An Analysis of the Respiratory Dynamics of Preterm Infants

by
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Thesis presented in fulfilment of the requirements for the degree of Master of Engineering (Mechatronic) in the Faculty of Engineering at Stellenbosch University

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April 2019

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Abstract

Poor understanding of preterm infant physiology attributes to the high infant mortality rates, as well as its corresponding financial burden. Prematurity compromises the respiratory and regulatory systems of infants. This manifests itself in characteristic respiratory dynamics consisting of apneas, periodic breathing and regular breathing. These dynamics, if captured, quantified and visualised have potential to track maturational changes in infants. This can aid physicians in the difficult task of assessing a preterm infant's level of physiological maturity and offer insight into the infant's regulatory systems.

The primary objective of this study was to develop a transition model representing the behaviour of and temporal relationship between the different respiratory states of preterm infants. Secondary objectives consisted of the following: Analysing 2 – 5 s cessations, their contribution to breathing cessation and relationship to apnea; temporally tracking the respiratory stability of preterm infants; and studying the relationship between breathing cessations and heart rate behaviour.

Transition models were developed that adequately represented the respiratory dynamics of preterm infants. It showed that respiratory events are related in time, but that periodic breathing rarely precedes apnea of prematurity. On average 9% of breathing cessation and less than 1% of periodic breathing was found in the dataset. It was found that the contribution of short cessations were large, and that there is a temporal periodicity to the percentage cessations in the respiratory signal. Coupling between the respiratory and cardiac systems could be observed, with an apparent common temporal periodicity between some heart rate variability measures and percentage cessation in breathing signal.

In conclusion, all objectives were successfully addressed and greater insight was gained into the physiology of preterm infants. Future value exists in applying these analyses on a larger, more longitudinal and clinically annotated dataset.

Uittreksel

’n Swak begrip van premature kinderfisiologie dra by tot wêreldwye hoë kindersterftesyfers, asook die ooreenstemmende finansiële las. Prematuriteit kompromieer die respiratoriese en regulatoriese stelsels van babas. Dit manifesteer in kenmerkende respiratoriese dinamieke wat bestaan uit apnee, periodiese asemhaling en normale asemhaling. Indien hierdie dinamieke gemonitor, gekwantifiseer en gevisualiseer kan word, het dit die potensiaal om die volwassewording van premature babas te monitor. Dit kan dokters help in die moeilike taak om 'n premature kind se vlak van fisiologiese volwassenheid te bepaal. Dit kan ook insig gee rakende die regulatoriese stelsels van die baba.

Die primêre doel van hierdie studie was om 'n oorgangsmodel te ontwikkel wat die gedrag van en tydelike verband tussen die verskillende respiratoriese toestande van premature babas verteenwoordig. Sekondêre doelwitte het bestaan uit die volgende: Studie van 2 - 5 s asemhalingstakings, hul bydrae tot die totale asemhalingstaking en verhouding tot apnee; om die respiratoriese stabiliteit van premature babas relatief tot tyd te bestudeer; en die verband tussen asemhalingstake en variasie in hartklop te observeer.

'n Oorgangsmodel is ontwikkel wat die respiratoriese dinamika van premature babas voldoende verteenwoordig het. Dit het getoon dat respiratoriese gebeure verbonde is in tyd, maar dat apnee van prematuriteit selde deur periodiese asemhaling voorafgegaan word. Gemiddeld is 9% asemhalingstaking en minder as 1% periodieke asemhaling in die datastel gevind. Daar is bevind dat die bydrae van kort asemhalingstakings groot was en dat daar 'n temporale periodisiteit is vir die persentasie stakings in die respiratoriese sein. Koppeling tussen die respiratoriese en kardiale stelsels kon waargeneem word, met 'n skynbare algemene temporale periodisiteit tussen sommige hartklopveranderings-maatreëls en persentasie staking in die asemhalingssein.

Ten slotte is alle doelwitte suksesvol aangespreek en is meer insig verkry in die fisiologie van premature babas. Toekomstige waarde bestaan in die toepassing van hierdie ontledings op 'n groter, meer longitudinale en klinies geannoteerde datastel.

Acknowledgements

Thank you to my supervisors for their guidance, insights and patience throughout this process. They have taught me the value of collaboration and mentorship.

Thank you to my family and friends for all their support and for understanding all the missed events and cancelled plans.

Thank you to the Hillensberg Trust for their financial support and to Mev. Amos for identifying me as a candidate for this trust. I appreciate it more than I can say.

Lastly, as always, all honour to God, without whom it all means nothing.

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List of symbols and abbreviations

AC	Acceleration capacity
ANS	Autonomic nervous system
AOP	Apnea of prematurity
AV	Atrioventricular
Bpm	Beats per minute
BPRSA	Bivariate Phase Rectified Signal Averaging
BR	Breathing rate
CFTA	Continuous Fourier transform
CPAP	Continuous positive airway pressure
CWT	Continuous wavelet transform
DC	Deceleration capacity
DFT	Discrete Fourier transform
ECG	Electrocardiogram
EMI	Electromagnetic interference
HR	Heart rate
HRV	Heart rate variability
IQR	Interquartile range
JTFA	Joint time-frequency analysis
MDG	Millennium Development Goals
NICU	Neonatal intensive care unit
PB	Periodic breathing
PICS	Preterm Infants Cardiorespiratory Signals
PLI	Power line interference
PMA	Postmenstrual age
PNA	Postnatal age
PNS	Parasympathetic nervous system
PRSA	Phase Rectified Signal Averaging
REM	Rapid eye movement

RSA	Respiratory sinus arrhythmia
SDG	Sustainable Development Goals
SIDS	Sudden Infant Death Syndrome
SNR	Signal-to-noise ratio
SNS	Sympathetic nervous system
SpO2	Oxygen saturation
UN	United Nations
WAD	Weighted apnea duration
L	Length of PRSA window
T	Number of points over which anchor points are averaged
X	Signal used to calculate AC and DC
a	Constant for Lee et al. cessation detection algorithm
b	Constant for Lee et al. cessation detection algorithm
f	Frequency
i	Current
l	Inductance
$u(t)$	Signal
v	Voltage
$\gamma(s,\tau)$	Measure of convolution
C_ψ	Wavelet's constant
$\psi(t)$	Mother wavelet
$\psi(\omega)$	Continuous Fourier transform of wavelet
$\psi_{s,\tau}$	Daughter wavelet

1 Introduction

1.1 Background

Prematurity compromises the respiratory and regulatory systems of infants. This manifests itself in characteristic respiratory dynamics consisting of apneas, breathing cessations, periodic breathing and regular breathing [1–3]. These dynamics, if captured, quantified and visualised have potential to track maturational changes in infants. Not only can this aid physicians in the difficult task of assessing a preterm infant's level of physiological maturity, but it could also potentially aid in the rapid identification and treatment of diseases such as apnea of prematurity, bronchopulmonary dysplasia and sepsis. Standalone, respiratory dynamics should provide physiological insights into the infant's regulatory systems. More accurate measurement and a deeper understanding of these dynamics can have a positive impact on neonatal healthcare as well as its accompanying financial burden.

This project proposes an in-depth study of preterm infant respiratory dynamics. It will analyse respiratory signals and classify them into periods of apnea (or breathing cessations), periodic breathing and regular breathing. An extensive literature study will be done pertaining to the current definitions of these respiratory events, since the classifications are continuously evolving. Existing bio-signal measurement tools from literature and databases will be identified and used to develop the algorithms necessary to detect and quantify respiratory events.

Furthermore, relationships between the classes of breathing will be explored using descriptive analytics and statistical methods. These will eventually be summarised in a transition model. This will give a clear visualisation of these relationships and enable a holistic picture of the respiratory activity in preterm infants. Development of this transition model serves as the primary objective of this research project, summarising the key aspects explored and insights gained, as well as offering the possibility to track respiratory maturity.

In addition to this, three secondary areas of interest will be explored. Firstly, unlike other studies, short cessations in breathing (2 – 5 s) will be specifically analysed. This will help to better quantify respiratory dynamics as well as aid in the investigation of whether short cessations in breathing are related to apneas. It will also enable a comprehensive picture of exactly how large their routinely ignored contribution is to the overall time a preterm infant spends in breathing cessation. Secondly, this project aims to track respiratory stability temporally, investigating whether there is a periodic time-relationship in the behaviour of cessations. Lastly,

the relationship between breathing cessations and heart rate behaviour will be studied. This relationship, along with how it is currently quantified and analysed, will also be explored in the literature review.

Finally, the project will end in a discussion of the obtained results, focussing on their clinical relevance and potential, as well as how they fit into the context of the existing body of knowledge. The limitations of this study will be presented and the suggestions for future work outlined.

1.2 Objectives

The main aim of this thesis is to do a comprehensive analysis of the respiratory dynamics of preterm infants, enabling a better understanding of their respiratory regulatory systems. One primary objective and three secondary objectives have been identified in order to achieve this goal.

1.2.1 Primary objective

Objective 1: Develop a transition model representing the behaviour of and temporal relationship between the different respiratory states of preterm infants.

1.2.2 Secondary objectives

Objective 2.1: Analyse 2 – 5 s cessations, their relationship to apneas and their contribution to the overall time a preterm infant spends in breathing cessation.

Objective 2.2: Temporally track the respiratory stability of preterm infants.

Objective 2.3: Study the relationship between breathing cessations and heart rate behaviour.

1.3 Motivation

It is important to gain a deeper insight into the physiology of preterm infants. Global neonatal mortality rates are high enough to warrant concern from institutions like the United Nations (UN), with goals constantly being set to improve the chances of survival for these very vulnerable children. These mortality rates are even more concerning when the focus is placed on preterm infants. Adequate monitoring plays a very important role in helping preterm infants survive. However, even when monitoring is sufficient, large amounts of data are acquired but not effectively utilised. Analysing this data holds many possibilities to improve the outcomes of preterm infants. In particular, properly studying respiratory signals could aid in tracking the maturation of these infants, which

could aid clinicians in assessing whether they are healthy enough to be discharged from the neonatal intensive care unit (NICU).

Infants born before 37 weeks of gestation are clinically defined as preterm. Globally, 15 million of these infants are born per year and in 2015, almost one million of them died. Using current, cost-effective interventions could have prevented three-quarters of these deaths. Even if these infants do survive, many of them end up facing a life of disabilities [4].

In 2000 the UN held the Millennium Summit. Here they established eight international developmental goals to achieve by 2015, namely the Millennium Developmental Goals (MGDs). The fourth goal was to reduce child mortality, with one of its three subsections focusing specifically on infant mortality. Since the implementation of these goals, great strides have been made. The under-five mortality rate has dropped from 78 to 41 deaths per 1000 live births since the year 2000 [5].

Although the MDGs inspired positive progress in many areas around the globe, many children are still at risk. In 2016, 5.6 million children died before reaching their fifth birthday [5]. In addition, the neonatal mortality rate of neonates (infants up to 28 days of age) only decreased from 33 to 19 deaths per 1 000 live births. This is a less significant decrease than the under-five mortality rates, resulting in neonatal deaths now accounting for a growing share of these under-five deaths. This increase in relationship was seen in every region in the world [6]. In their 2015 report on the success of the MDGs, the UN places emphasis on the importance of keeping newborn and child survival at the heart of the post-2015 global development agenda [6].

In 2016, the MDGs were replaced by a collection of 17 new goals, formally known as “Transforming our World: the 2030 Agenda for Sustainable Development”. It is generally referred to as the 2030 Agenda or Sustainable Development Goals (SDGs). Goal three is specified as “Good health and well-being”, with a list of targets. Specific to preterm infants, all preventable deaths of newborns should be ended, with all countries aiming to reduce their neonatal mortality rate to at least 12 deaths per 1000 live births. In addition, through prevention and treatment, premature mortality from non-communicable diseases should be reduced by one third [5].

Presently, the chances of achieving these targets seem slim. 533 million children live in countries where these goals are currently unachievable [5]. If current trends continue, 10 million additional lives will be saved. However, around 60 million children under five will still have died between 2017 and 2030 due to largely preventative causes, with more than half these deaths occurring in sub-Saharan Africa. In addition, over 60 countries will miss the SDG 2030 neonatal mortality

goal. Nearly 40 of these countries need to more than double their current rate of progress to have a chance of meeting these goals [5].

Infant mortality is a higher risk among poorer communities, with children born into poverty being almost twice as likely to die before five years of age than those born to wealthier families [7]. In low-income communities half of the infants born at or below 32 weeks of gestation die due to a lack of cost-effective and feasible healthcare, such as basic care for infections and breathing difficulties [8]. Worldwide, 75% of neonatal deaths occur very early on with prematurity accounting for 40% of these and complications of asphyxia (oxygen deprivation, or suffocation) for 23% [9]. The UN reports similar statistics, attributing 35% of these neonatal deaths to preterm birth complications [6].

Of these early deaths mentioned, 44% are linked to healthcare related factors which are mostly avoidable. In 22% of deaths due to immaturity, administrative problems were reported. The main problem cited was a lack of adequate facilities and no access to an ICU unit with applicable equipment, therefore also indicating a lack of adequate monitoring. The 2010 – 2011 Saving Babies report lists the top two health-worker-related reasons as (i) fetal distress monitored but not detected and (ii) distress not monitored and therefore not detected [10].

A 2011 audit done on neonatal mortality at the Steve Biko Academic Hospital listed spontaneous preterm labour and intrapartum asphyxia (a condition associated with abnormal breathing) as two of the five primary obstetric causes of death. Constant monitoring and data collection play a large and important part in controlling conditions like these. In most cases, with proper monitoring and data screening present, these deaths could be avoided. In fact, inadequate resuscitation and monitoring was reported as one of the top personnel-related factors contributing to death [9].

The importance of adequate monitoring cannot be overstressed, especially with infants under 32 weeks and/or under 1500 g birth weight [11]. However, even when sufficient monitoring takes places, the large amount of data amassed normally remains underutilised. Further exploration and analysis of this data can offer insight into the physiological systems of infants, as well as the interactions between these systems. One area that can be aided by such analysis, is the discharge practices in the NICU.

Functional maturity serves as the main criteria in the clinical decision concerning an infant's readiness for discharge. This maturity is mainly demonstrated by the infant's control of breathing and respiratory stability, two factors that are greatly undermined by the occurrence of an apnea. Therefore, when an apnea occurs, it indicates that the infant is not medically stable enough to be discharged. This leads to a practice of implementing a safety period between the occurrence of an apnea

and the time at which the infant is discharged. However, very little data exist pertaining to what the optimum duration of this safety period should be. Lee et al. suggests a duration of eight days, but believes a better justification of this norm is needed [12]. Still, this practice differs widely among medical practitioners, with one study showing this disparity with a survey: 74% of neonatal specialists work with an apnea-free period of five to seven days; 14% suggest two to four days; 11% employ no safety period; while 9% suggest ten days or more; and less than 1% suggest one, eight or nine days respectively [13], [14].

The discrepancy above is worrisome for two main reasons. Firstly, neonates, especially those born preterm, are very fragile. They require proper care and often constant monitoring. Therefore, discharging an infant after five days when ten days is the more medically sound option could be potentially very dangerous. Secondly, the cost associated with keeping an infant in the NICU is very high. In the US, daily NICU costs can exceed $3 500, and it is possible for the entire NICU stay to exceed $1 million in costs [15]. Locally, this problem is just as evident. Netcare's tariff calculator determines that one day in a NICU in a private South African hospital will cost R16 114.80 [16]. These factors make detecting apneas critical to the discharge process.

Reducing preterm infant mortality is of great importance around the globe, not only to the parents of these infants, but also to institutions like the UN and the governments that work alongside them. A large percentage of infants die due to complications caused by prematurity, and many of these complications are related to the respiratory system. In order to solve these problems and reduce the mortality rate, a better understanding of the respiratory system of preterm infants is needed. Monitoring plays an integral role in this aim, particularly respiratory monitoring and the ability to detect respiratory abnormalities, such as apneas. There is a high likelihood that these signals may be useful to clinicians in assessing the respiratory maturity level of preterm infants. Tracking the maturation process of the respiratory system will lead to safer decision making on NICU discharges, which in turn will contribute to reducing preterm infant mortality rates. However, it is only possible to understand something once it has been quantified. Therefore this study undertakes to properly quantify and analyse the dynamics of the respiratory systems of preterm infants in the hopes of understanding how to improve their chances of survival.

1.4 Thesis structure

This project will start with the necessary background knowledge needed to fully comprehend the literature study and methods applied. This knowledge will also aid in clarifying the importance of the eventual conclusions made. Then an in-depth literature study will be done. It will discuss what has been done up to date

and clearly define the physiological events the study aims to identify. In addition, it will clarify this study's position in and contribution to the current body of knowledge. Then the methods applied will be discussed in detail, leading into the results obtained. Lastly, along with stating the limitations for this study and future work to be explored, these results will be discussed, and relevant conclusions will be drawn.

2 Background

This section offers background information in support of this study. It gives an overview of the physiology relevant to this study, discusses the acquisition and monitoring of the biosignals and concludes with a detailed discussion on the processing of these types of signals. It lastly summarises what has been learned throughout the section, and places it in the context of the study that follows.

2.1 Physiology

Physiological systems consist of a multitude of organs which are made up of biological tissue that enables them to perform complex functions. Three of these systems are relevant to this project, namely the circulatory, cardiac and respiratory systems, discussed in Sections 2.1.1, 2.1.2 and 2.1.4 respectively. The circulatory system links the respiratory and cardiac system to each other. Along with the cardiac system, heart rate variability, which is discussed in Section 2.1.3, is also relevant to Objective 2.3, while the respiratory system is relevant to all of the set objectives. The standard functioning of these systems differ in the physiology of a preterm infant, therefore prematurity and its effects are discussed in Section 2.1.5. A common consequence of prematurity is apnea of prematurity (AOP), which forms an integral part of the analysis done in this study and is therefore discussed in Section 2.1.6.

2.1.1 Circulatory system

The circulatory system functions as a distribution network consisting of cardiovascular, pulmonary and systematic components. The heart, blood and blood vessels make up the cardiovascular component, while the pulmonary component consists of the lungs. From the heart, several major arteries and veins are spread through the body to and from its extremities. These blood vessels (the systematic component) reach every part of the body via very thin capillary networks that branch out of the major vessels. This system delivers oxygen from the lungs to the heart via the pulmonary vein. The heart then pumps this oxygenated blood along with necessary nutrients and hormones from glands to the body through the aorta and various arteries [17]. No cell in the body is more than 100 µm from a capillary, ensuring that gasses can be transported to and from all cells in the body [18].

The circulatory system also regulates the body's temperature via various methods, for example by removing the heat generated by the body's metabolic processes. The capillary network makes it easy for small solutes (like O_2 and CO_2) to diffuse from and to the bloodstream, depending on the body's needs, as well as the concentrations and partial pressure gradient at a given moment in time.

The heart is the driving force behind this network. Its function is similar to that of two perfectly integrated pumps, one on the left side and one on the right side. Both consist of two chambers: the atrium, which receives blood, and the ventricle, that pumps the blood away from the heart. The right side receives the deoxygenated blood from the body and pumps it to the lungs so CO_2 can be expelled from the body. The left side then receives oxygenated blood from the lungs and pumps it to the rest of the body [17].

2.1.2 Cardiac cycle

The cardiac cycle is the repeating pattern of systole and diastole (contraction and relaxation) of the heart chambers. These patterns regulate the heart's activities and are illustrated in Figure 2.1. This pattern originates from a self-generating electrical pulse in the pacemaker cells of the sinoarterial nodes. The sudden electrical change in this node is due to ions moving across the plasma membranes of the cells. The plasma membrane's permeability to Na^+ ions (thus the layer's ability to let these ions move through it) increases dramatically and the ions rush into the cell. This process changes the electrical potential across the membrane and is called depolarisation. Depolarisation is the loss of the difference in charge between the inside and outside of the plasma membrane of a muscle or nerve cell due to this change in permeability and migration of sodium ions to the interior. As soon as depolarisation takes places, sodium-potassium pumps are activated to restore the ion balance in the cells, repolarising the cells. This occurrence is called an action potential, an electrical event where the potential of a plasma membrane rapidly reverses and is then quickly restored to its original position. Since cardiac cells are tightly linked, the action potential spreads throughout the heart [19].

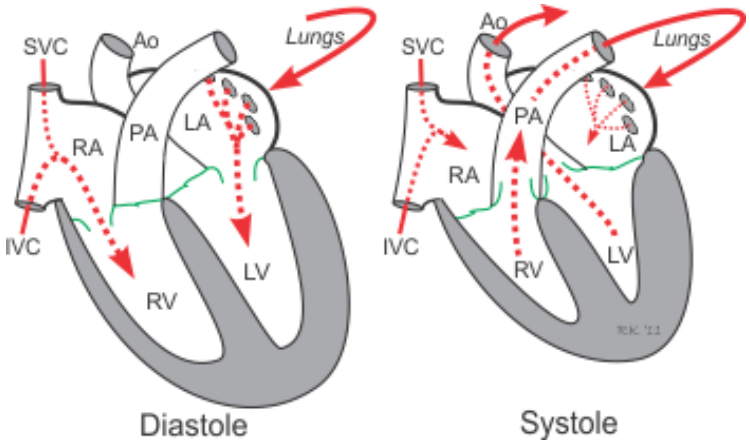

Figure 2.1: Cardiac cycle [20]

Contraction takes place when a cardiac cell depolarises and atrial systole moves blood from the atriums to the ventricles. Corresponding to this, the activation wavefront moves to the atrioventricular (AV) node. This allows the ventricles to be filled with blood from the atriums before this blood is transported to the rest of the body. When the activation wavefront leaves the AV node, it travels to the Purkinje system. This system consists of specialised conduction tissue that speeds up the wavefront and spreads it to multiple cells in both ventricles. Here it moves through to cause ventricular systole in both the chambers [19]. If the changes in voltage potentials caused by this process are measured, they result in an electrocardiogram (ECG).

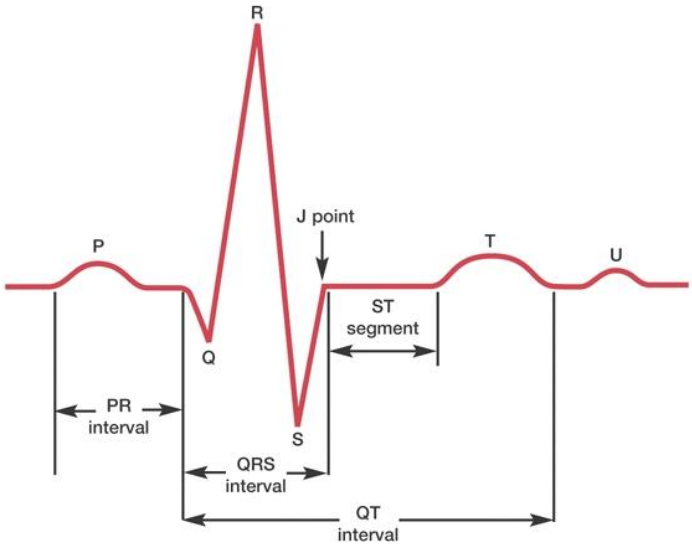

Figure 2.2: Characteristic ECG waveform [21]

A normal ECG is illustrated in Figure 2.2. The P-wave, a small deflection wave that represents arterial depolarisation, is the first characteristic that can be observed. This is followed by the PR-interval. The QRS-wave complex are three waves that represent ventricular depolarisation. The Q-wave is very small and often hard to see on an ECG. It corresponds to the depolarisation of the interventricular septum. The R-wave is much larger since it represents the depolarisation of the main mass of ventricles. The final depolarisation (at the bottom of the heart) is reflected in the S-wave. The ST-interval that follows represents a period of zero potential between ventricular depolarisation and repolarisation. When ventricular repolarisation occurs, it is reflected in the T-wave [21].

