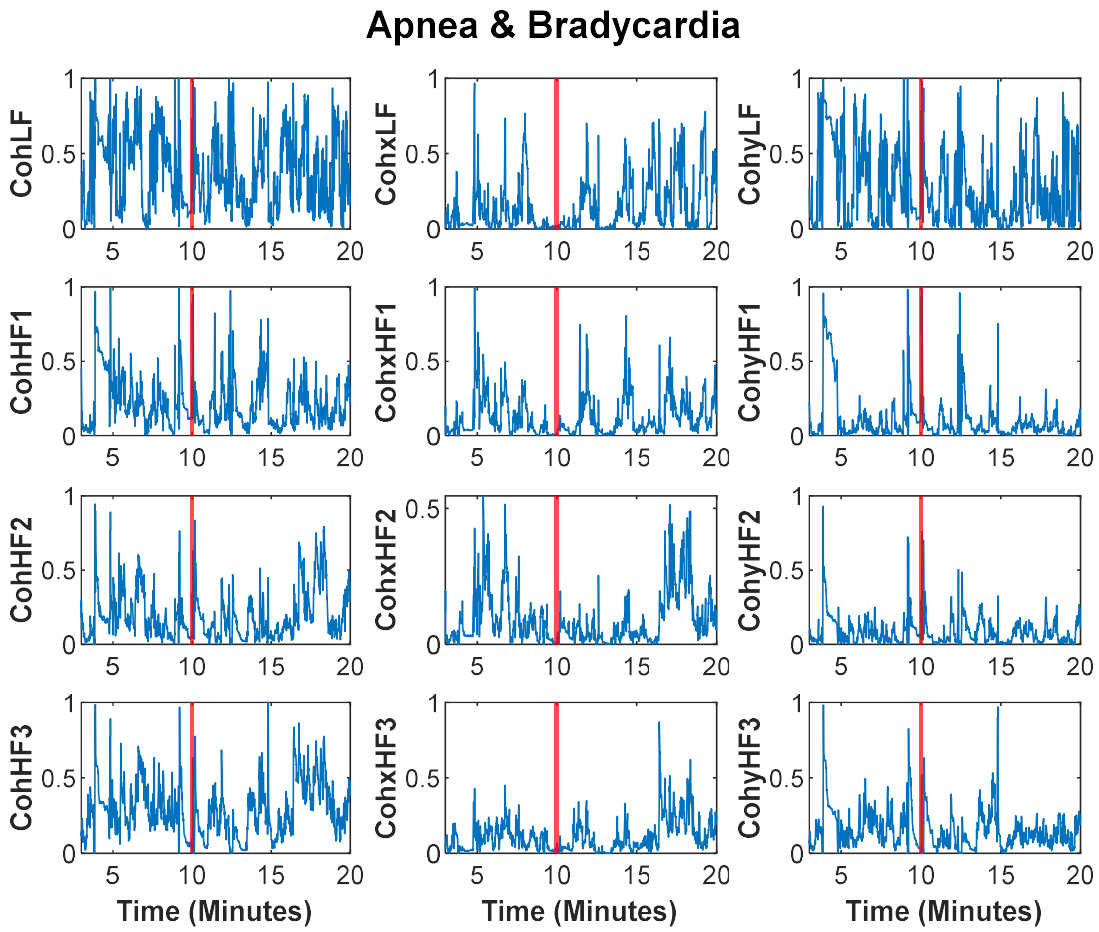

Figure A 4: Point Process Estimates during apnea- bradycardia event. Six point process estimates evaluated ten minutes before and after of apnea-bradycardia event (marked in red line). This segment has 15 seconds bradycardia and 10 seconds apnea