2.1.3 Heart rate variability

Heart rate variability (HRV) is the variation in the time between consecutive heart beats. It is predominantly dependent on the extrinsic regulation of the heart rate (HR) and represents the heart's ability to respond to unpredictable stimuli and changing circumstance within the body. It aids in assessing overall cardiac health, but also specifically the autonomic nervous system (ANS), which is responsible for regulating cardiac activity [22].

The ANS consist of the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS). The HR is slowed down via the release of acethylcholine, which is regulated by the PNS. The influence from the PNS is dominant during resting conditions, often referred to as 'rest-and-digest'. The SNS is dominant during more stressful or stimulating situations, and is called the 'fight-or-flight' system. It accelerates the HR by releasing epinephrine and norepinephrine from the nerve terminals and adrenal glands.

At rest, a high HRV indicates good autonomic and cardiorespiratory response, suggesting that the body can quickly respond to stimuli and equally quickly return to its baseline state. Therefore, the body has a high stress tolerance and can quickly recover from prior accumulated stress. In contrast to this, low HRV suggests that the PNS and SNS aren't coordinating well enough to deliver an appropriate response. Therefore fluctuations in HR are indicative of the relationship between the PNS and SNS [23]. PNS, SNS and hormonal factors influence HR instantly. HRV reflects the dynamic, rapidly occurring changes in autonomic regulations caused by primary systems controlling the HR [24].

Studying HRV can show signs of impending disease. Extracting and analysing HRV parameters can be a very useful diagnostics tool. It is commonly used in the surveillance of post-myocardial infarction and diabetes patients. The advantages of measuring HRV is that it is non-invasive and HRV measures are fairly easy to compute [22]. There is, however, a lack of understanding concerning what these measures mean in relation to preterm infants. It is important to note that the behaviour of a neonatal heart differs from that of an adult hart, and that prematurity amplifies these differences [22]. This physiological dissimilarity urges caution when interpreting HRV measures. Inherently, preterm infants exhibit a wider range of RR values, owing to their experience of acute tachycardia and bradycardia. Taking this into account, further exploration is needed concerning how traditional HRV measures relate to preterm infants.

2.1.4 Respiratory system

The respiratory system functions alongside the cardiac system to aid the circulatory system in facilitating gas exchange throughout the body. It comprises three main parts: the lungs, its conducting airways and the respiratory muscles of

the thorax. These parts can be divided in the conduction zone and the respiratory zone. The conduction zone, consisting of the mouth, nose, sinuses, pharynx, trachea, bronchi and bronchioles, is responsible for warming, humidifying, filtering and cleaning the air that enters the body. The respiratory bronchioles, alveoli and clusters of alveolar sacs make up the respiratory zone and form the surfaces for gas exchange between blood and air [19]. Figure 2.3 illustrates this biology.

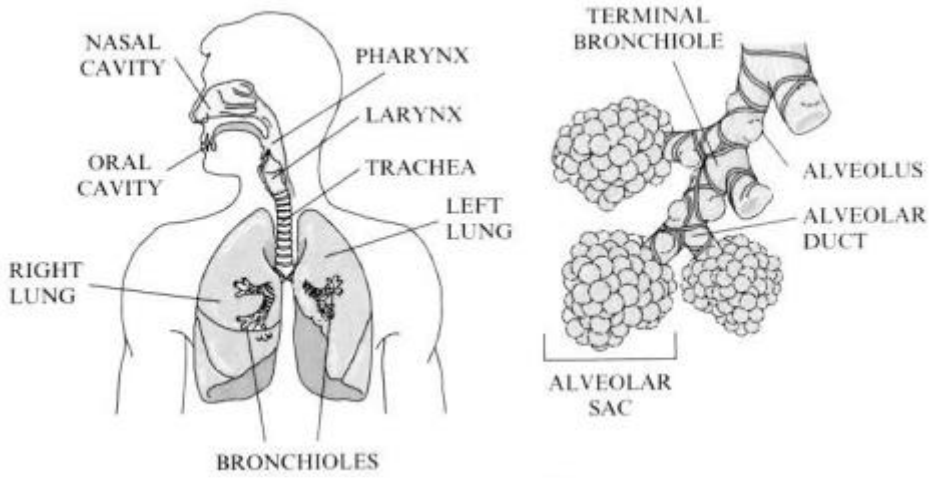

Figure 2.3: Respiratory system [19]

Functioning together, this system mechanically moves air into and out of the lungs with movements referred to as inspiration and expiration respectively. In addition, the system facilitates gas exchange between the air and blood in the respiratory zone [25]. Rhythmic ventilation is an automatic process. It is controlled by the central nervous system, where groups of cells in the brainstem are responsible for generating this basic rhythm. The rhythm is modulated by conscious actions, as well as reflexes. Chemoreceptors regulate the carbon dioxide and oxygen levels in the blood [26].

With inspiration, a process takes place whereby oxygen is diffused through the gas exchange surfaces into the blood. Here it binds with the haemoglobin in the red blood cells and is subsequently transported through the circulatory system, enabling oxygen delivery to the body. Excess carbon dioxide is also diffused to the air to remove it from the body [25].

The blood vessels of the pulmonary circulation carry the deoxygenated blood from the heart to the lungs and return oxygen-rich blood from the lungs to the heart. The development of these structures are essential for a newborn infant's overall respiratory function [19]. However, in preterm infants these systems are often underdeveloped.

2.1.5 Prematurity and its effects

Birth before 37 weeks of gestation is considered preterm, with full-term defined as 40 weeks. The final weeks before birth are crucial for weight gain as well as the full development of vital organ systems. Prematurity often leads to mortality, but modern medical advances have significantly increased the chances of survival for preterm infants. Still, prematurity remains the leading cause for infant mortality and one of the main contributing factors to long-term nervous system disorders in children. It can also result in other long-term health issues, both mental and physical [27].

It is often unclear why preterm labour occurs, although health issues like diabetes and high blood pressure increase the chances. There are also several pregnancy-related factors that can contribute to the possibility, for example poor nutrition, smoking, certain infection and an abnormal uterus. After birth, preterm infants are typically placed in a NICU, where the focus is on supporting the development of their vital organ systems. There is no set timeframe for how long an infant spends in the NICU. The time can vary from days to months. Apart from the evident low body weight, preterm infants can also have trouble breathing and an inability to regulate their body temperature. Therefore, infants are placed in incubators to control their environment, with attention given to regulating temperature. Routine NICU monitoring will dictate if equipment will be attached to the infant to monitor their HR, blood oxygen levels and breathing. Life-threatening conditions that are commonly encountered include haemorrhaging (bleeding) in the brain (meningitis) or lungs, as well as neonatal respiratory distress syndrome and AOP [27].

2.1.6 Apnea of prematurity

A major concern associated with prematurity is the underdevelopment of an infant's lungs and respiratory regulatory systems. This can result in problems like respiratory distress syndrome, pneumonia or AOP [28]. AOP is a common manifestation of preterm infants' immature respiratory control. A decrease in gestational age increases the vulnerability for apnea.

Upper airway obstruction often accompanies apnea, with the location of the obstruction usually being within the pharynx (see Figure 2.3). The presence of this obstruction leads to classifying apnea into one of three categories. Firstly, during obstructive apnea, obstructed breaths can be observed. Chest wall movements persist throughout the entire apnea, while no nasal air flow can take place. Secondly, during central apnea, all inspiration efforts cease, and no breaths can be observed. Central apneas are a direct result of an immature nervous system. Thirdly, when central and obstructive apnea occur in conjunction, it is referred to as mixed apnea. This is the most commonly observed apnea in preterm infants

and is responsible for 50% to 75% of occurrences. The proportion of pure central apnea decreases the longer an apnea episode persists, while the chances for mixed apnea increases [25]. An example can be seen in Figure 2.4. Note where there is activity in the signal, respiration is occurring. The part of the signal that seems to flat-line is the central apnea.

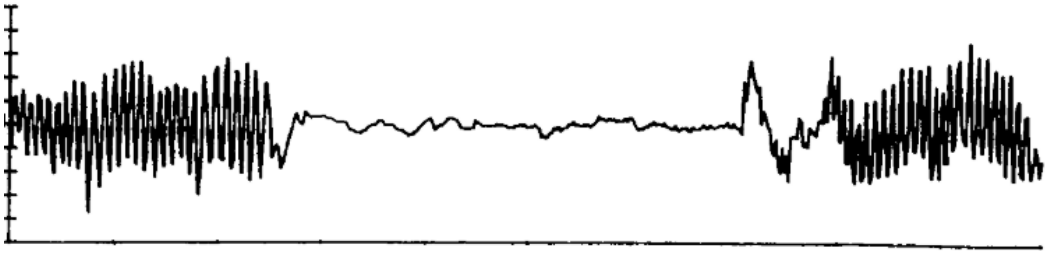

Figure 2.4: Chest impedance respiratory signal with central apnea [29]

Mostly, the frequency of apnea decreases as the infant matures, making an underlying neuropathological process unlikely. It has been hypothesized that when central and peripheral chemoreceptor responses have developed sufficiently to maintain blood gas levels, the presence of apnea is resolved. The development of the medullary respiratory control centres' ability to activate upper airway dilating musculature synchronously with increasing ventilatory drive [25].

The cessation of respiration during apnea has serious ventilatory and reflex cardiovascular consequences for preterm infants. Prolonged apnea is accompanied by hypoxemia (low oxygen levels in blood) and hypercarbia (abnormally elevated carbon dioxide levels in blood). The body's reflex behaviour to apnea includes changes in HR. Bradycardia (abnormally low HR) can occur within seconds of apnea onset [25], [30]. Reflex control between HR and breathing presents a complex relationship. Allowing increased ventilation to offset hypoxemia can result in tachycardia (abnormally high HR), but preventing this reflex increase in ventilation leads to bradycardia. When an apnea starts, cessation in ventilation and hypoxemia occurs quickly and simultaneously, producing bradycardia. Whether apnea with accompanied bradycardia and hypoxemia has a long-term negative impact on development is currently still under speculation.

It is believed that idiopathic apnea, i.e., apnea that occurs suddenly and without any clear cause, and prematurity are related. Although rarely occurring, underlying specific familial neuropathology can manifest as apnea. Examples of such conditions are: olivopontocerebellar atrophy, which is marked by degeneration of neurons in specific parts of the brain; myotonic dystrophy, which is associated by decreasing muscle function; and brain stem infarction that result from asphyxia

(suffocation), therefore a stroke due to lack of blood to the brainstem. A main factor in the pathogenesis of AOP is depression of immaturity of the central inspiration drive. This could explain why apneas can be preceded by a diverse group of specific clinicopathologic events. Another proposal has been that neural networks consisting of immature circuits are susceptible to inhibitory neurotransmitters and neuroregulators, such as adenosine. Unfortunately, no ideal animal model of spontaneous apnea has been identified to study in the non-anesthetized state. The maturation of infants' central respiratory integrative mechanisms as well as their biochemical neurotransmitters to date are inaccessible to study [25].

Contributing to the theory that apnea is caused by immature brain stem development, it has been found that brain stem conduction times of auditory evoked responses are longer in preterm infants with apnea than in preterm infants without. The absence of respiratory muscle activity during central apnea and its partial absence during mixed apnea indicates a depression in respiratory centre output [25].

There are other factors that can increase the chances of AOP occurring. Apnea occurs more frequently during active (or rapid eye movement (REM)) sleep than during indeterminate (or transitional) sleep, since active sleep is accompanied by breathing patterns that are irregular both in regard to their timing and amplitude. Sepsis also makes infants more prone to respiratory compromise, which includes susceptibility to apnea. Apnea is sometimes attributed to gastroesophageal reflux, however, this is not necessarily the case. Although this reflux often coexists with apnea, they are not usually temporally related, meaning that the occurrence of one does not usually result in the occurrence of the other.

Several therapies exist to treat AOP. Apart from physical stimulation, a nonpharmacological approach that is often used is continuous positive airway pressure (CPAP). It is considered safe, and most preterm infants tolerate nasal CPAP well. This therapy limits upper airway closure and stabilizes the lungs. It is particularly useful because most apnea involve an obstructive component. Since the 1970s, mythelxanthine therapy has been used to prevent and treat AOP pharmacologically. Xanthines inhibit nonspecific adenosine receptors and in so doing excites respiratory neural output. The most commonly used xanthine is caffeine, which increases central respiratory drive. To do this, it elicits complex neurotransmitter interactions, making the safety of its use a concern, with the long term effects still unknown.

Studying the long-term effects of these treatments, as well as studying anything else related to physiology, requires data, specifically biosignals. This allows for the quantification of processes and effects, and enables conclusions to be drawn, as is discussed next in in Section 2.2.

2.2 Biosignals

A biosignal, often referred to as a physiological signal, is defined as an endogenous (natural) or exogenous (manmade) record that is time-varying and continuous, containing information on the internal functioning of a physiological system [31]. In physiological systems a signal can be one of many things, for example a force, pressure or, as is the case with this study, an electrical potential. Biosignals are generally acquired by a sensor which converts it to a current or voltage for further processing. There are two main rationales behind biosignal processing. Firstly, it aims to extract desired information about a physiological system. Secondly, to interpret the nature of physiological processes based on the signal observed, or the characteristic changes in a signal based on a physical change [32].

These signals are inherently noisy due to interfering noise from other processes occurring simultaneously in the body. Ambient noise also contaminates the signal [31]. It is very important for a user to be able to distinguish between noise and the desired signal. Struggling to discriminate noise from signal is a common problem, since biosignals usually have a low signal to noise ratio. Accurate processing and filtering of these signals are crucial, since an abnormal signal can indicate disease or health deterioration.

All physiological systems are to some degree interconnected [31]. Indications of interconnection between signals suggest that there is a relationship between two signals. Generally, there are two possibilities. Either one signal directly activates or influences the second one, or a third unobserved signal influences both the first two [32]. Physiological systems are usually multiple input, multiple output systems, with interactions and cross-couplings with other systems. This cross-coupling is a result of shared nervous system pathways, hormones affecting more than one system or sharing an effector organ. Physiological systems also have lag times between their nodes, which can be reflected as instabilities in their representative signals. These systems are always non-linear. Physiological systems consist of a magnitude of cells that work in coherence to achieve a goal, making these systems massively parallel [31].

An additional problem is that many biosignals do not adhere well to the principles of Fourier analysis [22]. These signals are inherently nonstationary, since the processes at their origin changes over time [31]. Many research efforts are focussed on alternative methods for decomposing these signals. Time-frequency analysis is a prominent and relevant field of interest and is further discussed in Section 2.4.2.

Due to the fragility of preterm infants, continuous monitoring is employed in NICU setups. A cardiopulmonary monitor is usually used to monitor respiration and heart activity, in most part to determine HR and breathing rate (BR), as well as

problems arising from these rates deviating from their expected norms. Details concerning the methods for monitoring these are discussed in Section 2.3. Oxygen saturation and temperature are also routinely continuously monitored, but these are outside the scope of this project and are therefore not further discussed.

2.3 Biosignal monitoring

The electrical potentials relevant to this study are impedance plethysmography or inductance plethysmography, both of which represent respiratory activity, and ECG signals, which reflects cardiac activity. These are discussed in Sections 2.3.1 and 2.3.2 respectively.

2.3.1 Respiration monitoring

Chest wall motion is commonly measured using impedance plethysmography, otherwise known as pneumography. If the volume in a chosen electrical field varies, this causes a change in electrical resistance within that space. This is useful, since if an alternating current is applied across this volume, the resistance can be measured. This type of resistance is called impedance. When measuring the respiratory activity of preterm infants, the source currents applied are of high frequency, or what can be seen as “constant”. This makes it possible to measure resistive breathing changes without biological potentials interfering [33]. Bedside monitors employ algorithms that detect apneas based on continuous monitoring of chest impedance [12].

Another method that is frequently used to monitor respiratory activity is inductance plethysmography. Inductors are passive elements relating the voltage-current relationship with Equation 2.1, with *v* referring to voltage, *l* referring to inductance and *di* and *dt* representing the changes in current and time respectively. In circuits containing inductors, changes at the source being measured do not result in an instantaneous change in the signal, but more natural and reflective of the form of response of the change at the source [19].

$$v = l\left(\frac{di}{dt}\right) \tag{2.1}$$

Inductance plethysmography monitors breathing patterns without airway instrumentation and is often used in critical care setups. Two degrees of freedom of chest wall movement are monitored by placing two sensors on the body, at the level of the nipples and one at the level of the naval. The sensors are calibrated to obtain volume-motion coefficients reflective of the setup of each of the two signals. These signals are then summed to give an output signal representing the change in lung volume [34].

2.3.2 ECG monitoring

The electrical manifestation of the heart's contractile activity is called the ECG, as was previously mentioned in Section 2.1.2. It can be recorded by placing surface electrodes on a subject's chest or limbs. In a conventional ECG measurement setup, 12 leads are used. They are placed at different angles to record the overall magnitude of the electrical potential of the heart as well as the depolarisation that takes place [35].

The electrical activity across an infant's heart is monitored by placing three leads with sensors on the infant's chest. These leads are often in a band and are connected to a monitor. It can record and display an electrocardiogram (ECG) waveform, representing the activity in the cardiac cycle. This waveform, which can be seen in Figure 2.2, provides a visualisation of HR trends as well as beat-to-beat variability [36]. Various measures can be extracted from signals like an ECG by means of signal processing, which is discussed next in Section 2.4.

2.4 Biosignal processing

Signal processing is the manipulation of a signal through analysis, synthesis and modification with the goal of extracting information or gaining insight from the signal. It is usually based on mathematical processes, but qualitative methods are just as valid when studying biosignals. There are three main reasons for signal processing. Firstly, removing unwanted components that interfere with the signal that needs to be detected. Secondly, to render the signal in a more convenient form where useful information can be more easily seen. Thirdly, to predict future values to understand the potential behaviour of the source.

Overall standards, for example the Nyquist theorem in Section 2.4.1, ensure that the signal is properly acquired to aid analysis. Yet even at adequate sampling frequencies, signals recorded from the body are often contaminated with noise and artefacts, as are outlined in Section 2.4.3. This often obscures the signal desired for analysis. Applying linear and non-linear filtering is necessary to improve the signal-to-noise ratio (SNR). Sometimes simple linear band pass filtering has merit, but the non-linear and non-stationary nature of these signal often require more complex methods. Standard operations exist, such as Fourier analysis, but often a time-frequency analysis is necessary when processing biosignals, as will be explained in Section 2.4.2.

2.4.1 Nyquist sampling theorem

An important basis for the processing of any biosignal, is ensuring that it has been acquired at a sampling rate that adequately captures all of the necessary information. Implementing a very high sampling rate will result in accurate

information but can waste memory and computational energy. A too low sampling rate can lead to a misrepresentation of data resulting in aliasing. The Nyquist sampling theorem, shown in Equation 2.2, states that aliasing can be prevented if the sampling rate is twice the frequency of the original signal [37]. The expected maximum activity that needs to be monitored is represented by f_{max}, while $f_{nyquist}$ refers to the desired Nyquist frequency.

$$f_{nyquist} = 2 * f_{max} \tag{2.2}$$

Technically, adhering to the Nyquist theorem should ensure that aliasing does not occur. However, sampling is usually done at five to ten times the maximum frequency of the analogue signal to ensure no important data is lost [37].

2.4.2 Time-frequency analysis of biosignals

Joint time-frequency analysis (JTFA) is a mathematical tool to describe non-stationary biosignals [31]. Examples of these are short-term Fourier analysis, Gabor transforms and wavelets. These methods transform a signal that is one-dimensional in time into a two-dimensional distribution, enabling the study of the signal at different frequencies. The decision concerning which method to use is based on considerations of the computational complexity and time, the trade-offs in time-frequency resolution and lastly, what the best algorithm to use is considering the expected artefacts. The analysis done in this study relies heavily on JTFA, specifically on wavelets.

Wavelets are an active field of development, with many new applications being constantly discovered. It offers a very adaptable and flexible method for studying non-stationary signals. Wavelets have plenty of application in biomedical sciences. Since most biosignals are localised in both the time and frequency domain, wavelets are very useful in aiding their analysis. In addition to the application to detect periodic breathing (PB) in respiratory signals as will be discussed in Section 4.3, they are also useful in detecting abnormalities in ECG signals. Wavelet transforms are used to explain the patterns of cardiac rate control during reperfusion, a process where blood flow is restored to tissue after it has been blocked. These transforms have also been used to calculate time-frequency parameters extracted from nocturnal heart period analysis to aid in the diagnosis of obstructive sleep apnea syndrome in adults [22]. In addition, medical imaging has also benefited greatly from advances in wavelet technologies, with applications like compression, denoising and enhancement. One example is functional neuroimaging, where wavelets are used to investigate the neuronal activity of the brain [38].

A wavelet is essentially a finite-duration transient waveform, i.e., a waveform that ends after a specific time. Many different wavelets exist, each having their own

shape and specific properties. An original of a type of wavelet is often referred to as mother wavelet, and the scaled variations of the original are referred to as daughter wavelets.

Wavelets must adhere to three specifications. Firstly, the admissibility condition stated by Equation 2.3 specifies that the wavelet must have a zero mean. In this equation, $\psi(t)$ represents the mother wavelet, t depicts time and dt refers to the change in time [31].

$$\int_{-\infty}^{\infty} \psi(t)dt = 0 \tag{2.3}$$

Secondly, a wavelet's norm must also be of finite form, a condition represented by Equation 2.4. Here C_ψ is the wavelet's constant and $\psi(\omega)$ represents the continuous Fourier transform (CFT) of $\psi(t)$. The CFT is a representation of a continuous waveform in the frequency domain. Lastly, wavelets are also expected to have some variation of damped oscillation.

$$C_\psi = \frac{1}{2\pi}\int_{-\infty}^{\infty} \frac{|\psi(\omega)|^2}{|\omega|} d\omega < \infty \tag{2.4}$$

There are two types of wavelets transforms, the discrete wavelet transform (DWT) and continuous wavelet transform (CWT). Since biosignals are generally continuous, CWTs are necessary to accurately analyse them. Equation 2.5 depicts this CWT.

$$CWT(s,\tau) = \left(\frac{1}{\sqrt{s}}\right) * \int\int u(t)\psi * \left[\frac{t-\tau}{s}\right] dt \tag{2.5}$$

The time shift parameter is called the translation of the wavelet, and denoted as τ. The scale (or dilation) of the wavelet is represented by s. A mother wavelet is the case where s = 1 and τ = 0. $\left(\frac{1}{\sqrt{a}}\right)$ is for energy normalisation and * denotes the complex conjugate. The CWT is computed by integrating the wavelet over the length of the relevant signal denoted by $u(t)$, shifting it along by τ after each integration. Note that a close relationship exists between wavelet transforms and convolution, which is a measure of correlation or area overlap. It has even been argued that CWT is in fact a form of convolution [31].

2.4.3 Noise, interference and artefacts

During the acquisition of any biosignal, noise and interference contaminates signal recordings. These problems are often amplified in cases involving preterm infants. Artefacts can be divided into two main categories, physiological and non-physiological. Adequate filtering centres on the user's knowledge of the signal they are aiming to explore. They need to understand what constitutes their signal and what naturally cannot be their signal, and therefore contaminates it.

2.4.3.1 Physiological

Biological activity in the human body generates signals that interfere with the signal being acquired. There are many examples of this. Muscle (electromyogram) activity often interferes with biopotential recordings [35]. Hormonal changes can have a sudden impact on signals, while physical movement causes significant artefacts.

In many cases these artefacts are expected in signals, and as such standard filtering practices have been put in place. However, a type of artefact that remains a problem is the interference of cardiac activity in the respiratory signals of infants due to a potential frequency overlap between the HR and BR. Although ECG interference is not uncommon in most biosignal acquisition [32], with premature infants this is particularly concerning. Cessation in breathing results in a decrease in HR (i.e., bradycardia), as was discussed in Section 2.1.6. This causes ECG behaviour to move into the expected frequency range of the BR, essentially confusing monitoring devices. The artefacts caused by the cardiac activity result in changes in the measured electrical impedance that mimic respiratory activity. This perceived breathing activity is detected in lieu of the actual respiratory signal, which would at this point have indicated a lack of breathing.

This is particularly evident in chest impedance monitoring [12], [39]. Figure 2.5 gives an example from literature, and this type of interference is referred to as the cardiac artefact throughout this project. Outlined in red is the influence of cardiac activity on the respiratory impedance signal. Note the synchronisation between the artefact and the corresponding ECG signal below. An example of where this artefact was detected in this study can be seen in Appendix A.

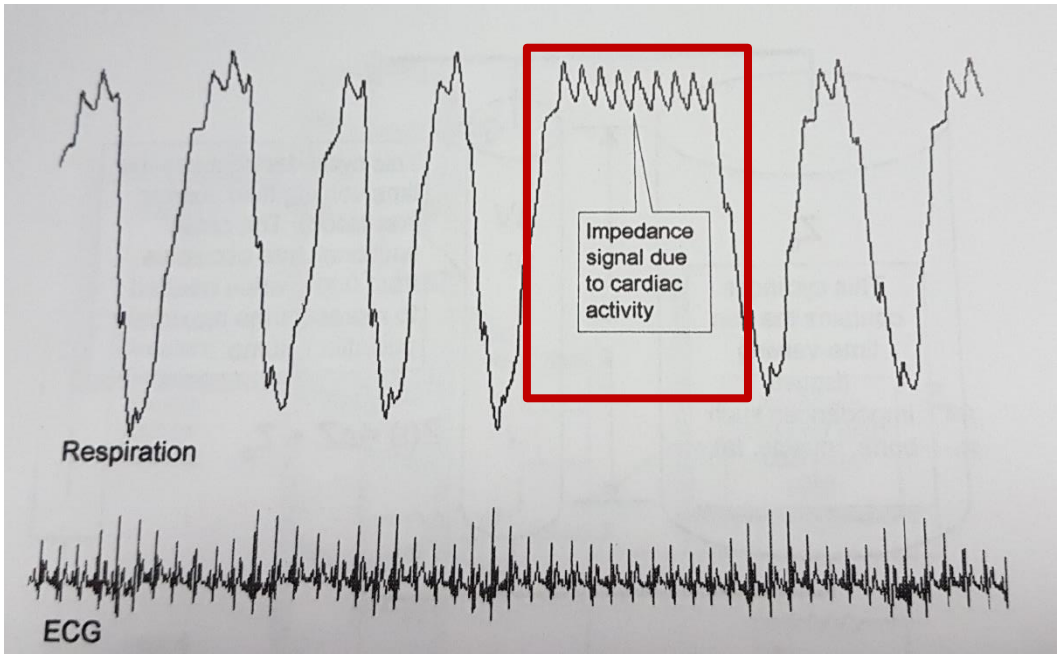

Figure 2.5: Cardiac artefact [39]

2.4.3.2 Non-physiological

In addition to physiological noise discussed in Section 2.4.3.1, ambient noise can also contaminate biosignal recordings. Various types of noise can occur during signal acquisition. Some noise can be persistent, as in the case of power line interference (PLI) and electromagnetic interference (EMI). PLI occurs due to differences in electrode impedance and stray currents in the cables that are connected to subjects, as well as the frequency of the power mains. Capacitive and inductive coupling are also sources that contribute to this. EMI arises in cables transferring signals from examination rooms to monitors due to ubiquitous power supply lines [35]. Baseline drift also often occurs, which is the short time variation of the baseline of a signal from the expected straight line. This drift can be caused by fluctuations in either the electric signal measured or the temperature of the contact surface.

Additionally, interferences occur in the measurement sensor due to friction or slippage between the sensor and skin. Poor conduction between the skin and electrodes results in reduced signal amplitude and thus low SNR [35]. It is challenging to acquire acceptable signals when working with preterm infants since so many variables affect the monitoring output. Inadequate electrode adhesion, improper positioning of electrodes and excess or inadequate gel on the contact area all contribute to poor waveform resolution and the presence of artefacts. With very low birth weight infants it is even more difficult, since removing the

electrode can strip the stratum corneum skin layer [2]. In addition, artefacts are also observed due to clinical handling and feeding.

2.5 Summary

This study will perform an in-depth analysis of the respiratory system of preterm infants in order to develop a transition model representing their respiratory dynamics. In the process, it will study short respiratory cessations, temporally track repository stability and study the relationship between respiratory cessations and heart rate behaviour. In order to achieve this, an understanding is necessary of two different disciplines.

Firstly, at its core, this is a study about an aspect of the physiology of preterm infants. Therefore, comprehension of the normal functioning of the circulatory, cardiac and respiratory system is needed (Sections 2.1.1, 2.1.2 and 2.1.4). This study in particular looks at how these systems function for an infant who has been born prematurely (Section 2.1.5). In keeping with the primary objective concerning the respiratory dynamics of preterm infants, AOP, is of particular interest (Section 2.1.6). However, nothing in the human body functions in isolation, so interest is also taken in HRV, a measure useful in studying certain interactions within the body (Section 2.1.3).

Secondly, quantifying and analysing these physiological systems and their irregularities requires techniques and knowledge from the discipline of engineering. The field of signal processing is continuously evolving to offer innovative tools to more effectively assess many natural processes. Section 2.4 offered insight into some of these tools. Keeping in mind the different noise and interference sources discussed, JTFA techniques will be employed to achieve the set out goals. The application of these, as well as several mathematical and statistical tools, are outlined in the methods in Section 4. The dataset on which these analyses are applied, as is further described in Section 4.1, contains the chest inductance and ECG waveforms discussed in Section 2.3.

Before commencing with the analysis proposed in this study, an extensive literature study is done in Section 3 to assess the current state of the art, as well as what has contributed to it.

3 Literature review

Preterm infants are arguably the most fragile members of society, yet much of their physiology is not well understood. These infants, born at gestational age younger than 37 weeks, often need to be continuously monitored. Due to their inability to express pain or discomfort, their heart and respiratory activity, as well as temperature and blood oxygen saturation levels need to be constantly examined to determining whether the infant is in distress. Modern technological advances have made this monitoring possible in NICUs, and increased storage space and software capabilities make it possible to record high resolution waveform data in great detail. Respiration and ECG are two such waveforms of which large amounts of information are never utilized [2]. They are primarily used to determine BR and HR, yet greater physiological insight can be gained from these waveforms regarding the cardiorespiratory systems of preterm infants. Capturing, quantifying and visualising the dynamics of these signals, and thereby their underlying physiology, has the potential to track maturational changes in infants. It could also possibly aid in the identification, treatment and prognosis of diseases such as AOP, bronchopulmonary dysplasia and sepsis.

3.1 AOP and its evolution in literature

Respiratory problems are very common in small infants, since the respiratory and regulatory systems of these infants are compromised by prematurity. This manifests itself in characteristic respiratory dynamics, or specific variations in the behaviour of the respiratory waveform. For the purposes of this study, these dynamics are defined as consisting of apneas, breathing cessations, PB and regular breathing [1–3]. These events usually occur in association with bradycardia (a drop in HR) and hypoxemia (a decrease in blood oxygen levels) and contribute to infant morbidity.

Although many advances have been made in neonatology over the past 60 years, there is still a great deal of uncertainty concerning AOP [40]. This is reflected in the continuously evolution of the definition of apnea from the 1960s to the present day. Currently, AOP is clinically defined in one of two ways. AOP is seen as a cessation of breathing exceeding 20 s. Alternatively, a cessation of at least 10 s accompanied by bradycardia under 100 beats per minute (bpm) or desaturation below 80% is also considered AOP [41]. One of the difficulties in studying AOP and its developmental correlation has been the discrepancies between the different definitions of apnea used by researchers in the field [25]. It is widely accepted that AOP has a negative effect on the health of an infant, as it can increase the risk of hypoxemia, hypoglycaemia, neurological injury and sepsis. These are all factors that contribute to infant morbidity [2], [12]. The theory exists that apnea without associated bradycardia or hypoxemia is clinically irrelevant, but this hypothesis

remains unproven [12]. A study found that AOP of more than 45 s could lead to mottling (patch-like discoloration of the skin), cyanosis (blueish discolouration), hypotonia (lack of muscle tone and strength) and unresponsiveness to breathing stimulation. They conclude that early intervention is crucial in order to prevent hypoxia and central respiratory depression from apnea [33]. AOP is directly linked to a lack of maturation in brain centres for respiratory control. An increase in post menstrual age (PMA) and postnatal age (PNA) will cause a progressive decrease in the presence and severity of AOP [42].

Consequently, if an apnea is identified in an infant, caregivers typically intervene by mechanical or physical intervention (i.e., delivering CPAP or physical stimulation), as well as by administering pharmacological therapy (i.e., caffeine, theophylline or aminophylline) [43]. However, the long-term effects of these physical and pharmacological interventions are not well understood [41]. Preterm infants have an immature neurological system, making them especially susceptible to AOP [12]. While AOP occurs in 50% of all preterm infants, it almost always occurs in infants with birth weight under 1000 g, making the burden of AOP considerable due to this underdevelopment of their respiratory and regulatory systems [3], [41]. Symptomatic AOP can still be a problem in late preterm infants, with prevalence rates of up to 10% [42].

Many issues remain regarding the study of and knowledge concerning AOP. Importantly, the long-term effects of AOP in neurodevelopmental outcomes are unknown. These effects are difficult to study, since not intervening when AOP occurs can lead to infant morbidity. The effects of oxygen loss on neurodevelopment and other organs can be very severe or even fatal. In addition, there is a lack of standardization and definition for AOP. There is also a dearth of real time data on the monitoring AOP events as well as associated documentation, with no baseline studies available [41].

3.2 PB in literature

PB is a common physiological event in newborns which is closely associated with AOP [33], [44]. It occurs due to the immaturity of the respiratory cycle, meaning the more severe the prematurity, the more frequently it occurs [45]. In a case several years ago, excessive amounts of PB were observed in both the respiratory patterns of an infant who died of Sudden Infant Death Syndrome (SIDS) as well as her sibling [46], causing increased interest in this physiological event. A widely accepted version of the continuously evolving clinical definition of PB is a pattern of at least three cycles (a cycle representing one-part cessation, one-part regular breathing). In 1973 it was seen as breathing of 10 to 15 s alternating with cessations of durations 5 to 20 s [45]. Cessations should be a minimum of 3 s in duration with a maximum of 20 s of regular breathing between cessations. One

study suggests that on average PB lasts for 15 s [47], while another reports that the cessations are generally 10 to 20 s [48], with a third study indicating that cessations up to 20 s should be taken into account [29].

However, Mohr et al. [49] believe that these definitions are not broad enough to show signs of impeding pathology. Brief episodes as described above are very common, even where no pathology is evident. In addition, physiological models of PB show clear distinction between transient and sustained oscillations. Hypersensitivity of chemoreceptors in infants trigger breaths in response to changes in the blood gasses. During the transition from fetus to neonate, there is an acute increase in blood oxygen, causing the desensitization of chemoreceptors at birth. This physiological change resets after about a week postpartum, causing PB to emerge during the neonatal period. This study suggests that it is common for PB to occur during quiet sleep [29], while another observed it more frequently during REM sleep [1].

A study performed on PB found that it occurred in 36.1% of infants over 2 500 g birth weight and in 94.5% of infants with low birth weight under 2 500 g. Typically, PB starts a day or two after birth and continues for a few weeks. This study defined PB as cycles of apneas of 5 to 10 s followed by regular breathing periods lasting 10 to 15 s. They reported the mean respiratory frequency where PB is present to be 30 to 40 breaths/minute, in contrast to the regular breathing frequency of 50 to 60 breaths/minute. PB is most likely to occur in small infants, it peaks in week two or three and the more premature the infant, the longer PB persists. It is unlikely to occur in infants with birth weight over 2 kg and more than 36 weeks' gestational age. The frequency of PB differed not only from infant to infant, but also between different episodes experienced by the same infant [1].

Currently, some studies suggest PB has no pathologic significance. It is seen as benign, and therefore needs to be sharply distinguished from apnea, which is not. [45]. Contradictorily, another study suggests that PB is a common cause of prolonged desaturation in preterm infants at discharge, and therefore is in fact not benign [50]. The exact relationship between AOP and PB is unclear, in some part because the definitions of these respiratory events keep evolving. One study aimed to correlate these events. In 1116 apnea spells, they found only one occurred within an epoch of PB. In addition, less than 0.6% of significant apneas occurred within two minutes of a PB epoch ending, implying that PB is not a precursor for apnea [1].

3.3 AOP, PB and alarm fatigue

The detrimental effects of AOP and PB are poorly understood, largely because breathing dynamics are difficult to measure due to the inaccuracy of the current solutions for monitoring [51]. The two most common methods, inductance

plethysmography and impedance plethysmography, both fail to reliably detect apnea events due to the non-stationary, noisy and unstable nature of infant respiratory signals [52]. The continuous monitoring of these signals in NICUs generates a high number of alarms. Frequently, these alarms are false. An excess of these leads to a well-known condition called alarm fatigue [53].

Several options have been suggested to combat alarm fatigue. Two of these are customization of alarm threshold and judging the appropriateness of continuous monitoring for a patient population [53]. However, given the fragility of preterm infants, the first seems preferable. There is a need to recognize relationships among events in order to group them as a one-alarm event or grouping recognised clusters into a single alarm. Ideally, work should be done towards diagnostic alarms [53]. Alarm fatigue is evident throughout all populations, but the preterm neonate population is especially susceptible due to their developmental immaturity. The loud sounding has negative short-term effects on cardiovascular and respiratory systems of preterm infants. It also disrupts their sleep and is believed to have a negative effect on their neurodevelopment [53], [54].

3.4 AOP and NICU discharge

Accurate detection of apnea is important, since, in addition to reducing false alarms, it is often a key factor in the clinical decision to discharge an infant from hospital [12], [55]. The discharge readiness required is demonstrated by functional maturity, therefore clinicians need to be able to assess whether these infants are physiologically mature enough to be discharged. This is important, since the environment they will then be exposed to will lack the continuous cardiorespiratory monitoring of the NICU [13].

Simply waiting for the infant to reach an agreed upon PMA will not suffice, since the more premature an infant is born the longer it takes for respiratory control to become fully functionally mature [13]. Since no clear measure is available on this, they aim to assess control of breathing and respiratory stability. These two factors are greatly undermined by the occurrence of an apnea. The practice of the “safety period” between apnea and discharge is followed by most neonatologists.

However, the length of this period is debated, mainly because very little concrete data exist to support a specific duration. In 1997, Darnall et al. tried to resolve this disagreement concerning the existing quasi-standard. They concluded that for otherwise healthy infants, eight days is an appropriate duration [13] . Lee et al. agrees with this eight day duration, however, they suggested that a better justification of this standard is necessary [12]. One survey determined that 45% of neonatal specialists suggest seven days, while 9% work with a period ten or more days free from apnea [14].

This discrepancy is disconcerting for two main reasons. Firstly, neonates, especially preterm infants, need to be properly cared for, therefore discharging a preterm infant after five days when ten days is the more medically sound option could be dangerous. Secondly, the cost associated with keeping an infant in the NICU is significant. In the US, daily NICU costs can exceed $3 500 per infant, and it is not uncommon for the total costs of a prolonged stay to exceed $1 million [15]. Therefore, precise discharge protocol is necessary for cost management.

3.5 NICU monitoring and respiratory detection algorithms

Monitoring in the NICU has significantly advanced since the detection of AOP started. Until the 1960s vital signs were merely noted down by a bedside nurse if the infant was believed to be ill enough to warrant it. Once it was realised that prolonged apnea could have detrimental long term effects, apnea monitors using impedance (as discussed in Section 2.3.1) were introduced [33]. The monitors had alarms set to go off if the infant stopped breathing for more than 15 s. After this continuous heart rate monitors were also introduced, and cardiorespiratory monitoring became a standard procedure in NICUs. In the 1970s speculation existed pertaining to the link between apnea and SIDS, which is as of yet unproven. However, this induced parental fear of SIDS paved the way for a home apnea monitoring industry, creating monitors that parents could use in their nurseries at home [56].

Recently, significant progress has been made towards improving the understanding of infant respiratory dynamics with the development of algorithms which can retrospectively detect apneas and PB. Traditionally the automated detection of apnea is based on simple threshold techniques. However, this offers poor specificity. In 2011, three new methods were designed and tested against clinical opinion. These were based on combinations of the HR, RR and oxygen saturation (SpO2). The first method looked at the sum of these measures' time series, along with the sum of their Shannon entropy. This yielded a performance of 94.53% sensitivity, 74.72% specificity and 77.84% accuracy. Secondly, an artificial neural network was used to correlate the here signals. This gave a performance of 81.85% sensitivity, 75.83% specificity and 76.78% accuracy. The last method employed a derivative of the three time series. This yielded 100% sensitivity, 96.19% specificity and 96.79% accuracy [57].

In 2012, a novel apnea detection algorithm was proposed by Lee et al. Along with addressing the presence of a cardiac artefact which is known to interfere with accurate apnea detection, it also only requires the respiratory and ECG waveform, not the SpO2 [12]. Their results showed an accuracy of over 90%. This research group also made further advances, proposing a second algorithm which identifies

and analyses PB events in infants [58]. This algorithm aims to detect PB by determining whether cessations are occurring in a sustained pattern, adhering to the definition of PB [49]. Previous methods have also characterized PB by comparing the respiratory signal behaviour with an amplitude-modulated signal [59].

3.6 HRV in literature

In addition to an immature respiratory system, these infants also have an immature ANS. HRV is regulated by the ANS and therefore provides insight into changes in autonomic regulations [24]. A better understanding of autonomic regulation could also aid in quicker diagnoses of abnormal developmental trajectories [60]. See Section 2.1.3 for a discussion on HRV, as well as how it differs between adults and preterm infants.

In 1965 researchers first appreciated the clinical relevance of HRV when it was noted that when fetal distress occurs, variance in the interbeat intervals can be seen before a significant change in HR is observable. In the 1970s it was discovered that reduced HRV is associated with a higher risk of death post-infarction, solidifying its importance as an analytic and diagnostic tool. In the 1980's power spectral analysis was introduced to quantitatively evaluate beat-to-beat cardiovascular control [61]. Subsequently, in 1997, the Task Force of the European Society of Cardiology noted that the HRV of preterm infants is an important field of investigation which could provide early warning of distress. In addition, proper application of HRV can offer insight into the autonomic maturation of the developing fetus, and by association preterm infants [61]. Continuous measures of physiological interaction could be useful in assessing the maturity of infants in the NICU. They may also be useful in making decisions concerning developing illness, as well as hospital discharge [62].

3.7 Cardiorespiratory coupling

Determining whether a preterm infant has an acceptable level of physiological maturity is an important and difficult task for the clinician caring for them. Investigation of the functional organization of cardiorespiratory systems is profusely challenging. Only noninvasive observation can be used, and these systems are inherently complex [60]. In addition, this interdependence is very difficult to monitor due to the variability in BR and HR, as well as the quality of the signals being lower than desired. Cardiorespiratory synchronization is achieved by the connection that the heart and lungs share through brain stem chemosensory pathways as well as the ANS. This preferential tendency for two systems to function in connection with each other is referred to as coupling. The nervous system or extracellular signaling enables organs to couple together. One such

example is respiratory sinus arrhythmia (RSA), which refers to heart rate increase or decreasing along with BR. This is controlled by the baroreflex and respiratory gating. The presence of RSA correlates with good ICU outcomes [62].

Several studies have very recently been done on cardiorespiratory coupling. In 2012, Clark et al. looked at the continuous changes in cardiorespiratory interaction in preterm infants. They determined the probability of heartbeats as a function of respiratory phase to serve as a measure of cardiorespiratory coupling. This theory hinges on the fundamental assumption that the differential distribution of heartbeats within the respiratory cycle serves as evidence for cardiorespiratory coupling [62].

Their main hypothesis was that measuring this coupling could be useful in assessing developmental maturity. They aimed to achieve this by studying the temporal association of heartbeats within the respiratory phase to quantify cardiac dependence on respiration. The study found that cardiorespiratory interaction increased with postnatal age, however, this relationship was independent of both birth weight and gestational age at birth. No direct evidence for RSA was observed in their NICU patient dataset. They concluded that a multitude of mechanisms contribute to cardiorespiratory coupling, and the uncertainty surrounding these mechanisms lead to an inability to quantify them [62].

They urged further studies to investigate the underlying physiology of cardiorespiratory interaction. However, they confirmed that cardiorespiratory interaction in preterm infants coincides with brain stem development and that increasing PMA coincides with decreasing prevalence of AOP, indicating improvement of the central respiratory control in the ventrolateral medulla. Surprisingly, the rate of increase is not affected by gestational age at birth [62]. They emphasized that it is too uncommon to get waveforms from the NICU that are uninterrupted for long enough to apply conventional time- and frequency domain measures to study cardiorespiratory interaction. They recommended that future studies should employ techniques that are less sensitive to missing data, as well as look for the link between this coupling and other factors that reflect brain stem maturity, such as a decrease in the incidence of apnea [62].

While infants are sleeping, autonomic control is responsible for modulating respiratory activity and HRV. The mechanisms responsible for these modulations have been studied but are not yet fully understood. Complex mutual relationships modulate respiratory and cardiovascular systems. Many approaches have been tried to measure linear and non-linear relationships between these systems, one example being cross-spectral analysis. However, these techniques are limited as they cannot do a directional analysis. This led to a study in 2017 that looked at the interaction between respiratory variability and HR in newborn infants,

particularly relating to the differences in this interaction pertaining to sleep state, mainly active versus quiet. This study determined a novel parameter, namely Transfer Entropy, which quantifies the flow of information between the respiration and RR series, as well as vice versa. This enabled the study of the bidirectional flow between these systems, taking into account both linear and non-linear aspects [60]. In June of 2018, this same research group aimed to study system interrelationships by looking at the possible presence of casual or directional interplays. They proposed that the parameters calculated in this study be used as a tool for the development of early markers of cardiorespiratory dysregulation in these infants [63].

3.8 Conclusion

This study aims to test the hypothesis that the ability to monitor, quantify and visualise the respiratory dynamics and HRV of preterm infants is useful in the clinical assessment of the maturation of these infants. As discussed, many tools exist and are continuously developed to assess the respiratory and cardiac systems of preterm infants. Yet, the signals representative of these processes have not been exhaustively explored, and quantifying the different dynamics in respiratory signals could offer a more holistic picture of the maturation of respiratory regulatory processes in preterm infants. It may offer clinicians the possibility to better track the maturation of a preterm infant's respiratory system, enabling them to make more informed clinical decisions regarding an infant's readiness for discharge from the NICU. Also, it may provide physiological insight into the infant's regulatory system, helping clinicians to better understand why cessations in breathing occur.

4 Methods

This section will discuss in detail the methods applied to achieve the set objectives. It will start by looking at the dataset chosen, as well as how it was selected. Sections 4.2 and 4.3 will discuss the cessation and PB detection algorithms, which form the foundation for all the other analyses. Section 4.4 discusses the setup of the transition models, which serve as the primary objective for this project. Sections 4.5 to 4.7 discuss how the HRV will be quantified and related to the respiratory activity. Section 4.8 gives an overview of how these data are then analysed. All algorithms and analysis were implemented in MATLAB (MathWorks, Natick, MA, USA).