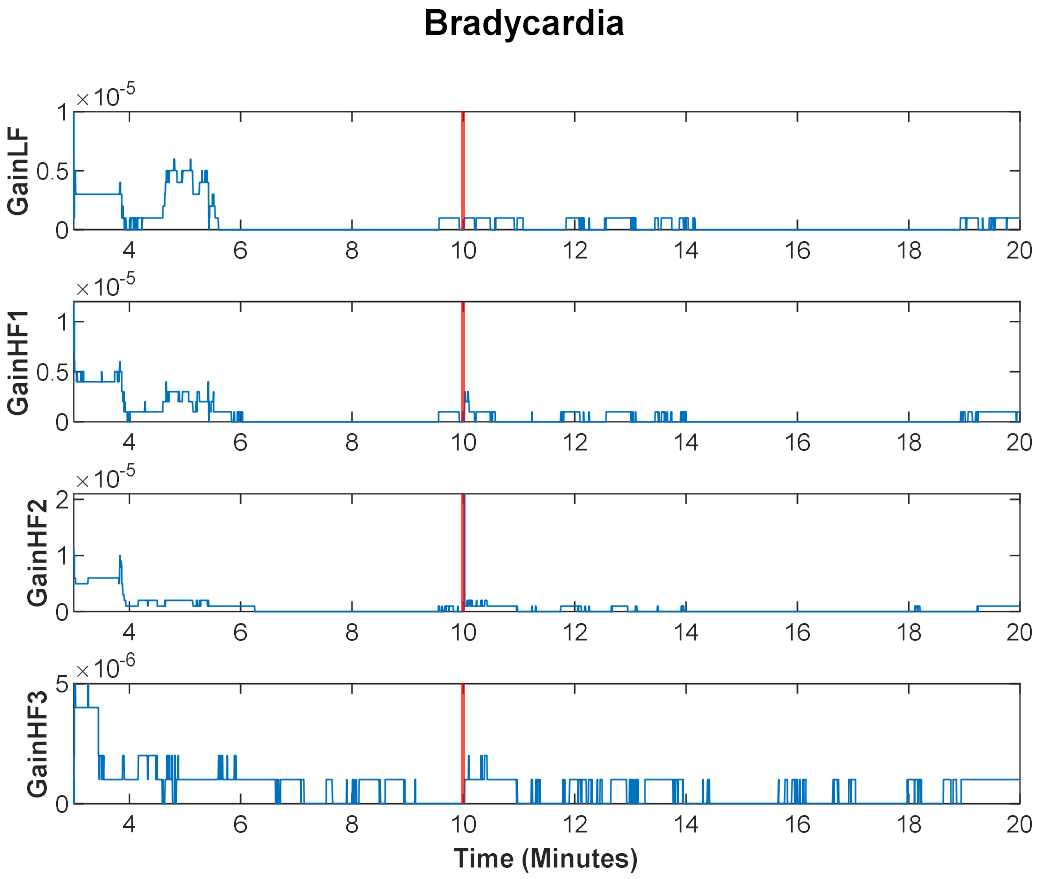

Figure A 5: Point Process Estimates during a bradycardia event. Six point process estimates evaluated ten minutes before and after of a bradycardia event (marked in red line). This segment has 12 seconds bradycardia with no apnea

Appendix A (continue)

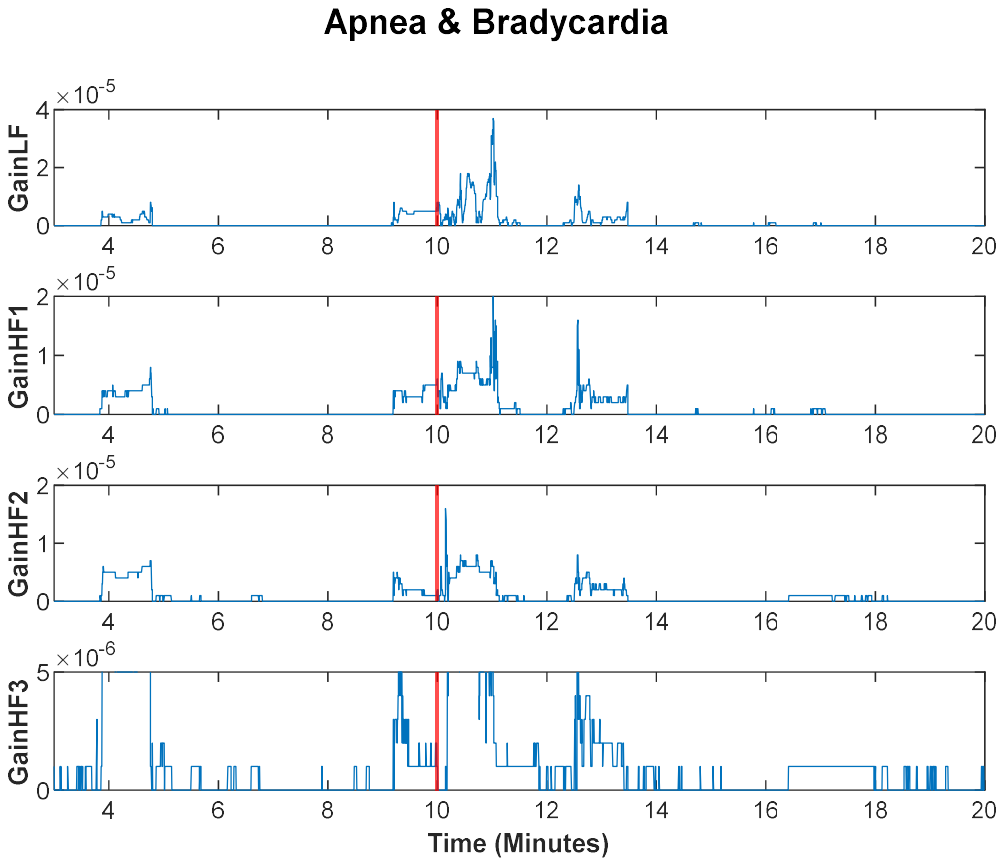

Figure A 6: Point Process Estimates during apnea- bradycardia event. Six point process estimates evaluated ten minutes before and after of apnea-bradycardia event (marked in red line). This segment has 15 seconds bradycardia and 10 seconds apnea