4.1 Dataset

A dataset from PhysioNet, the Preterm Infants Cardiorespiratory Signals (PICS) database, was identified for the evaluation of these methods [64], [65]. This included the raw waveforms for chest inductance and ECG of ten preterm infants as described in Table 4.1 (mean PMA was 31 1/7 weeks and ranged between 29 3/7 and 34 2/7 weeks, while the mean weight was 1468 g, with a range from 843 to 2100 g). No oxygen saturation data were available. The recordings of the chest inductance and ECG signals are synchronised in time, and had sampling frequencies of 50 Hz and 250 Hz respectively. Each infant contributed between 20 and 70 hours of data, with the total being 401 hours. This dataset was chosen because it provided the necessary respiratory and cardiac signals with synchronised start times. It was also readily available from a trusted source, was recorded in a NICU and contained sufficient data to serve the purpose of this study. Further details on the PICS dataset are available in Gee et al. [65].

Table 4.1: Description of dataset

Infant no.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
PMA (weeks)	29 3/7	30 5/7	30 5/7	30 1/7	32 2/7	30 1/7	30 1/7	32 3/7	30 4/7	34 2/7
Weight (kg)	1.20	1.76	1.71	0.84	1.67	1.14	1.11	2.10	1.23	1.90
Signal length (hrs)	45	43	43	47	23	47	20	22	70	41

Two other datasets were explored but were ultimately found unsuitable for these purpose. Firstly, MIMIC II was examined [66], [64]. Although the information the

database has to offer was suitable and sufficient, they urge against using the waveforms for frequency sensitive analysis. Since this dataset's respiratory and ECG recordings are slightly out of sync, the cardiac filter, which requires precisely time-synchronized signals, cannot be applied. By default, this excluded this dataset.

Secondly, the CHIME dataset was explored, which is a large infant home monitoring project [67]. This database had sufficient information on preterm infants, but it was unclear whether it contained enough continuous data for this study. In addition, it was uncertain what the quality of the waveforms would be, since the home monitoring was administered by primary caregivers and not clinical professionals. Although these caregivers had received some measure of education on how to work with the equipment, it is likely that the data are less reliable than if acquired in a NICU.

4.2 Cessation detection

The Lee et al. algorithm was implemented to detect apneas in preterm infants. After removing the cardiac artefacts from the respiratory signal, the algorithm can retrospectively identify periods of breathing cessations [12]. It was also modified to include the 2 – 5 s cessations ignored by Lee et al.'s original algorithm. A high level overview of this algorithm is illustrated in Figure 4.1. This algorithm was tested and extensively validated by Lee et al., where there proved to be a more than 90% agreement between the algorithm and expert analysis.

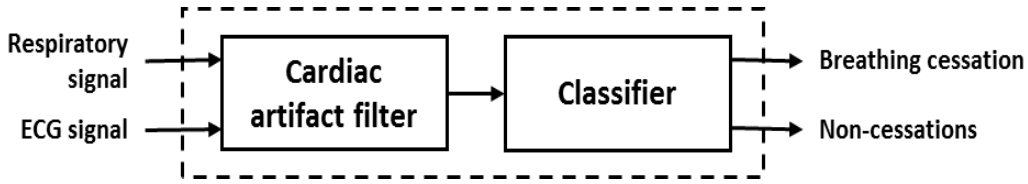

Figure 4.1: High level overview of Lee et al. algorithm

4.2.1 Cardiac artefact filter

Cessations in breathing often occur in association with bradycardia. This results in the HR slowing down and moving into the normal frequency range of breathing, causing in difficulties in discriminating between them. Section 2.4.3.1 offers a more in-depth explanation of this. To overcome this challenge, Lee et al.'s algorithm detects the RR intervals (i.e., the time between consecutive R peaks in an ECG signal) and then resamples the respiratory signal using the RR intervals as the clock. Therefore instead of the sampling frequency being related to seconds, it is related to the RR intervals. An existing peak detection algorithm was used to

detect R-peaks in the ECG waveforms [68], as can be seen in Figure 2.2. At this stage, the cardiac artefacts can be visualised by applying a Discrete Fourier Transform (DFT), which yield clear peaks at integer or half-integer frequencies. These artefacts are then removed using a band stop filter, which was implemented using a low order Butterworth filter that removes values at 0.5, 1, 1.5 and 2 Hz (±0.02 Hz). Once the cardiac artefacts have been removed, the respiratory signal is resampled to its original sampling rate for further analysis [58]. Appendix A provides a detailed overview of this filter. It gives an example of RR peaks detected with the specified algorithm in the ECG waveform. In addition, it provides examples of the artefact detected and removed in both the frequency and time domain, both from this study and from the original Lee et al. study.

4.2.2 Breathing cessation detector

After the cardiac filter has been applied, the signal is passed through a detector adhering to Lee et al.'s specifications to determine the periods of breathing cessation. The aim is to get an output of the probability of apnea versus time, which is referred to as Weighted Apnea Duration (WAD). This is accomplished by applying a high pass filter at 0.4 Hz, since information of a lower frequency than this are seen as irrelevant to respiratory activity [12]. It is then divided by a moving low pass filter envelope of 0.0025 Hz to smoothen the signal, applied to facilitate localised normalisation. It requires eight minutes of future information, as well as eight minutes of past information to perform this normalisation. This operation is applied with a two-minute moving window. Next, a weighted probability that an apnea is occurring, namely P_{fit}, is determined by applying Equation 4.1,

$$P_{fit}(\sigma) = \frac{1}{[1+\exp[b(\sigma-a)]]}, \tag{4.1}$$

where a and b are constants set to 0.44 and 12, respectively [12]; while σ represents the moving standard deviation of the respiratory signal. Parameters a and b were determined by Lee et al. and meticulously validated by three experts who worked through 500 relevant events to distinguish between apnea and regular breathing. The area under this yielded probability of apnea function is defined as the WAD. This WAD is then classified according to four rules. Firstly, if it has a magnitude of less than 0.1 it is disregarded. Secondly, if a WAD event has a duration of less than 2 s, it is also ignored. For the third rule, they consider the proximity of shorter events in relation to longer ones. WAD events of between 2 and 5 s which are within 5 s of another cessation event are retained, while isolated segments are disregarded. Lastly, cessation events within 3 s of each other are merged [58]. Appendix B provides more details on this method, specifically pertaining to an evaluation between the recreated algorithm and the original, as well as the low pass moving envelope filter, the programming logic applied, and an example of breathing cessations detected using it.

4.2.3 Modification of the Lee et al. algorithm

The Lee et al. algorithm focuses on the detection of apneas according to the current clinical definition of AOP outlined earlier. However, in this study, a differentiation is made between apneas and cessations in breathing. This is done to investigate whether cessations in breathing 2 – 5 s are prognostically significant. To make this possible, the Lee et al. algorithm was modified slightly by ignoring the third rule. This ensures that the isolated 2 – 5 s breathing cessation events are retained thereby enabling further analysis [58]. Figure 4.2 illustrates all the rules applied according to Lee et al. The omitted Rule 3 is highlighted in red on this figure.

4.2.4 Limitations of Lee et al. algorithm

All of the methods applied, including detection of PB, build on this cessation detection algorithm. This merits a discussion of the inherent limitations of this algorithm. Firstly, it is important to note that time-synchronised respiratory and cardiac signals are essential. The method is set up for retrospective analysis, it does not work in real-time. Obstructive apnea cannot be detected with this method, since it is accompanied by struggling motions of the infant. As with all signals, motion artefacts or other noise contaminants make the signal uninterpretable to the algorithm at times. The low pass envelope filter mentioned in Section 4.2.2 requires at least 16 minutes of uninterrupted respiratory and cardiac waveforms to function. A reliable analysis is also difficult if the respiratory signal has a very low amplitude [12].

This algorithm forms the basis for Mohr et al.'s algorithm to detect PB, a condition associated with AOP [49]. Therefore, the above stated limitations also apply to the PB detecting algorithm discussed in Section 4.3 that follows.

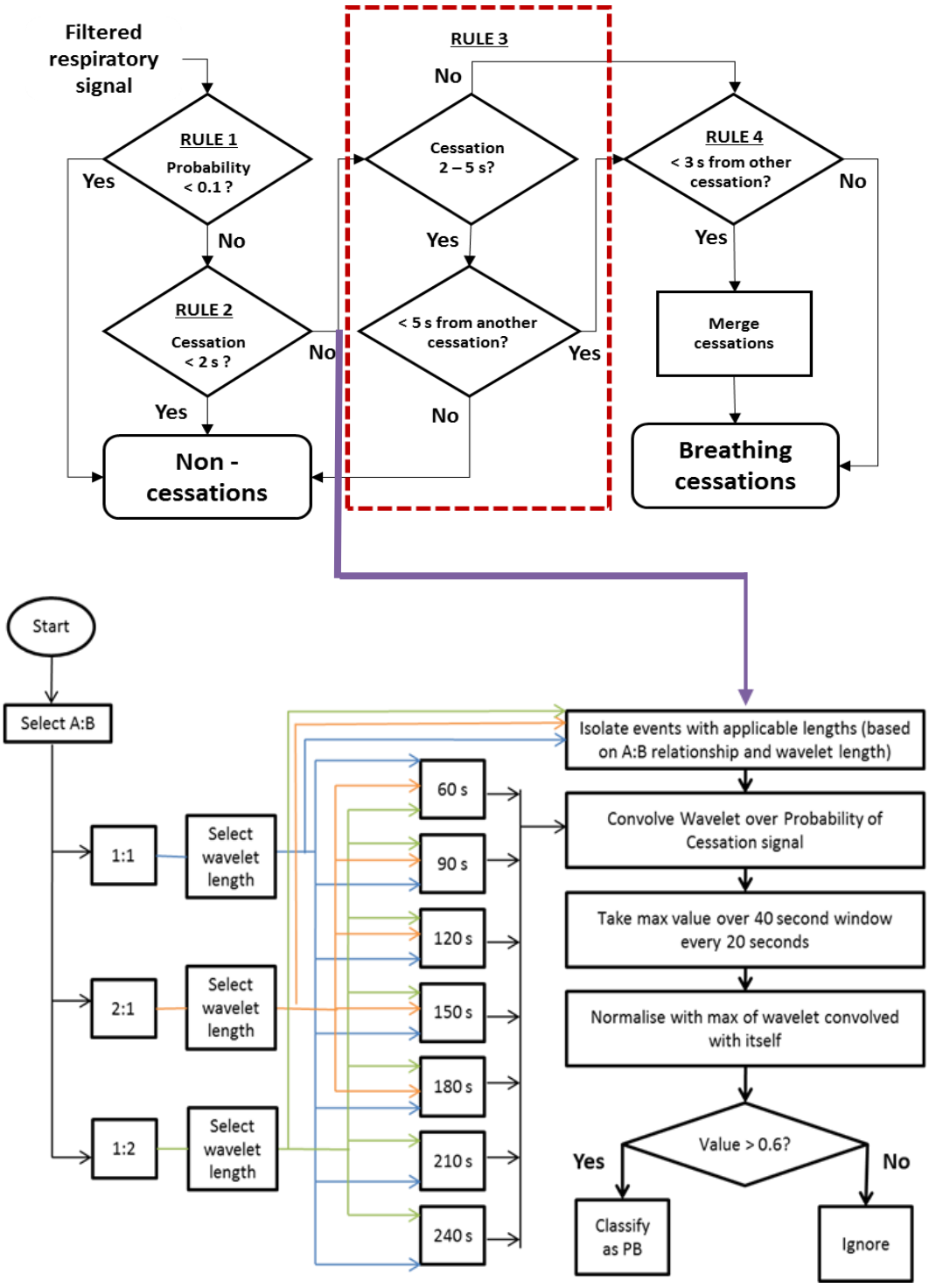

Figure 4.2: Overview of the: (top) Lee et al. cessation detection algorithm and (bottom) Mohr et al. PB detection algorithm (bottom). The purple line highlights the link between them.

4.3 PB detection

This algorithm builds on the algorithm in Section 4.2 and aims to distinguish between breathing cessations and PB. Normally, serious cessations are detected in conjunction with bradycardia and oxygen desaturation. However, PB is usually observed in cycles with cessation too short to lead to bradycardia and oxygen desaturation significant enough to cause alarm [49]. The proposed method therefore enables PB to be detected without monitoring of oxygen desaturation and bradycardia, essentially bypassing this problem and adhering to the dataset limitations.

It employs wavelets, which were discussed in more detail in Section 2.4.2, and through continuous template matching, aims to identify the characteristic pattern of PB. Two mother wavelets, $\psi(t)$, were designed with six cycles each. These wavelets were designed to model the appearance of the probability of apnea signal discussed in Section 4.2.2. A sine window was used to weight the middle of each mother wavelet heavier than the ends. This allows for detection after as few as three cycles of breathing and cessation, which satisfies the definition that PB is a pattern of at least three cycles (a cycle representing one part cessation, one part regular breathing) [1]. The first mother wavelet, seen in Figure 4.3, represents PB with a A:B ratio of 1:1, meaning that equal amounts of time is spent in apnea (A) (or cessation) and breathing (B) (or non-cessation).

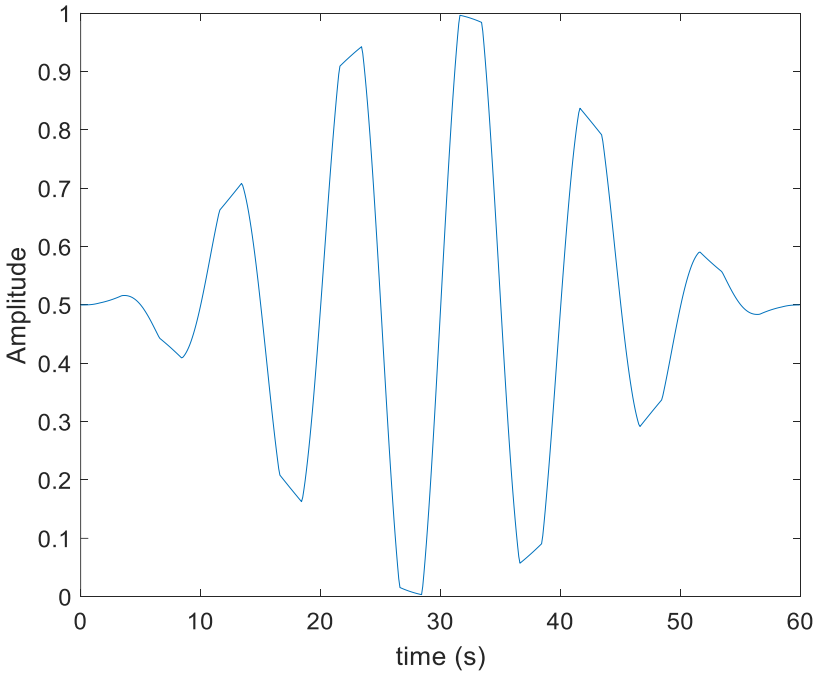

Figure 4.3: Mother wavelet with a ratio of one-part cessation and one-part breathing (A:B = 1:1)

The second mother wavelet represents a A:B ratio of 2:1, therefore PB with double the time spent in cessation comparatively to the time spent in non-cessation. Figure 4.4 shows a representation of this. This same mother wavelet can be used for a A:B ratio of 1:2, thus half the time spent in cessation compared to non-cessation. If Figure 4.4 were to be vertically flipped, it would represent a wavelet of this ratio. Using these wavelets are sufficient to detect PB with A:B ratios ranging from 1:4 to 4:1 [49].

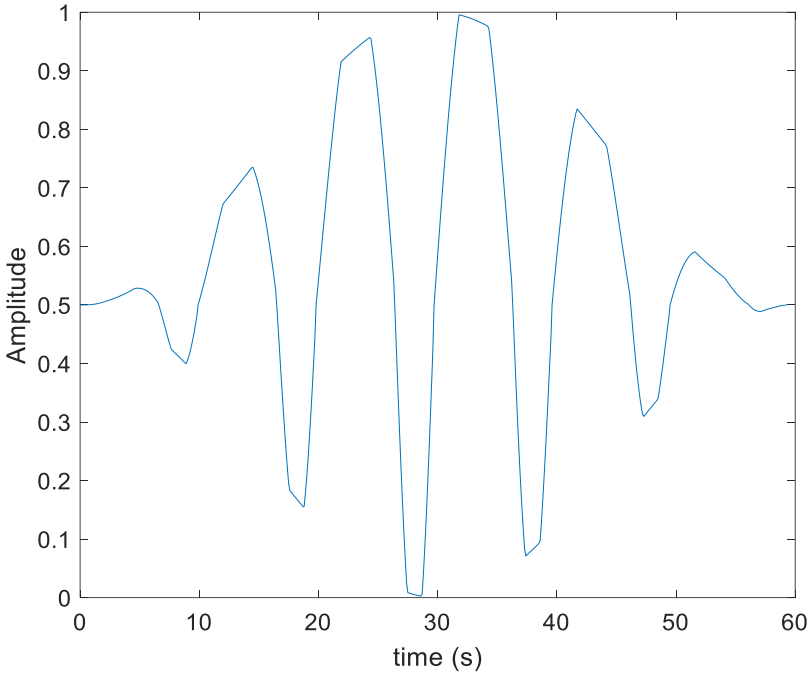

Figure 4.4: Mother wavelet with a ratio of two parts cessation and one part breathing (A:B = 2:1)

Daughter wavelets, $\psi_{s,\tau}(t)$, are then created by expanding or contracting these mother wavelets with regards to time (thus along the x-axis). This accounts for the varying length of PB cycles of durations of 10 to 40 s [49]. The basic formula for the wavelet is seen in Equation 4.2, with p = ½. The mother wavelet is represented by ψ, t refers to time, and τ and s refer to coefficients of time and scale respectively.

$$\psi_{s,\tau}(t) = |s|^{-p}\psi(\frac{t-\tau}{s}) \tag{4.2}$$

Each wavelet is continuously convolved (Note: Convolution refers to a measure of correlation or area overlap.) with the WAD signal, moving the wavelets at quarter second intervals. For this analysis, the WAD signal is taken right after Rule 2 is applied, as illustrated with the purple arrow in Figure 4.2. At this stage the only

constraints placed on the WAD is that it must have a magnitude larger than 0.1 and be of duration greater than 2 s. Cessation of lengths corresponding to the cycle lengths of the wavelets are isolated to aid in the analysis. These are outlined in Table 4.2. Blue rows represent A:B of 1:1. Red rows and green rows represent A:B of 1:2 and 2:1 respectively. Note that the cells marked with N/A indicate that designing a wavelet for those specifications would contradict the definition of PB. (Figure C-2 in Appendix C gives an explanation of such a case.) This isolation of cessations was done to avoid high convolution values due to mismatched areas between a wavelet and the WAD signal. An example of such a mismatch would be if a wavelet with cycle length 40 s was convolved over an area with many short cessations. The convolution will pick up a significant overlap in areas, but this is not a reflection of periodicity in cessations occurring. It is important for this algorithm to be able to distinguish between PB and clustered apneas [49]. Examples of this are also given in Appendix C.

Table 4.2: Lengths of cessations analysed per wavelet

Wavelet length (s)	Length of one cycle (s)	A:B	Length of A (s)	Length of cessations analysed (s)
60	10	1:1	5	2 – 6.25
		1:2	3.33	2 – 4.15
		2:1	6.67	4 – 8.3
90	15	1:1	7.5	6.25 – 8.75
		1:2	5	4.15 – 5.85
		2:1	10	8.3 – 11.7
120	20	1:1	10	8.75 – 11.25
		1:2	6.67	5.85 – 7.5
		2:1	13.33	11.7 – 15
150	25	1:1	12.5	11.25 – 13.75
		1:2	8.33	7.5 – 9.8
		2:1	16.67	15 - 18.3
180	30	1:1	15	13.75 – 16.25
		1:2	10	9.8 – 10.85
		2:1	20	18.3 – 20
210	35	1:1	17.5	16.25 – 18.75
		1:2	11.67	10.85 – 12.5
		2:1	N/A	N/A
240	40	1:1	20	18.75 – 20
		1:2	13.3	12.5 – 14.15
		2:1	N/A	N/A

The outcome of this convolution, $\gamma(s,\tau)$, is a parameter that is a measure of both time and frequency, as can be seen in Equation 4.3. Here $\bar{\psi}_{s,\tau}(t)$ refers to the scaled daughter wavelet. The function that the wavelet is convolved with is referred to as $u(t)$, in this case the WAD as discussed earlier in this section. This study makes the differentiation between pure wavelet transforms as discussed in Section 2.4.2 and using the wavelet for template matching, as is discussed here.

$$\gamma(s,\tau) = \int_{-\infty}^{\infty} u(t)\bar{\psi}_{s,\tau}(t)dt \tag{4.3}$$

The output of the convolution was normalised by dividing by the maximum value of the wavelet's convolution with itself. This output value is referred to as the PB index, and instances where the PB index output is higher than or equal to 0.6 were then identified as PB [49]. A preliminary analysis of the PB index done by Mohr et al. aided them in empirically determining this threshold. This research group validated their method by having four neonatologists evaluate 200 instances of possible PB, and comparing it to the results from the algorithm. The maximum value over a 40 s window was recorded every 20 s, since the aim is detect PB with cycle duration of up to 40 s [49].

Appendix C offers more insight into the working of this algorithm. It shows the programming logic applied to execute it, an example of the wavelet being moved over the probability of cessation signal, as well as a examples of PB detected.

4.4 Transition models

The algorithms in Sections 4.2 and 4.3 were used to create models that represent the relationship between different respiratory events. This enables a more holistic view of the relationship between the respiratory dynamics of these preterm infants.

Note that the idea for these transition models were derived from a Markov model. Decision trees are often used in clinical decision making, however they are not always sufficient to represent every type of clinical problem. In some cases employing a decision tree would require an oversimplification of the problem. Markov models are often preferred when the following is true: there is a risk involved that is continuous over time; the events in question can occur more than once; and the timing of the events are important. The ability of the model to represent repetitive events and their corresponding time dependence and probability makes it useful to represent clinical issues. In the model, the assumption is made that a patient is always in one of a finite number of specified states, and that within a cycle of specified duration, they can transition from one to another. Arrows between states indicate one transitioning into the other, while an arrow leading from a state to itself indicates that the patient can stay in that state for consecutive cycles [69].

It should, however, be clearly noted that the models developed in this section are not Markov models, since the models allow for more than one state to precede another state, while in Markov models a state can only be preceded by a singular state [69].

4.4.1 Respiratory transition model

This model aims to illustrate the probability that, given a current respiratory event is occurring, another event will occur within a certain timeframe. Three events were identified to create a model that visualises the breathing dynamics of preterm infants. Each of these represent a state of breathing, and a fourth state constitutes a lack of events, essentially normal breathing. These are outlined in Table 4.3. Note that while discussing these models Cessation and Apnea are capitalised to indicate that they are part of the model and adhere to the specifications of Table 4.3.

Table 4.3: Events and states of transition model

State	Event	Description
1	Cessation	A pause in breathing of 5 – 20 s
2	Apnea	A pause in breathing longer than 20 s
3	PB	Periodic breathing using all A:B relationships
4		The absence of events

Cessations were broken into two events. The first ('Cessations'), represents cessations 5 – 20 s. This is distinguished from cessations over 20 s, which can be classified as apneas even without the detection of bradycardia or hypoxemia [12]. 2 – 5 s are ignored in this model due to the frequency of their occurrence. For a specific Δt (length of time), the algorithm retrospectively searches the signal before an event occurs to check whether a certain event has occurred. If, for example, Event 2 is within Δt of Event 1, the assumption is made that Event 2 'leads into' Event 1, as illustrated in Figure 4.5. If no events occur within Δt of Event 1, the assumption is made that normal breathing 'leads into' Event 1.

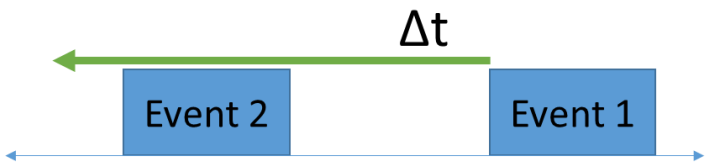

Figure 4.5: Analysis done in respiratory transition model

The analysis for each event is done as follows. Firstly, the WAD signal is adapted to remove all identified 2 – 5 s cessations. Throughout the signal for all ten infants, the event is identified as well as the index of where it starts occurring. A count is done of the total number of times this event occurs, as well as the percentage of each infant's signal taken up by this event. From these percentages the median and interquartile ranges (IQR) are determined. To determine the events transitioning into this one, a search is done retrospectively over Δt. A count is done of how often another event occurs within the preceding Δt, and from that a percentage is calculated representing the probability of the preceding event transitioning into the studied event. A percentage is also calculated of how often no events precede the studied event within Δt. This is then denoted as normal breathing preceding the event. This model enables the study of the relationships between these respiratory dynamics. An example of this model is shown in Figure 4.6. Note that normal breathing is a state, not an event, and therefore no events lead into it.

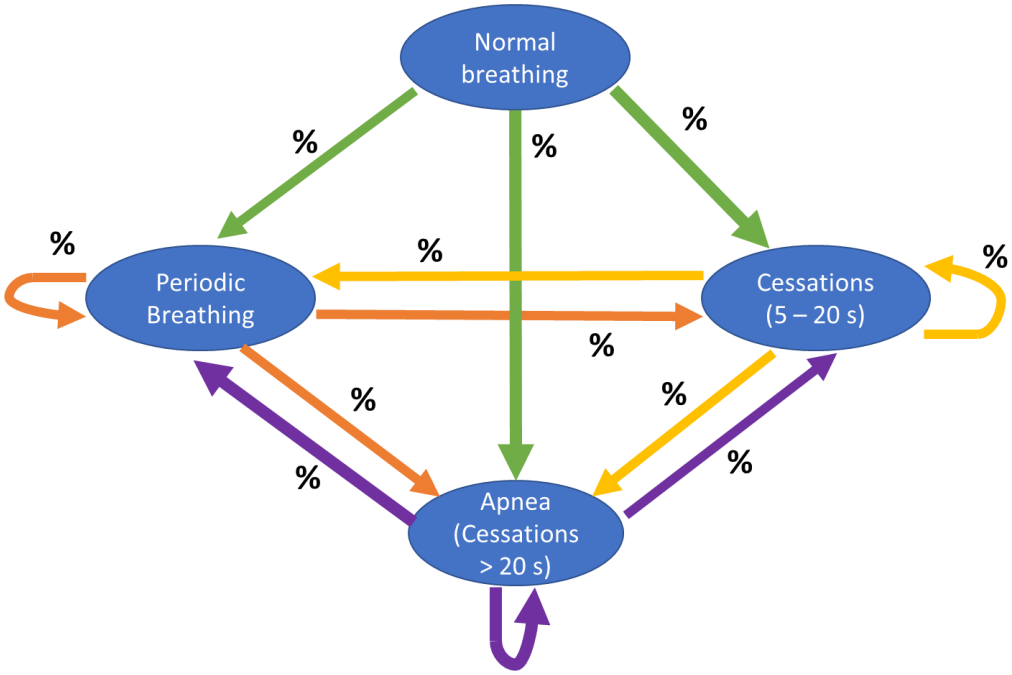

Figure 4.6: Respiratory transition model

4.4.2 Event centred transition model

This model, which is an adaptation from the model described in Section 4.4.1, looks at the respiratory behaviour surrounding a specific event. Once again it detects the specified event and searches retrospectively over Δt for events preceding it. However, in addition it also finds the index where the specified event

ends, and searches *Δt* into the future to see what the probability is of certain events following the studied event. This is outlined in Figure 4.7 below.

Figure 4.7: Analysis done in event centred transition model

Figure 4.8 illustrates the model gained as output, with the event in the middle representing the event under consideration. All percentages leading into the studied event represents the frequency of another event occurring within *Δt* before the studied event occurs. Likewise, the percentages leading out of the studied event represent how often an event occurs within *Δt* after the studied event. This enables the study of behaviour surrounding a specific respiratory event.

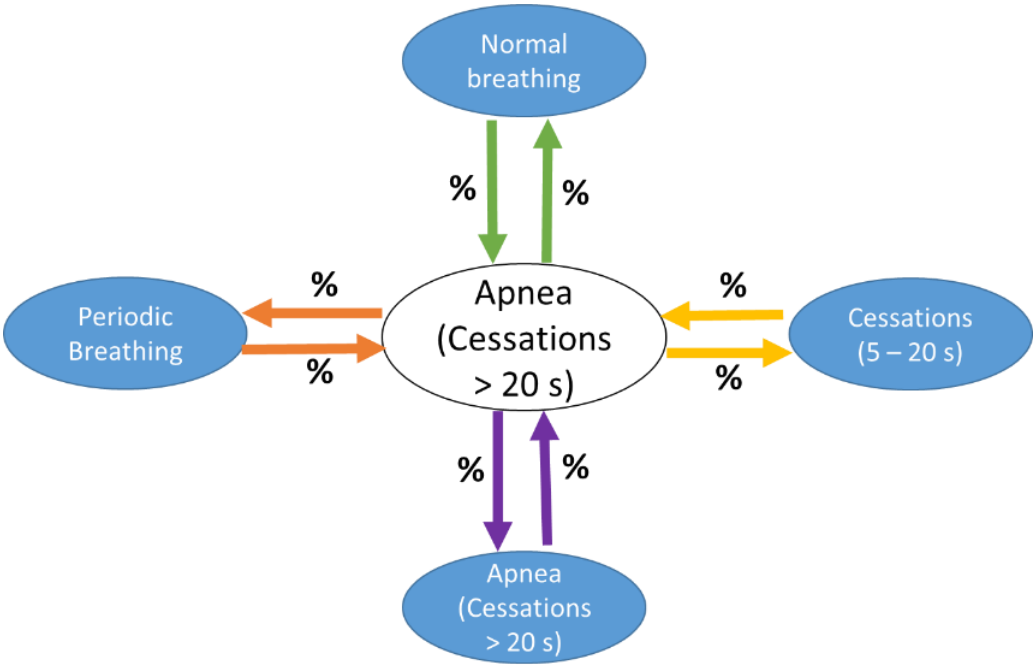

Figure 4.8: Event centred transition model

4.5 Heart rate variability

As mentioned in Section 4.2.1, R peaks were extracted from the ECG waveform using an existing algorithm [68]. From this the interbeat intervals were calculated, or as referred to from henceforth, the RR signal. (The time series of these RR beats is called a tachogram.) HRV can be studied using frequency and time domain related measures. Two advantages of using HRV measures are that they are non-invasive and fairly easy to perform [22]. All time-domain techniques start out with calculating the beat-to-beat interval, considering only QRS complexes and ignoring any abnormal beats. In this case only beats between 200 ms and 600 ms are considered physiologically reasonable and taken into account [24]. The RR interval is also often called the NN (normal to normal) interval, and all the measures outlined below refer to it as such.

The standard deviation of the NN intervals is calculated over a certain time as shown in Equation 4.4 to yield the *SDNN*.

$$SDNN = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(RR_i - \overline{RR})^2} \tag{4.4}$$

This measures the total variability that arises from both periodic and random sources. However, *SDNN* cannot differentiate between sources that contribute to variability. *RMSSD* is calculated by taking the square root of the mean squared difference between successive RR intervals, as shown in Equation 4.5. This measure assesses the beat to beat variability in the RR signal.

$$RMSSD = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n-1}(RR_{i+1} - RR_i)^2} \tag{4.5}$$

In addition, *pNN50* is calculated in Equation 4.6, representing the percentage (or proportion) of successive RR intervals differing with more than 50 ms. It is calculated every minute based on data from the previous five minutes. This aims to solve the problem concerning *SDNN* by extracting periodic variability from a baseline heartbeat. Note that n represents the total number of RR intervals in the series.

$$pNN50 = 100 * (\sum_{i=1}^{n}(|RR_{i+1} - RR_i| > 50\,ms))/n \tag{4.6}$$

Although at higher respiratory frequencies, as are present here, this technique is less accurate and struggles to quantify dynamic changes in HRV on a beat–to-beat basis [23].

Two additional measures are calculated that are specifically applicable to preterm infants. Since transient, repetitive decelerations of HRV are potential signs of illness or distress, *pDec* is calculated. The percentage of decelerations, calculated

as the percentage of NN intervals longer than the mean NN interval of the previous five minutes. It aims at explicitly extracting variations in HRV that arises due to decelerations [24]. There is also a need to capture the magnitude of these decelerations. For this *SDDec* is calculated, which represents the standard deviation of decelerations and therefore the standard deviations of all the NN intervals that contribute to *pDec* [24]. Figure 4.9 shows a high level overview of how these measures are extracted from the RR signal.

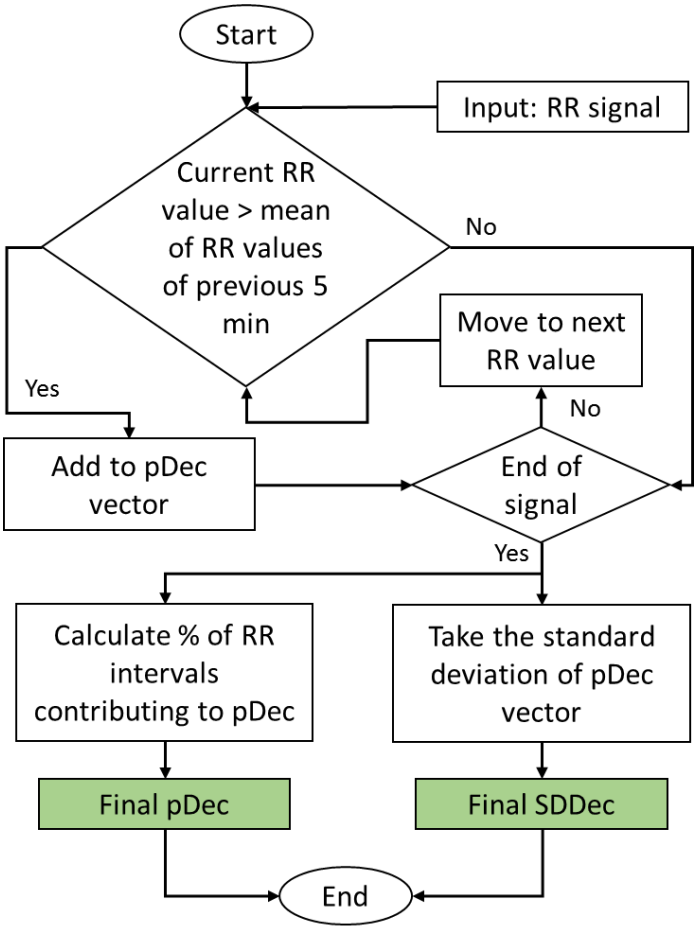

Figure 4.9: Logic flow diagram for pDec and SDDec

4.6 Phase Rectified Signal Averaging

Phase Rectified Signal Averaging (PRSA) can be used to study quasi-periodic oscillations in non-stationary signals, enabling the assessment of a system despite the presence of noise and phase-resetting. This technique is capable of not only detecting these oscillations, but also quantifying them. It was first applied on

tachograms to predict mortality after myocardial infarctions, where it proved to be more successful than traditional measures [70].

This signal processing operation is performed by identifying anchor points to phase-rectify the signal by aligning fluctuating oscillations and averaging the points surrounding them [71]. Firstly, the anchor points are chosen. This can be done according to a variety of criteria. Equation 4.7 gives one such a method.

$$\frac{1}{T}\sum_{j=0}^{T-1} u_{i+j} > \frac{1}{T}\sum_{j=1}^{T-1} u_{i-j} \tag{4.7}$$

u represents the signal analysed, and *T* is a variable determining the amount of points over which the averaging is done. This is freely changeable, and increasing it essentially has the effect of low pass filtering, thereby smoothing the signal. Choosing *T* as one would result in every increased point being identified as an AP. In this case, *T* is chosen as five, meaning that an anchor point is identified when the mean of five values are greater or smaller than the mean of the previous five values. *T* set to one will highlight mechanism responsible for beat-to-beat changes in heart rate, while choosing a higher *T* obtains the underlying mechanisms for more sustained HR increases and decreases. Anchor points corresponding to an increase in signal aims to capture decelerations in the signal, and anchor points based on signal decreases aim to capture accelerations. By these definitions, it is natural that about half the signal points are identified as anchor points. Bauer et al. specify that at least 1000 anchor points are needed for an accurate analysis [72].

Secondly, *L* number of points are identified both before and after the anchor point to create the PRSA window of length 2*L*. Anchor points too close to the beginning or end of signal are disregarded since the full PRSA window is not available. Many of these windows overlap. The parameter *L* should exceed the expected coherence time of periodicities in data, in this case chosen as 20 s (thus window of 40 s). This ensures that the window should be larger than the period of slowest oscillation that needs to be detected.

Thirdly, the output, namely the PRSA waveform, is determined by averaging over all anchor point- centred windows. Figure 4.10 gives a high level overview of this method applied on a RR signal. Due to this averaging, non-periodic components that are not time synchronized with the anchor points, will cancel out. These include noise, non-stationaries and artefacts due to sensor-inefficiencies, other physiological processes, movements, etc. Only events that have a fixed point relationship with the anchor points (thus any periodicities or quasi-periodicities) will survive this averaging [71].

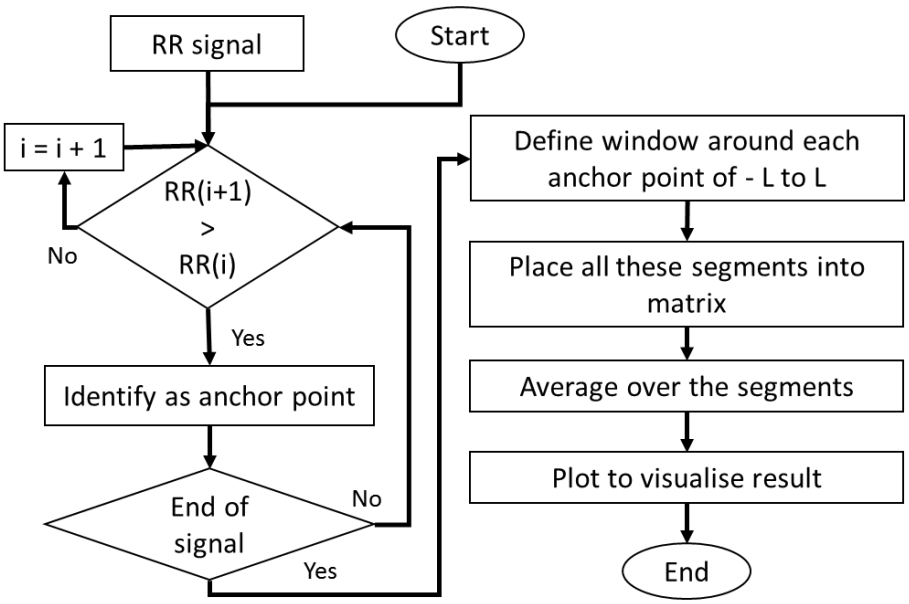

Figure 4.10: Logic flow diagram of applying PRSA on RR signal

Corresponding to this, deceleration capacity (*DC*) and acceleration capacity (*AC*) are also calculated. These measures are used specifically to study HR and cardiac vagal modulation, essentially looking at the relationship between accelerations and decelerations in the signal. It is used in conjunction with the PRSA technique [70], [73]. Equation 4.8 depicts this measure, with $X(0)$ denoting the anchor point. In literature, these values are generally calculated across four points. The *AC* is calculated in the same way, just using a PRSA window created by using increases in the signal as anchor points.

$$DC = \frac{X(0)+X(1)-X(-1)-X(-2)}{4} \tag{4.8}$$

4.7 Bivariate Phase Rectified Signal Averaging

Bivariate phase rectified signal averaging (BPRSA) is an adaptation of the PRSA method that allows the study of correlation between two different, time synchronized biosignals. Natural systems generate periodicities at different time scales. In living systems, periodic modulations often reflect closed loop regulation processes. This method is based on the assumption that the periodic modulations in one signal, the trigger signal, cause the periodicities in another, denoted as the target signal [74].

BPRSA follows the same structure as PRSA, with the main difference being that the anchor points are identified in the trigger signal and then translated to the target signal. Initially, the anchor point criteria, for example Equation 4.7, is applied to

the trigger signal. The potions of the anchor points detected are then noted, and at these same positions, anchor points are positioned on the target signal. From there the remaining steps are performed, namely identifying the windows of length 2*L* with the anchor point in the centre and averaging the signal segments over that window to obtain the result. Figure 4.11 gives a high level overview of applying this method.

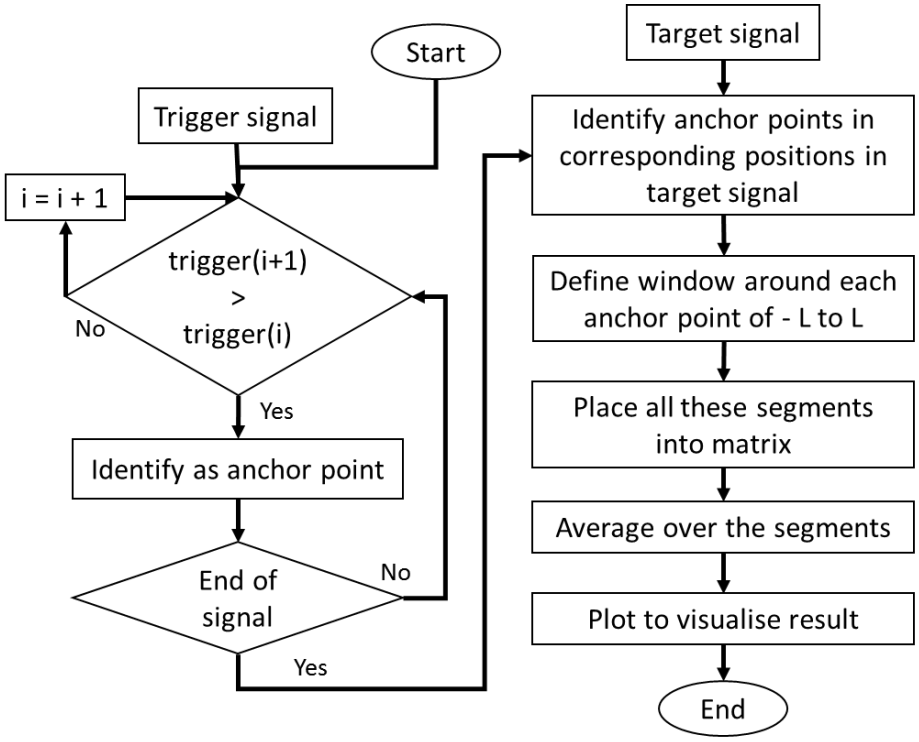

Figure 4.11: Logic flow diagram of applying BPRSA

4.8 Data analysis

Each signal was preprocessed by removing segments in which sensor detachment had occurred and then subtracting it by its own mean to obtain a zero mean signal. Both the cessation detection and PB detection algorithms were then applied to the entire dataset, classifying each infant's respiratory signal into cessations, non-cessations and PB. The temporal evolution of the percentage breathing cessation was examined. To do this, a moving percentage of cessation was calculated based on one hour segments and a sliding window of 15 minutes. This calculation accounted for all cessation events, as well as cessation events of duration 2 – 5 s, 5 – 10 s and more than 10 s, respectively. All outputs were then plotted against each other to visually examine their level of correlation.

The algorithms were also used to identify events outlined in Table 4.3, enabling the creation of the transition models described in Section 4.4. The behaviour surrounding each detected event was studied, regardless of which infant displayed this behaviour. The model in Section 4.4.2 was set up for apnea, since it is regarded as the most threatening respiratory event studied here. In addition, short respiratory cessations tend to be self-limiting, while ones as long as apneas often require intervention [25]. In both cases Δt is taken as two minutes. This Δt was chosen empirically. Since one of the events in the model is Apnea, which is cessations of more than 20 s, Δt less than two minutes was deemed too short. Models were also determined with Δt of longer durations, but two minutes was used for the main model due to the rapidly changing nature of preterm infant physiology.

The HRV was calculated and studied temporally in relations to the percentage cessation. The average HRV measure was calculated based on one hour segments, averaged every 15 minutes, similar to the percentage cessation. In addition, the PRSA was calculated using the RR signal, as described in Section 4.6. Before the PRSA and BPRSA analyses were done, the signals were divided by their 75^{th} percentile value, normalizing them to oscillate roughly between 1 and -1 in magnitude.

The *DC* and *AC* were calculated using adaptations of Equation 4.8, where the measures are calculated over 4 s, 8 s and 20 s, all centred on the anchor point. In calculating the BPRSA in Section 4.7, this RR signal also serves as the trigger signal. BPRSA was calculated twice, using variations of the respiratory signal as the target signal. The first BPRSA was calculated with the output of Equation 4.1, therefore the WAD signal. The second result was determined using the respiratory signal after only the cardiac filter had been applied. *L* and *T* were still chosen as 20 s and five respectively, with the goal to obtain the mechanisms for more sustained increases and decreases, as was discussed in Section 4.6. Addition calculations were also done with *T* chosen as one and ten to observe the influence of changing this parameter.

Additionally, applying the BPRSA requires that both the trigger and target signal are uniformly sampled. Due to this, the RR signal needed to be resampled using spline interpolation to correspond to the both target signals' sampling in time. Figure 4.12 gives an overview of the steps executed to achieve this.

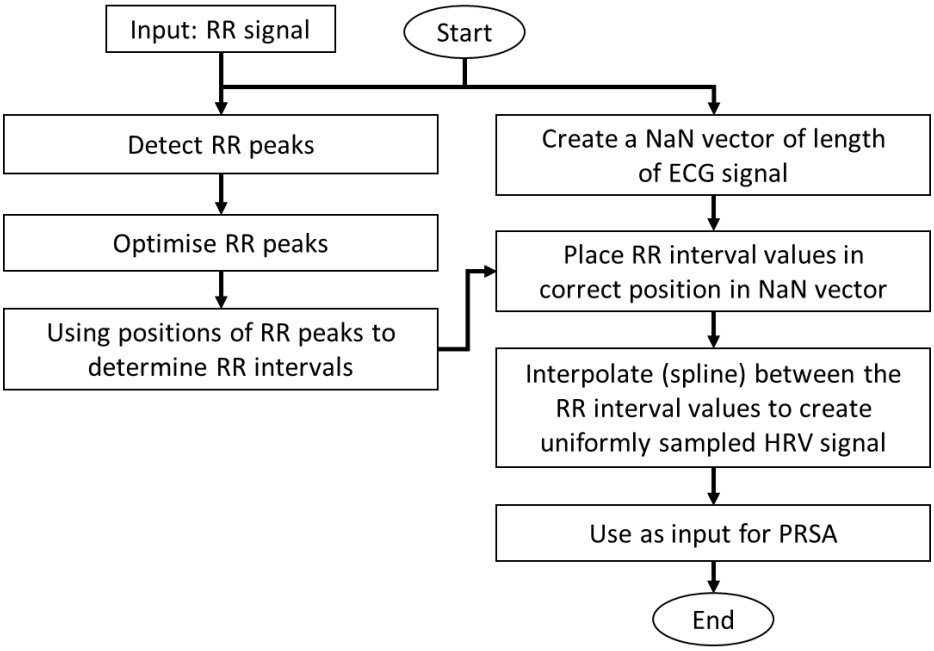

Figure 4.12: Logic flow diagram of uniformly resampling the RR signal (trigger) to correspond to the target signal

5 Results

The most significant results obtained are presented below. Section 5.1 focuses on the cessation and PB detected by the Lee et al. and Mohr et al. algorithms. The output for these algorithms form the basis for all the following results. Section 5.2 discusses the transition models created, which serves to satisfy Objective 1. An analysis of the 2 – 5 s cessations is done in Section 5.3, which aligns with Objective 2.1. Section 5.4 supports Objective 2.2 by temporally analysing cessations. Lastly, Sections 5.5 and 5.6 look at the relationship between the cardiac and respiratory systems in preterm infants, thereby addressing Objective 2.3.

5.1 Cessation and PB detection

On average 89.9% of each infant's data was usable. Table 5.1 shows the total percentage of time spent in cessation per infant, according to the Lee et al. algorithm and the modified version of it, respectively. As expected, with the modified algorithm the time spent in cessation was higher, since this includes the 2 – 5 s cessations disregarded by the original algorithm (see Sections 4.2.2 and 4.2.3). The absolute increase in the percentage of time spent in the cessation of breathing was between 3.0 – 4.3%. The mean time spent in cessation computed by the Lee et al. algorithm for the dataset was 9.1%, with a range from 2.6% to 17.3%. For the modified algorithm, the mean was 12.5%, with a corresponding range between 5.8% and 21.1% [58].

Table 5.1: Percentage time spent in breathing cessation

	Original algo* %	Modified algo+ %	Severity
Infant 1	12.0	15.0	M
Infant 2	14.4	17.9	H
Infant 3	17.3	21.1	H
Infant 4	2.6	5.8	L
Infant 5	11.1	14.4	M
Infant 6	5.4	9.0	L
Infant 7	6.8	10.5	M
Infant 8	5.1	8.1	M
Infant 9	3.9	6.5	L
Infant 10	13.2	17.5	H

*: Includes all > 5 s cessations and 2 -5 s segments in close proximity to other cessations
+: Includes all > 5 s cessations and all 2 -5 s segments
Abbreviations used: H = high, M = medium, L = low, algo = algorithm

The average amount of PB detected was 0.63%. Infant 4 and 8 displayed no PB within their respiratory signal and excluding them the average PB is 0.79%. The maximum percentage PB is 3.1% for Infant 3, which is also the infant with the highest percentage cessations. The PB results for each infant are presented in Table 5.2. On average there was a 0.27% overlap (0.34% ignoring Infants 4 and 8) in the signals between cessations and PB. Looking at the percentage PB detected, this is consistent with the idea that PB consists of equal parts breathing and cessation.

Table 5.2: Percentage time spent in PB

Infant	% PB	% Overlap with cessations	% Overlap with cessations > 10 s	% Overlap with cessations > 20 s
1	0.7	0.3	0.1	0
2	1.3	0.6	0.2	0
3	3.1	1.3	0.4	0
4	0	0	0	0
5	0.2	0.1	0	0
6	0.2	0.1	0	0
7	0.4	0.2	0	0
8	0	0	0	0
9	0.1	0	0	0
10	0.3	0.1	0.1	0

The overlap between PB and cessations longer than 10 s is 0.08%, or 0.1% ignoring Infants 4 and 8. Another aspect of the results that was explored is the frequency of PB being detected by wavelets of different A:B relationships. It can be noted that A:B = 1:1 and A:B = 1:2 detect the vast majority of PB, with mean values 57.3% and 53.8% respectively. On average, the PB detected by these two relationships overlap by 12.5%. Very minimal PB was detected by A:B = 1:2, with mean value of 3.7%. The details of these results are presented in Table 5.3. Note the N/A for Infants 4 and 8, since no PB was detected in their respiratory signals.

Table 5.3: PB detected by different A:B ratios

Infant no.	% detected			% overlap		
	A:B relationship			A:B relationship		
	1:1	2:1	1:2	1:1 and 2:1	1:1 and 1:2	2:1 and 1:2
1	51.7	56.7	0	8.3	0	0
2	45.7	59.6	8.5	7.6	4.1	6.7
3	57.0	74.3	8.1	33.6	2.1	5.1
4	N/A	N/A	N/A	N/A	N/A	N/A
5	43.9	71.4	0	14.3	0	0
6	83.3	38.9	0	22.2	0	0
7	33.3	73.3	13.3	14.3	16.7	0
8	N/A	N/A	N/A	N/A	N/A	N/A
9	100	0	0	0	0	0
10	43.5	56.5	0	0	0	0
Mean	57.3	53.8	3.7	12.5	2.9	1.5

5.2 Transition model

5.2.1 Respiratory transition model

Figure 5.1 depicts the transition model for Δt equal to two minutes and taking into account all ten infants. It shows how frequently events (namely PB, Cessations and Apnea, as outlined in Table 4.3) were preceded by states (all the events and normal breathing). It also shows the median and inter quartile range (IQR) for each state, along with the total number of each event detected. The number of PB, Apnea and Cessations events detected were 103, 682 and 12004 respectively, therefore enabling the model to be built. The median PB detected was 0.3% (IQR: 0.1 – 0.8%), the median Apnea 1.6% (IQR: 0.5 – 2.8%) and median Cessations 6.8% (IQR: 4.4 – 10.4%).

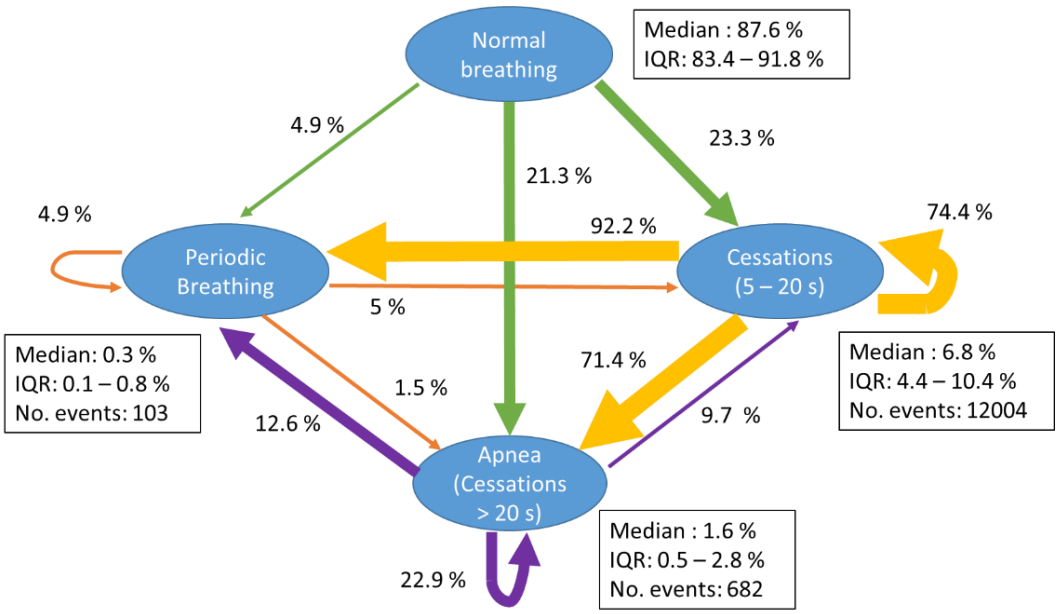

Figure 5.1: Respiratory transition model for *Δt* of two minutes

All events were strongly preceded by Cessations, which was the most frequently occurring event. Events were rarely preceded by PB, and Cessations were rarely preceded by Apnea. Normal breathing precedes PB less than 5% of the time, while preceding Cessations and Apnea more than 20% of the time. An increase in *Δt* strengthened the relationship between events, and subsequently reduced the likelihood of an event being preceded by normal breathing. Figure 5.2 demonstrates this model for *Δt* of ten minutes.

Cessations, Apnea and PB had a 95.8%, 96.9% and 99.0% chance of being preceded by cessations. There was a less than 3% chance that any event was preceded by the state of normal breathing. In the ten minutes leading up to an Apnea, there was a 50.1% chance of another apnea occurring.

5.2.2 Event centred transition model

This model centres on Apnea, since it is seen as the most clinically significant breathing event out of the three considered. It illustrates its interaction with all four states. It quantifies the interaction both preceding and following Apnea within *Δt* of two minutes. Figure 5.3 illustrates this.

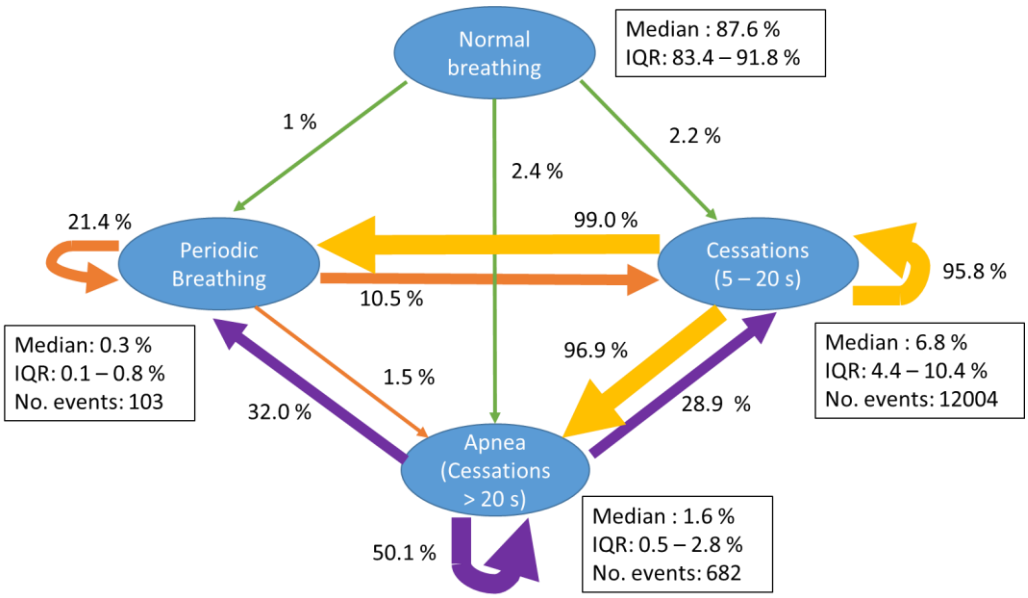

Figure 5.2: Respiratory transition model for *Δt* of ten minutes

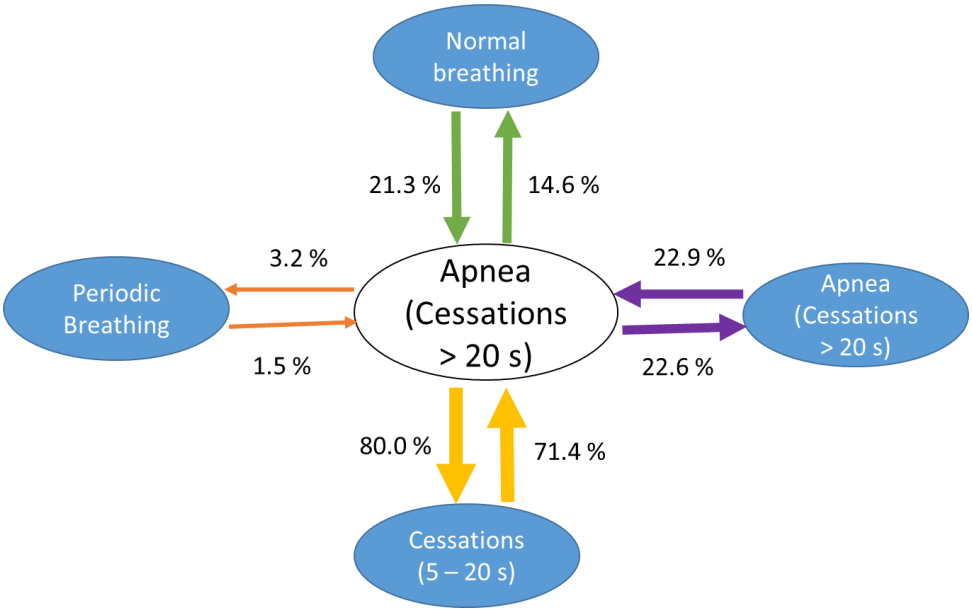

Figure 5.3: Apnea centred transition model with *Δt* of two minutes

The strongest relationship is both preceding and following Apnea (80 % preceding, 71.4 % following), is with Cessations. There is a notable, albeit less prominent, relationship between Apnea and itself (22.9 % preceding, 22.6 % following), as well as Normal breathing (21.3 %preceding, 14.6 % following). The relationship between Apnea and PB is the weakest (22.9 % preceding, 22.6 % following).

Figure 5.4 illustrates these relationships for *Δt* of ten minutes. The preceding and following relationship between Apnea and other states appear to be symmetrical. There is about a 50% chance that Apnea will precede or follow itself. The likelihood that Apnea was preceded or followed by Cessations is close to 100%. There is an approximately 7% chance that Apnea is preceded or followed by PB, while there is an even lower chance of normal breathing surrounding Apnea, with the probability being lower than 3%.

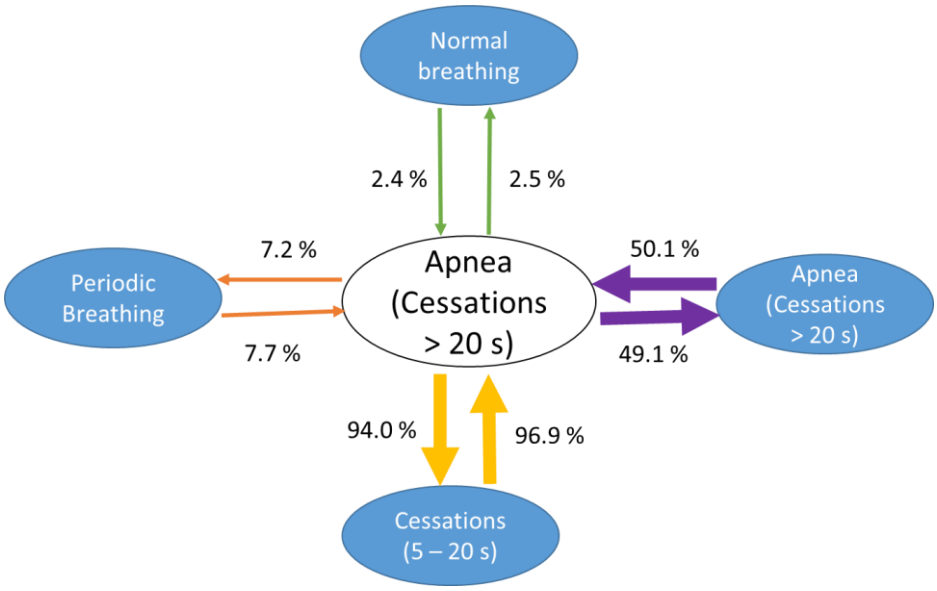

Figure 5.4: Apnea centred transition model with *Δt* of ten minutes

5.3 Short cessation (2-5 s) prevalence

The results presented in Figure 5.5 and 5.6 show representative results from one infant of each of three classes of breathing cessation identified. Infant 4 had a low severity level and the lowest percentage of cessation, Infant 5 had medium severity level, closest to the mean; while Infant 3 had a high severity level, with the highest percentage cessation. The figures show the contribution of each of the specified events to the total percentage of time spent in cessation for each of these three infants, with the first bar representing the 2 – 5 s cessation events.

Figure 5.5 shows these results for the cessations detected by the original cessation detection algorithm (from Section 4.2.2), while Figure 5.6 shows the results for the modified algorithm (from Section 4.2.3). In Figure 5.5 the contribution 5 – 10 s overshadows that of 2 – 5 s cessations for all severity levels. However, for the modified algorithm in Figure 5.6 this is not the case. In the top plot (high severity), an almost equal number of 2 – 5 s events and 5 – 10 s events can be seen.

However, the contribution of the 5 – 10 s events to the overall time spent in cessation is higher. In the middle plot (medium severity) both the contribution and number of 2 – 5 s cessation events increase, while in the low severity case seen in the bottom plot the 2 – 5 s events outweigh both the number and contribution of 5 – 10 s events. In fact, for Infant 4 it outweighs all other cessations combined, with 88 s per hour spent in cessations longer than 5 s and 119 s spent in the 2 – 5 s cessation category. It can also be noted that there are almost no cessations above 20 s duration present.

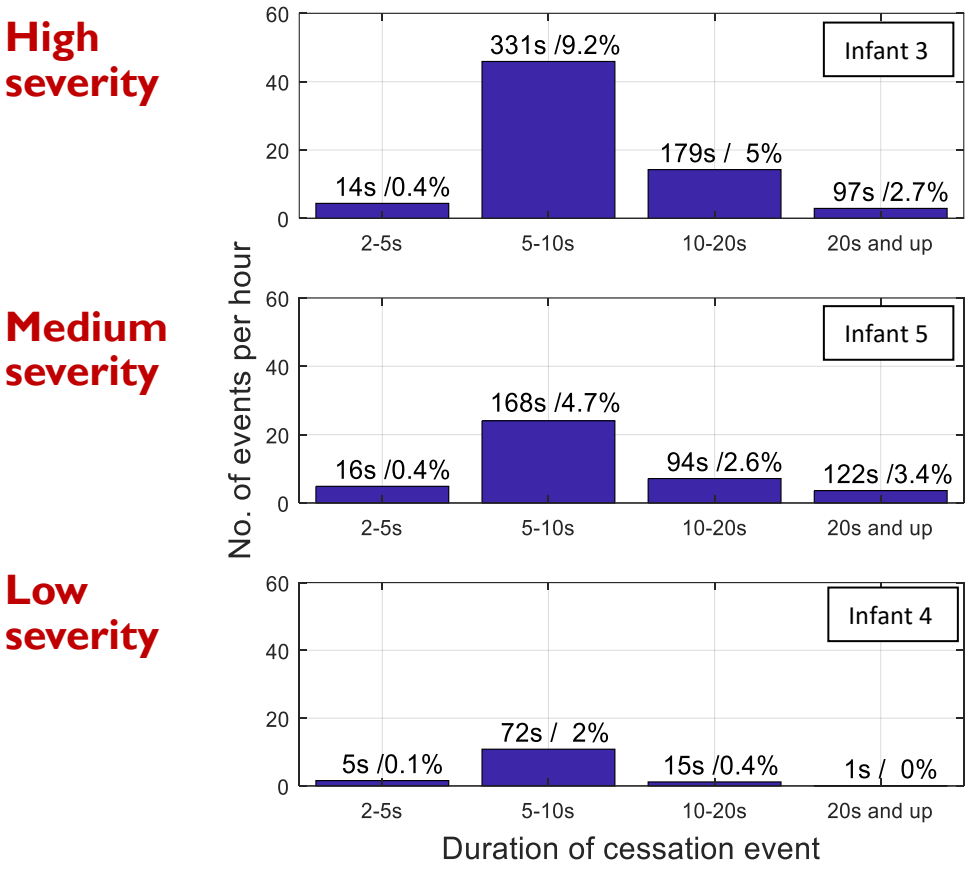

Figure 5.5: Contribution of cessation events of different lengths with the corresponding time and % spent in cessation per hour displayed on top of each bar for the original algorithm. Top: Infant 3, high severity. Middle: Infant 5, medium severity. Bottom: Infant 4, low severity.

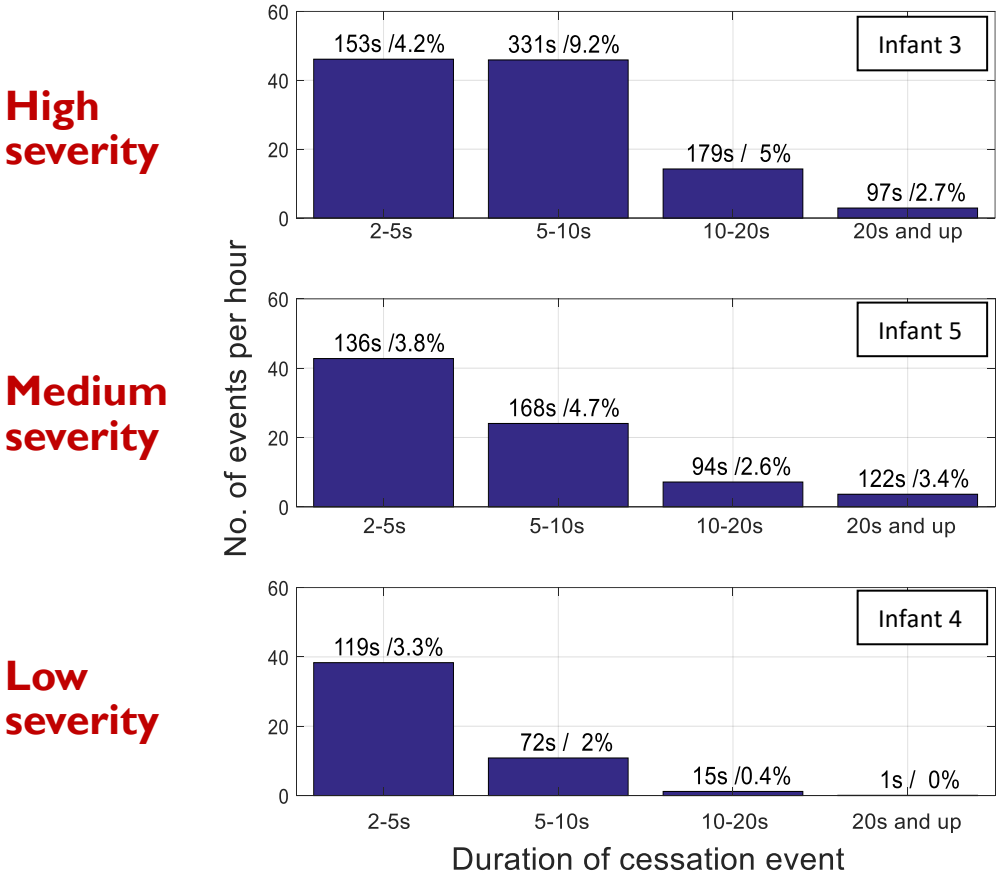

Figure 5.6: Contribution of cessation events of different lengths with the corresponding time and % spent in cessation per hour displayed on top of each bar for the modified algorithm. Top: Infant 3, high severity. Middle: Infant 5, medium severity. Bottom: Infant 4, low severity.

Figure 5.7 visualises the relationship between the 2 – 5 s cessation events, and longer cessation events with a scatter plot. The relationships are evaluated with 5 – 10 s events (X), longer than 10 s events (■) and longer than 20 s events (●). A line of best fit is plotted for each, and the accompanying correlation coefficients (R2) is 0.53, 0.38 and 0.23, respectively. The closest correlation is observed between 2 – 5 s and the 5 – 10 s events, followed by 10 s and up, and 20 s and up.

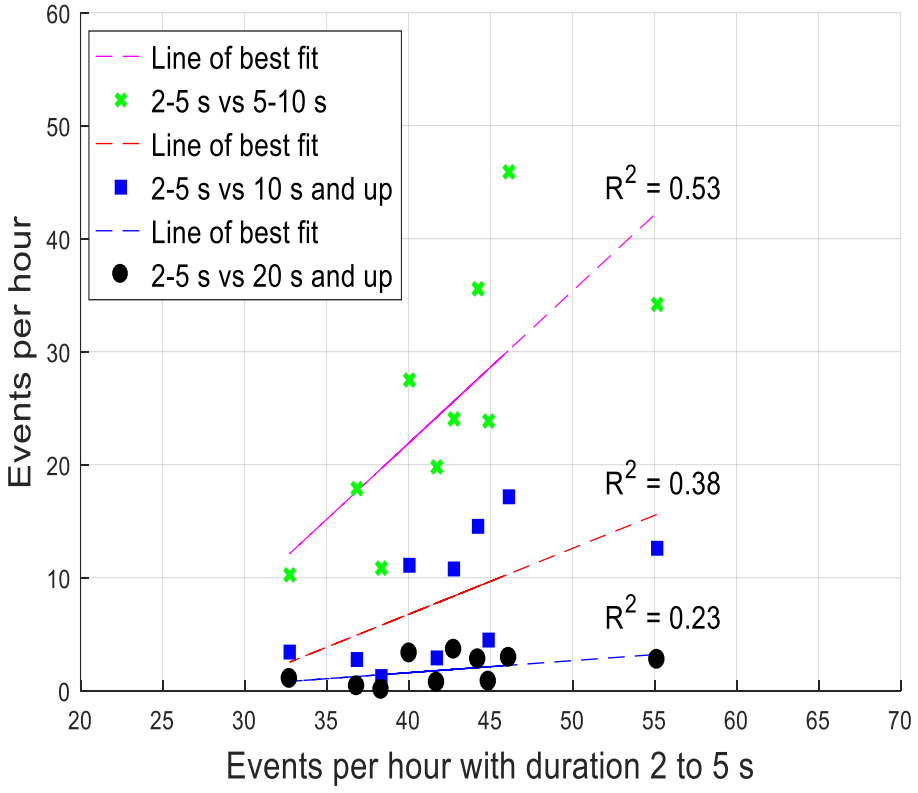

Figure 5.7: Relationship between 2 - 5 s events and longer cessation events.

5.4 Temporal evolution of percentage cessations

Figure 5.8 shows how the percentage of cessation changes over time for each of the three identified infants, while Figure 5.9 shows this change for Infant 9. This infant has the longest available signal, enabling an observation of the temporal changes in cessation over a longer period. These figures indicate the total percentage cessation (--), as well as the contribution of the grouped duration events over time, specifically the contributions from > 10 s (- -), 5 – 10 s (-·-·) and 2 – 5 s (···) events respectively. Periodic trends are present in all four plots, regardless of the severity level. The plot for events of 5 – 10 s and more than 10 s seem to correlate with the trend of the overall percentage cessation.

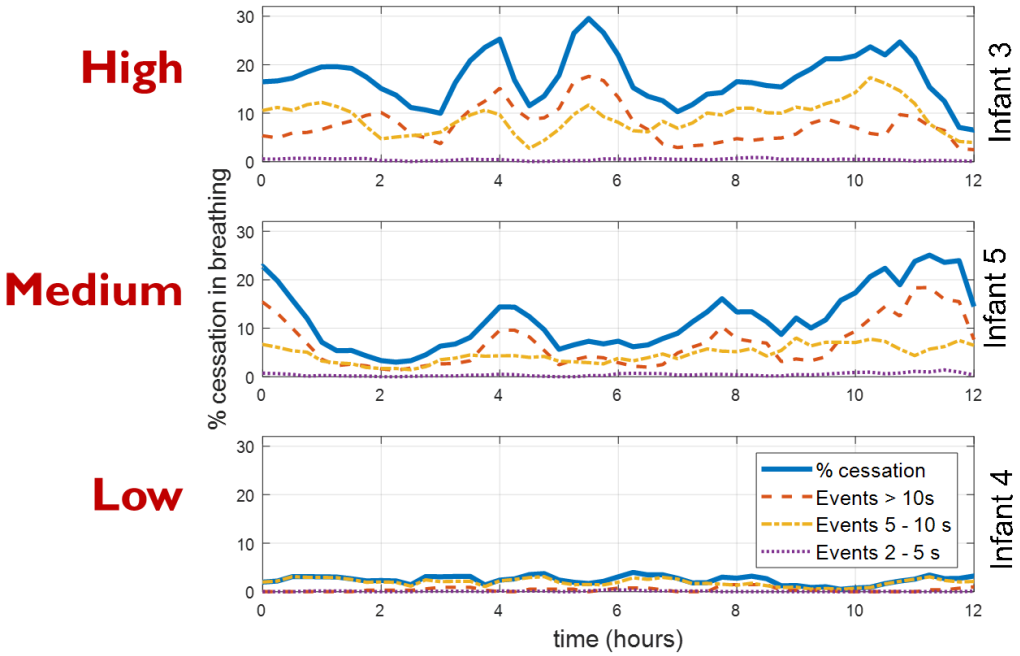

Figure 5.8: Temporal evolution of percentage cessation in breathing over a 12-hour period. Top: Infant 3, high severity. Middle: Infant 5, medium severity. Bottom: Infant 4, low severity.

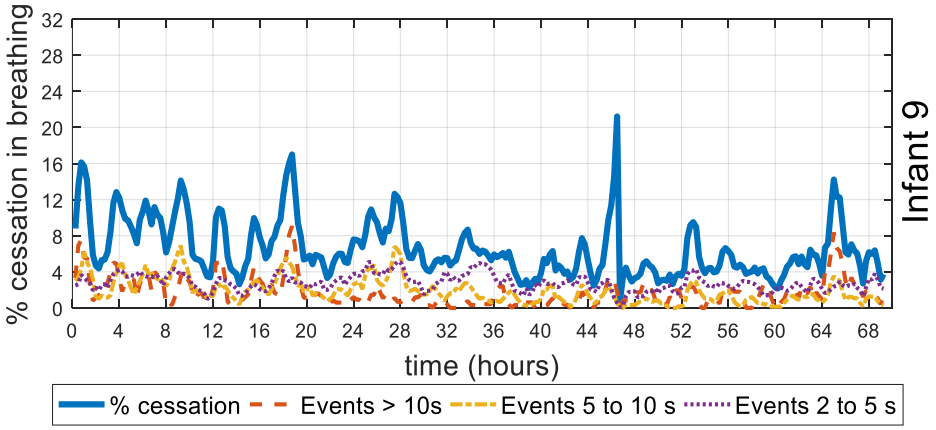

Figure 5.9: Temporal evolution of percentage cessation in breathing over a 70-hour period for Infant 9

5.5 Temporal evolution of HRV

Figures 5.10 to 5.14 below show the temporal evolution of measures that track HRV. In all cases, the top graph displays the temporal evolution of total cessations, as discussed in Section 5.4. In each case, the bottom graph represents the HRV measure. It was found that SDNN appears to have the closest temporal relationship to cessation. Figure 5.10, using data from Infant 1 over 24 hours, gives a clear indication of this relationship.

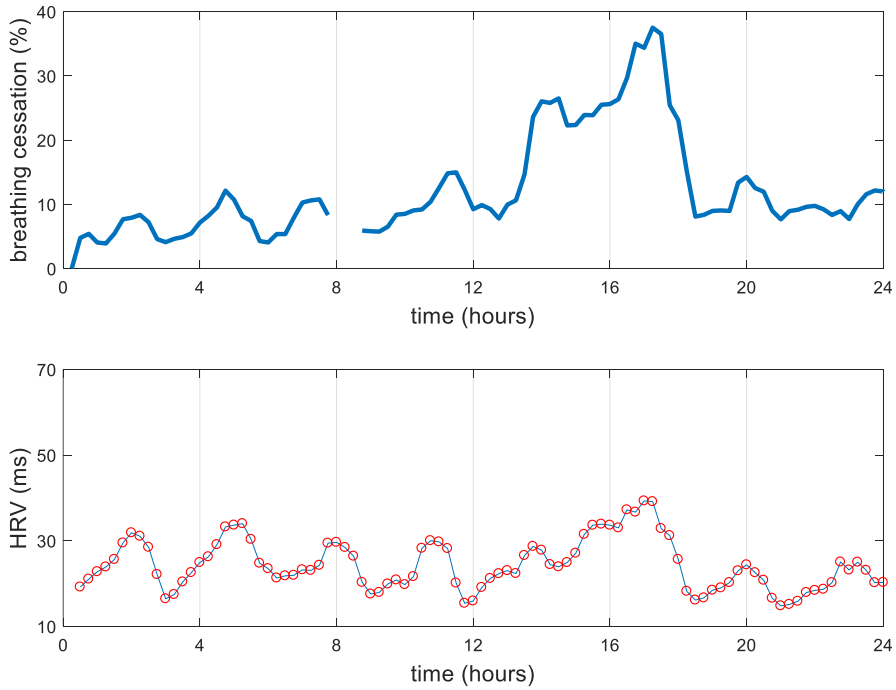

Figure 5.10: Both for Infant 1. Top: Temporal evolution breathing cessations. Bottom: Temporal evolution of SDNN

The SDNN in the bottom graph of Figure 5.10 has a similar periodicity to the percentage of breathing cessations. Visually it seems to be that the peaks coincide at similar points in both waveforms. Note that at some points a lack of signal is evident due to too many NaN values being present at that point to accurately calculate the relevant measure.

Similarly, Figures 5.11 to 5.14 display these temporal trends for RMSSD, pNN50, pDec and SDDec respectively, all for Infant 1.

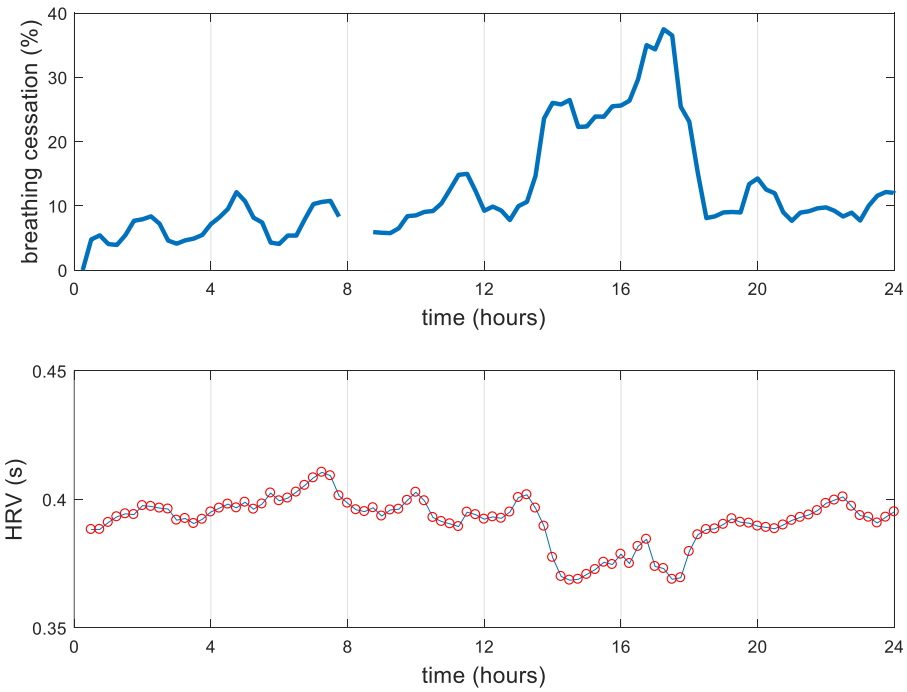

Figure 5.11: Both for Infant 1. Top: Temporal evolution breathing cessations. Bottom: Temporal evolution of RMSSD

Figure 5.11 shows the same figure for RMSSD versus percentage cessation. Although periodicity is noted in both signals, they seem less closely related since the peaks in both signals seem to coincide less clearly than in the case of SDNN. The behaviour of pNN50 and percentage cessation seem to once again mimic each other to some extent, as can be seen in Figure 5.12. The temporal evolution of pDec, as seen in Figure 5.13, does not seem to follow the same pattern as the percentage cessation.

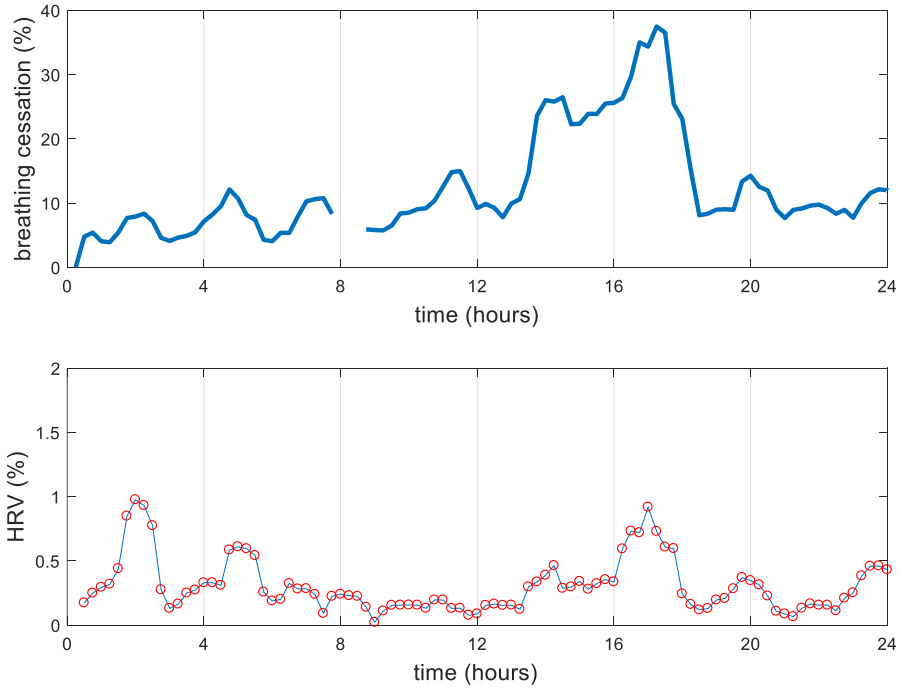

Figure 5.12: Both for Infant 1. Top: Temporal evolution breathing cessations. Bottom: Temporal evolution of pNN50

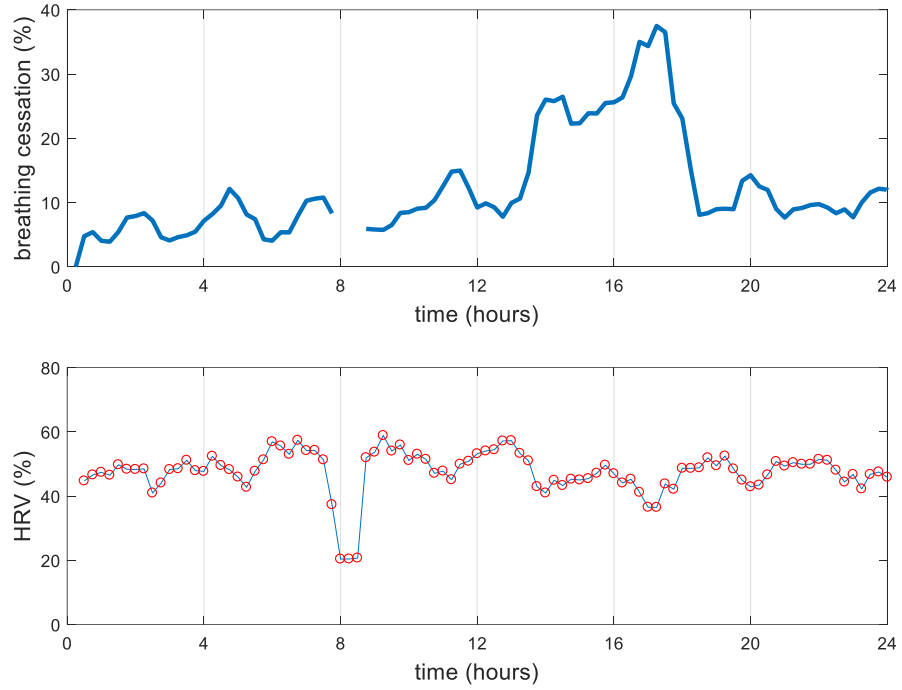

Figure 5.13: Both for Infant 1. Top: Temporal evolution breathing cessations. Bottom: Temporal evolution of pDec

However, looking at SDDec in Figure 5.14, once again visually it seems to be that the peaks coincide at similar points in both waveforms.

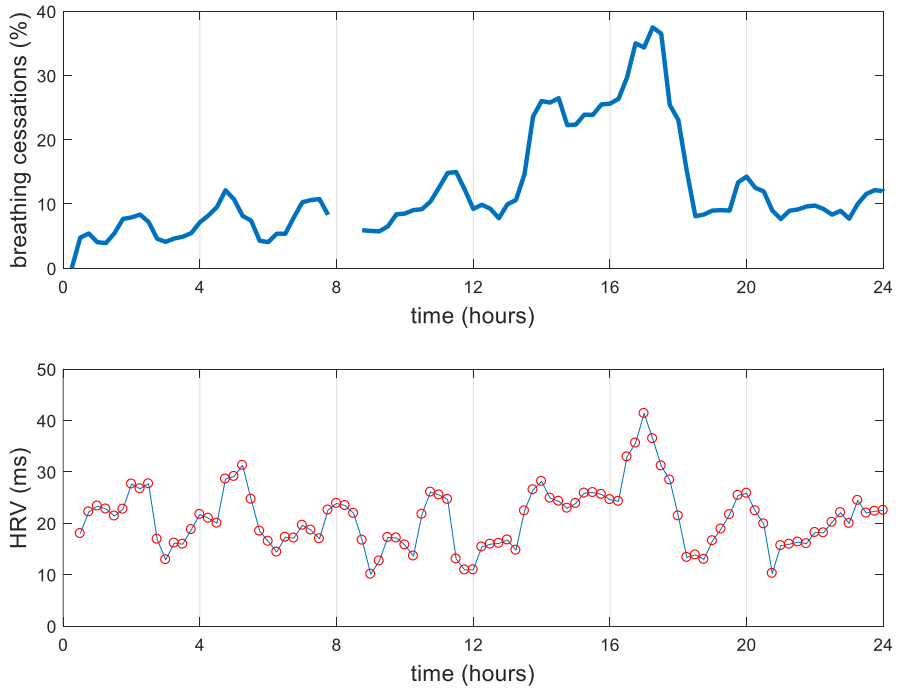

Figure 5.14: Both for Infant 1. Top: Temporal evolution breathing cessations. Bottom: Temporal evolution of SDDec

These results suggest that some relationship may exist between percentage cessation and HRV measures. However, this is not definitive since the signals had been heavily processed to allow this temporal analysis relative to the percentage cessations detected. This indicated the need for a more detailed and precise analysis, of which the results are presented in Section 5.6 that follows.

5.6 PRSA and BPRSA

The PRSA was determined for each infant. Sufficient anchor points could be determined for each analysis, as is outlined in Appendix D. The PRSA behaviour, seen in the top graphs of Figures 5.15 and 5.16, agreed with what was as expected from literature [71]. This was calculated for Infant 1 (- · - ·) as well as for the average of all ten infants (----), and the behaviour is similar for both.

The BPRSA with RR signal as trigger and WAD as target (middle graphs of Figures 5.15 and 5.16) show that there is a relationship between these two signals [75]. In Figure 5.15 (middle), it can be observed that decelerations in the RR signal are in

some way linked to an increased chance of cessations. Figure 5.16 (middle) represents the relationship between accelerations in the RR signal and the WAD. It should be noted that these graphs represent the interaction between the trigger and target signal, they do not represent direct numerical values of the signals. Therefore, although the target signal represents the probability of a cessation occurring, a negative value on the graphs does not represent a negative probability. This graph indicates that accelerations in the RR signal coincide with a decreased chance of cessations. This trend was evident in all infants except for Infant 5, which displayed no relationship at all (i.e., a flat line). Note the similarity in behaviour between the Infant 1 and Average plot. Appendix D contains these graphs for all infants.

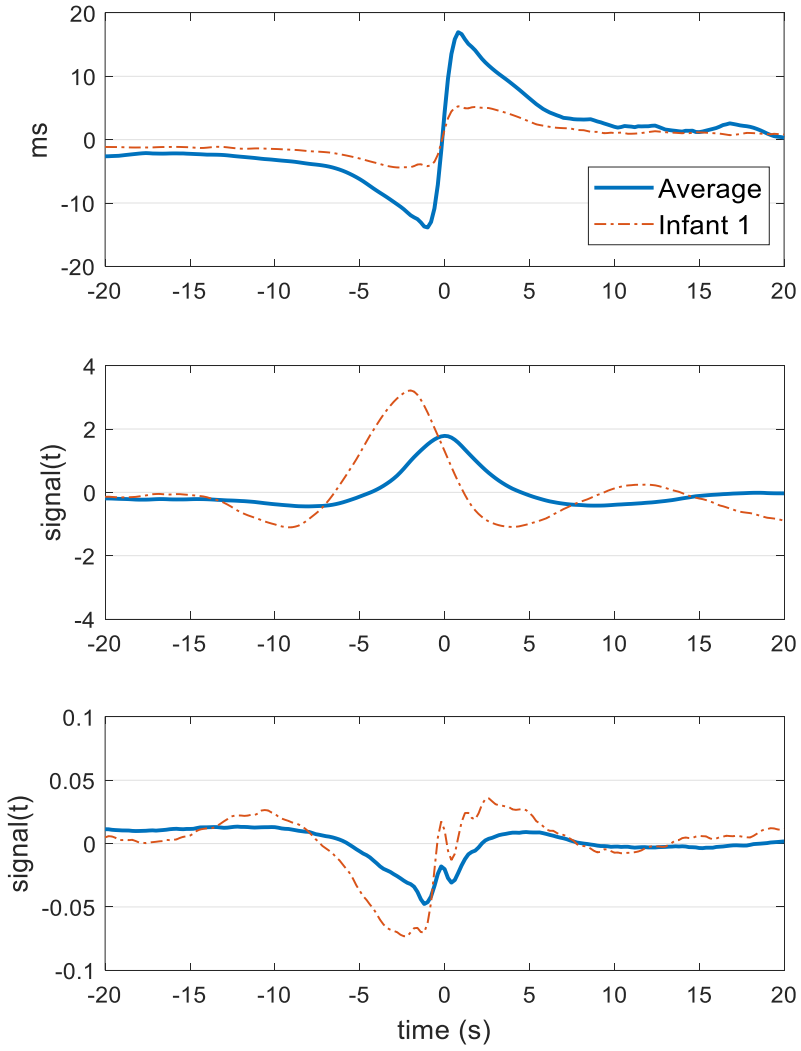

Figure 5.15: Top: Deceleration PRSA of RR signal. Middle: Deceleration BPRSA with RR signal as target signal and WAD as target signal. Bottom: Deceleration BPRSA with RR signal as target signal and respiratory signal as target signal

The bottom graphs in Figures 5.15 and 5.16 show the relationship between the RR signal and respiratory signal after it has been normalized and the cardiac filter has been applied. It clearly shows interaction between these signals, however, there is no evident trend throughout the behaviour for all infants. Note the dissimilarity between the Average plot and plot for Infant 1.

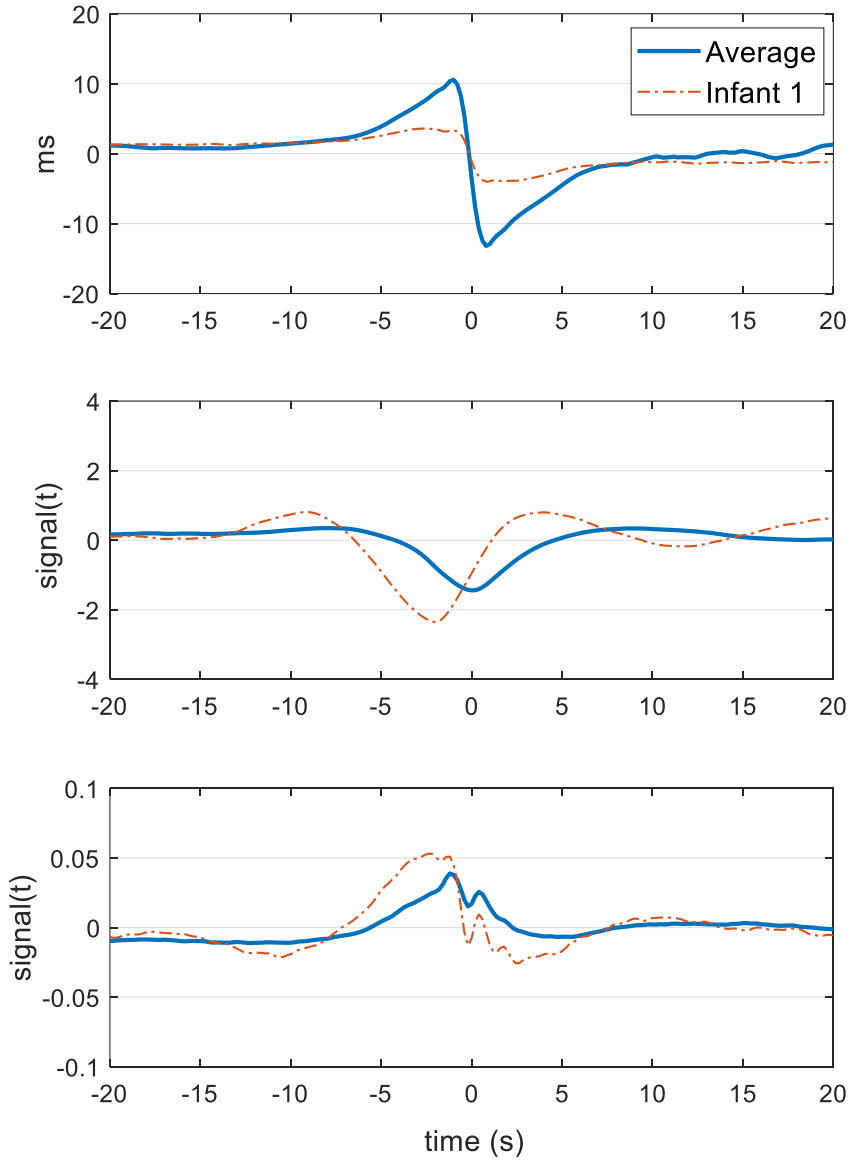

Figure 5.16: Top: Acceleration PRSA of RR signal. Middle: Acceleration BPRSA with RR signal as target signal and WAD as target signal. Bottom: Acceleration BPRSA with RR signal as target signal and respiratory signal as target signal

The average plot in each graph appears symmetrical about the y-axis (where time is 0 s), particularly the middle graphs in both Figures 5.15 and 5.16. It can also be observed that the set of deceleration graphs (Figure 5.15) and acceleration graphs (Figure 5.16) appear to be inverses of each other. The graphs for all ten infants can be seen in Figures D-2 to D-11 in Appendix D. As mentioned in Section 4.6, more than 1000 anchor points are needed for an accurate analysis. In the case of these signals, the number of anchor points identified were much higher than this. For Infant 1 there were 344 666 anchor points for deceleration and 471 334 for acceleration. The anchor points for all infants can be found in Appendix D.

The DC and AC values were calculated for the PRSA of the RR signal and can be seen in Table 5.4. The cessation severity levels from Section 5.1 were added to aid analyses. Increasing the window time decreases the mean AC and DC values. For a window of 4 s, the mean DC is 12.33 ms and the mean AC is -9.46 ms. Increasing the window to 20 s reduces these to 7.07 ms and -4.90 ms respectively. These decreasing numbers show how the oscillatory behaviour in the PRSA dies down, indicating how the body responds to changes in HR and reacts to restore it to normal.

Table 5.4: DC and AC

Infant no.	Window: 4 s		Window: 8 s		Window: 20 s		Cessation severity level
	DC (ms)	AC (ms)	DC (ms)	AC (ms)	DC (ms)	AC (ms)	
1	4.00	-3.11	4.22	-2.21	2.95	-2.44	M
2	13.09	-11.28	10.83	-9.66	6.26	-6.28	H
3	6.93	-5.75	6.50	-5.39	4.24	-3.49	H
4	2.10	-1.89	2.25	-2.05	1.80	-1.70	L
5	28.89	-23.35	20.92	-17.46	8.84	-8.34	M
6	7.31	-6.26	6.17	-5.69	3.14	-3.73	L
7	21.80	-12.30	20.79	-9.83	14.89	-3.55	M
8	4.74	-3.56	5.58	-4.19	4.61	-3.44	M
9	6.12	-5.50	6.21	-5.68	4.77	-4.56	L
10	28.29	-21.64	29.57	-21.64	19.15	-11.45	H
Mean	12.33	-9.46	11.30	-8.38	7.07	-4.90	

Note that in addition to containing these graphs for each infant, Appendix D also contains the graphs for Infant 1 with *T* set to one and ten respectively, to show the effect of changing *T*.

6 Discussion

This study analysed a signal dataset of preterm infants, with the aim of gaining greater insight into their respiratory behaviour, as well as how it links to their cardiac behaviour. The results obtained provide new insight into the respiratory dynamics of preterm infants, addressing a variety of objectives. Firstly, the primary goal of the transition models is discussed along with the implementation of the algorithms to detect breathing cessations and PB. The secondary goals are addressed, namely the contribution of 2 – 5 s cessations, the temporal behaviour of cessations and the relationship between cessations and HRV. It is important to note that this study has several limitations, but also various opportunities for future work. Lastly, a conclusion will be drawn.

6.1 Objective 1: Transition model

The Lee et al. and Mohr et al. algorithms for detecting breathing cessations and PB respectively were implemented [12], [49]. The mean time spent in cessation for the dataset was 9.1%, with a range from 3.0% to 17.0%. On average only 0.63% PB was detected over all ten infants, with Infants 4 and 8 displaying no PB. Mohr et al obtained an average of 3%, which also indicates that PB does not occupy a large part of preterm infant respiration. It seems that an increase in cessation matches an increase in PB, as would be expected since PB is closely associated with AOP [33], [44]. As mentioned in Section 5.1 the maximum percentage PB is 3.1% for Infant 3, which is also the infant with the highest percentage cessations. The overlap between PB and cessations longer than 10 s is 0.08%. This corresponds with the findings by the original study that PB generally consists of cessations less than 10 s, specifically 6 - 9 s [49]. PB occurred in 80% of infants, while in another study it was reported that 94.5% of infants in a similar weight class to those in this study displayed PB [1].

Three A:B relationships (cessation : non-cessation) were employed to detect PB. Very minimal PB was detected by A:B = 2:1, meaning that within this dataset PB with cycles where cessations are double the lengths of breathing is rarely detected. This could suggest that computational cost could be wasted by testing for this ratio, particularly because the convolution method employed has a high computational cost and is very time consuming.

The transition model from Section 5.2.1 gives visualisation to the respiratory dynamics of preterm infants (Figure 5.1). It indicates that respiratory events are more likely to be preceded by other respiratory events than by a state of normal breathing, suggesting that these events are related. This relationship between respiratory events becomes stronger as Δt increases, which is to be expected. In all cases, there is a low probability that the identified respiratory events are

preceded by PB. This contradicts the theory that all apneas begin in expiration during PB [33]. It does, however, agree with Barrington et al., who found that less than 0.6% of significant apneas occurred within two minutes of a PB epoch ending. This study found a similar probability of 1.5%, which agrees with their conclusion that PB is not often a precursor for apnea [1].

Within a ten minute window, about half of apneas are preceded by other apneas, suggesting the event has a strong relationship with itself (Figure 5.2). It also indicates that when an apnea has ended, it does not necessarily mean that the infant has regained control of its respiratory system. However, due to the lack of clinical annotations of the dataset, it is also unknown whether an apnea was resolved naturally or due to clinical intervention.

The model presented in Section 5.2.2 suggests that the respiratory behaviour surrounding apneas is fairly symmetric (Figure 5.3). This behaviour holds true for an increase in Δt, as seen with Δt set to ten minutes in Figure 5.4. From this it seems that apneas are equally likely to be preceded and followed by an event. The increasing relationship between apneas and itself, as well as with cessations indicate that rather than occurring in isolation, apnea forms part of general respiratory instability. This could aid in the development of a dynamically changing 'respiratory stability index' (or 'risk of apnea' index) allowing more nursing attention to be directed to higher-risk infants [58].

Since it is known that respiratory instability is related to immaturity and underdevelopment of regulatory systems [2], [3], [12], [29], this respiratory transition model (Figures 5.1 and 5.2) holds the potential to track the maturation of these preterm infants in a novel way. The data used to develop this model is recorded as standard practice in NICUs all around the world. For example, this model could be automatically created at the end of each day, using information from the previous 24 hours. This would enable clinicians to visually track these respiratory dynamics, giving a holistic perspective to how these dynamics and their interactions with each other progress. Since respiratory stability is an important factor in infant discharge, this will aid clinicians in making better decisions, as well as drawing attention to infants who need closer observation than others.

Alarm fatigue is another well-known NICU problem. This model also has the potential to be used to help combat this. It could contribute to customization of alarm thresholds or the judging of the appropriateness of continuous monitoring for a particular patient. In future, it could even be used in research towards diagnostic alarms [53].

The second breathing dynamics model (Figures 5.3 and 5.4) can produce equally valuable clinical insights, however, it is tailored to a single respiratory event. Since AOP is known to have a negative impact on infant health [2], [12], it could be

beneficial to analyse the occurrence of apnea, as well as its interaction with other respiratory dynamics, over a selected period of time. Similarly, clinicians may want to specifically observe an infant's PB, since studies have noted excessive amounts of PB in the respiratory pattern of an infant who died of SIDS, as well as her sibling [46].

6.2 Objective 2.1: Analysis of 2 – 5 s cessations

This project analyses short cessations of breathing (2 – 5 s). Routinely, cessations in breathing are only noted when apneas are detected. This only happens after respiratory activity has already ceased for 20 s [12], or in some cases 15 s [57]. In their algorithm, Lee et al. mainly looks at cessations longer than 5 s, ignoring isolated 2 – 5 s cessations. All of this indicates a lack of understanding of the contribution of short cessations. Although there is a lack of understanding regarding the long-term neurodevelopmental effects of apnea, it is known that a lack of oxygen has detrimental effects on infant physiology [38]. Herein lies the danger on ignoring these short cessations, since they add to the total time a preterm infant spends without taking in oxygen.

This study shows that the contribution of these short cessations to the overall time spent in cessation is large (Figure 5.6). In particular, infants that tend to have longer cessations spend more time undergoing short cessations as well, as is also shown in Figure 5.7. This might be explained by the well-known, albeit variable and non-linear relationship between the underdeveloped brainstem and neural control of respiration that contributes to long cessations, including apneas [76]. In theory, infants with better-developed regulatory control mechanisms may be able to auto-stimulate respiratory activity following a short cessation and thus have fewer long cessations, including clinically defined apneas. Fortunately, such apneic cessations in breathing occur infrequently. However, by monitoring short cessations (which are typically considered clinically irrelevant), which occur more often, it may again be possible to develop a dynamically changing 'respiratory stability index' (or 'risk of apnea' index) as was discussed in Section 6.1 [58].

6.3 Objective 2.2: Temporally track respiratory stability

Figure 5.8 shows a prominent periodicity in the changes in the percentage breathing cessation over time for infants from all severity classes, with the behaviour following a two to three hour cycle. It is even more apparent in Figure 5.9, where it is tracked over a period of days. All event classes follow this trend, suggesting a physiological response to periodically performed clinical intervention, e.g., enteral feeding, nursing care, etc. [53], [77]. However, this remains uncertain since the dataset used lacks clinical annotations. Such analyses

of breathing dynamics might offer a useful metric for determining which amongst the multiple methods of enteral feeding cause the least physiological distress to infants. This knowledge could lead to change in clinical practice in NICUs, or at least an increased awareness of the possibility of apnea surrounding a particular feeding method. Although other studies have noted a suspected link between feeding and apnea, no study has looked at it temporally in this continuous manner.

6.4 Objective 2.3: Study relationship between breathing cessations and heart rate behaviour

Section 5.5 outlines the temporal relationship between the percentage cessation occurring and the different HRV measures. As discussed in Section 6.3, the percentage cessation shows prominent periodicity. Some of the HRV measures seem to mimic this periodicity, suggesting a relationship between cardiac and respiratory behaviour. It is a known fact that cardiorespiratory coupling exists, however, the mechanisms behind this are obscure. SDNN, a measure of overall variability, seemed to be the measure related the closest temporally to percentage cessation. Figure 5.10 shows a clear example of a similar trend in both the cardiac and respiratory behaviour. This indicates that when more cessations occur, more variation is found in the RR intervals of the HR.

Although these results seemed promising, further analysis in this line proved difficult, since the signals had been heavily processed. Therefore, the need arose for a more detailed analysis, which lead to the PRSA and BPRSA analysis in Section 5.6. This analysis was interesting, firstly, because it is a fairly new method. Secondly, because this analysis has rarely been applied to preterm infants. Thirdly, the BPRSA has never been analysed with the RR signal as trigger and the probability that a cessation is occurring as target so essentially between variability in cardiac activity and respiratory instability. This method is also robust, in that is can be applied even when there are missing values in signal [71], [72]. Clark et al. encouraged applying methods with this robustness, as a lack of continuous signal was a problem they encounter in their cardiorespiratory study [62].

Concerning the top graph in both Figures 5.15 and 5.16, the PRSA on the RR yields results that indicate that there is a quasi-periodic relationship within the RR signal, as is expected [71]. This added to the confidence that the method has been correctly applied. The second and third graphs in Figures 5.16 and 5.17 illustrates BPRSA relationships. It is important to note that in the absence of any sort of interrelationship between the trigger and target signals, the BPRSA would be a relatively flat line. Therefore coupling is evident in both the case of the respiratory signal and the probability of cessation signal acting as the target signal (in both cases the RR signal serves as the trigger signal).

Although coupling is evident between the respiratory signal and RR signal, there is no clear trend as to how this coupling manifests when taking into account all ten infants. Regarding the BPRSA of RR signal (trigger) and probability of cessation signal (target), a clearer pattern forms. Either this indicates that periodic modulations in one lead to corresponding behaviour in the other, or that a third physiological system is causing modulations in both. In all infants (except for Infant 5) the BPRSA curves for both deceleration and acceleration are symmetric about the y-axis (where time is equal to 0 s). The acceleration and deceleration graphs also seem to virtually be inverses of each other, leading to the conclusion that there is likely a third mechanism coupling with both these signals and causing them [75]. Concerning the *AC* and *DC* values calculated in Table 5.4, they demonstrate how the oscillatory behaviour in the PRSA dies down, indicating that the body responds to changes in HR and reacts to restore it to normal. However, there seemed to be no clear link between an infant's *AC* and *DC* values and their cessation severity levels.

6.5 Limitations

This study has several limitations, notably the absence of contextual information such as the enteral feeding routine and periods of nursing care as well as absence of useful vital signs such as oxygen saturation. The availability of such information would greatly aid a study of the physiological etiology of these findings. The availability of longitudinal data would also enable greater insight into respiratory dynamics over time. In addition, not knowing the PMA at which these recording were taken prohibits some comparisons to literature. The study also relies on the recreation of algorithms developed, tested and validated by other research groups, with no validation of its own done.

6.6 Future work

Ideally, this study should be applied on a larger longitudinal dataset to see whether the behaviour displayed in the transition model holds true. In addition, this transition model can be created for different infant populations to see the difference as well as similarities in trends. Different population groups should be studied, for example extremely preterm versus late preterm infants, or infants who developed sepsis versus those who did not. This could offer many interesting insights.

Applying the temporal tracking of cessations to a clinically annotated dataset can hold great promise. This can offer insight into the NICU schedule affects an infant's respiratory stability, as well as the effectiveness of the caffeine titration employed to stimulate breathing.

The HRV of preterm infants is an important field of investigation which could provide early warning of distress. In addition, proper application of HRV measures can offer insight into the autonomic maturation of the developing fetus, and by association preterm infants [61]. However, the Task Force of the European Society of Cardiology urges against over interpreting measures when it comes to health or diagnostic markers. They note the attractiveness of using markers for autonomic activity, but urge against it if there is no clear and defensible mechanistic link between the variables and the related physiological events. This could lead to misinterpretations and incorrect assumptions, which is particularly dangerous in this field [61].

Due to the time limitation of this study, many possibilities regarding the study of cardiorespiratory coupling could not be explored. Quantities measures should be explored to study the temporal link between HRV measures and percentage respiratory cessation. The power spectra for the PRSA and BPRSA is one such a possibility. Studying the frequency components can be used to analyse the contribution of different physiological processes to the overall. The BPRSA should also be calculated with the trigger and target signals swapped to see if the relationship holds true. This will also help establish whether there is in fact a third physiological system modulating both the respiratory and cardiac systems [72]. Various other newly developed measures could also be applied to study the interaction, such as Transfer Entropy [60].

7 Conclusions

The study completed an in-depth analysis of the respiratory dynamics of preterm infants and addressed various objectives successfully. Established algorithms were recreated to enable the detection of breathing cessations and PB. This aided in the development of transition models to study how respiratory dynamics interact with each other, confirming their relationship in time and offering a tool to visually track the maturation of the respiratory system. It was determined that the contribution of routinely ignored 2 – 5 s cessations to overall time spent in cessation is significant and that there is a pronounced periodicity to the evolution of percentage cessations in respiratory signal over time. An investigation was also done into cardiorespiratory coupling, concluding there is a common temporal periodic trend in percentage cessation and some HRV measures.

Determining whether a preterm infant has an acceptable level of physiological maturity is an important and difficult task for the clinician caring for them. This study provided new insights into aspects of the physiology of these infants. It also proposes a tool for quantifying and supporting the assessment of these difficult to measure physiological dynamics to better track maturation. The hope is that by adding to this body of knowledge, advances can be made in reducing the mortality rate of these fragile infants.

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Appendix A Cardiac filter

This Appendix offers additional insight into different steps in the cardiac filter discussed in 4.2.1. In short, the respiratory signal is resampled using the RR intervals as the clock. This allows for the cardiac artefact to be revealed at integer or half-integer frequencies when observed in the frequency domain, making it simple to filter out. The respiratory signal is then resampled to its original sampling rate, and the cessation detection analysis continues.

Firstly, an example is given in Figure A-1 of the RR peaks detected in the ECG waveform using the selected R-peak detection algorithm [68].

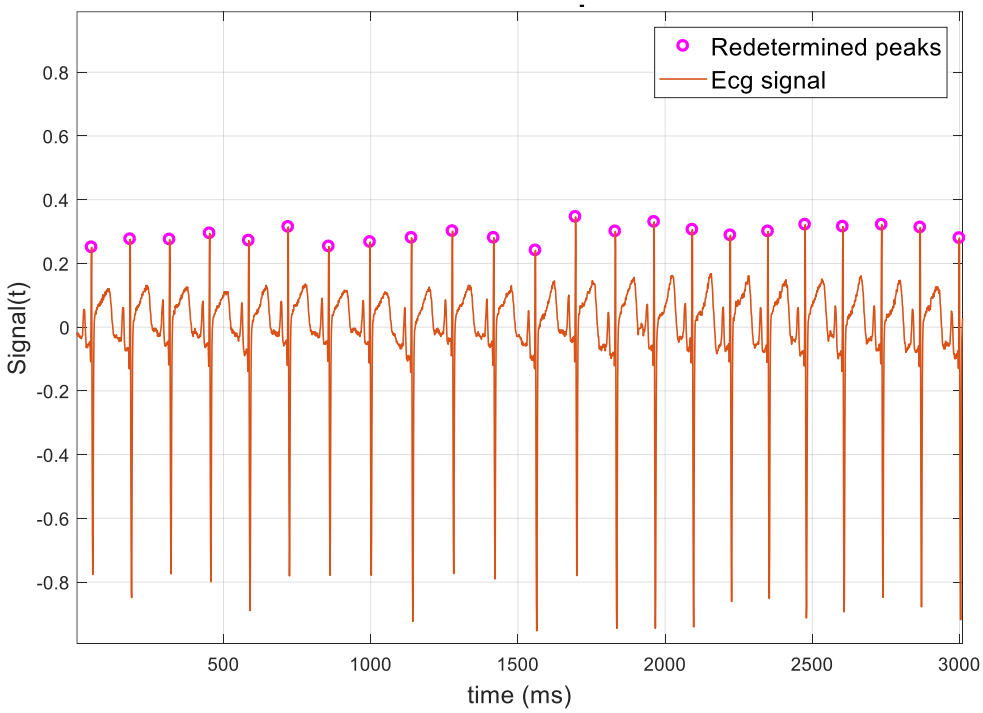

Figure A-1: ECG with RR peaks detected

As mentioned, when the respiratory signal is resampled with the RR intervals detected acting as the clock, the cardiac artefact becomes isolated at integer or half-integer frequencies. This enables easy filtering out of this artefact. Figure A-2 gives an example from this study of the isolated cardiac artefact before it is filtered out, outlined in red, while Figure A-3 shows it removed. In this figure, a chest impedance signal is seen instead of the chest inductance signals used throughout. Cardiac artefacts are more prominent in impedance signals than in inductance signals, therefore the filter was first tested on an impedance signal to ensure that it is working correctly before applying it to the PICS dataset.

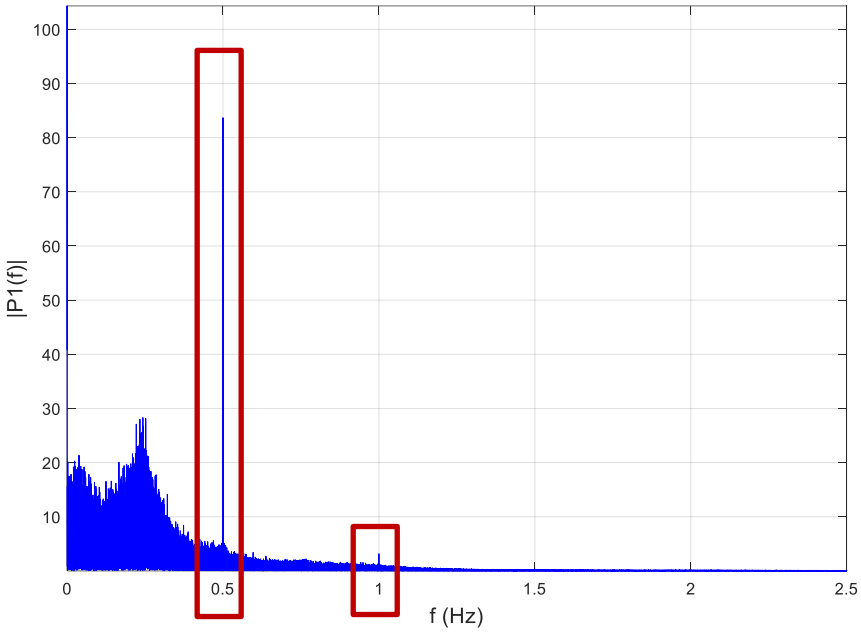

Figure A-2: Fft of resampled respiratory signal with cardiac artefact isolated at 0.5 Hz and 1 Hz

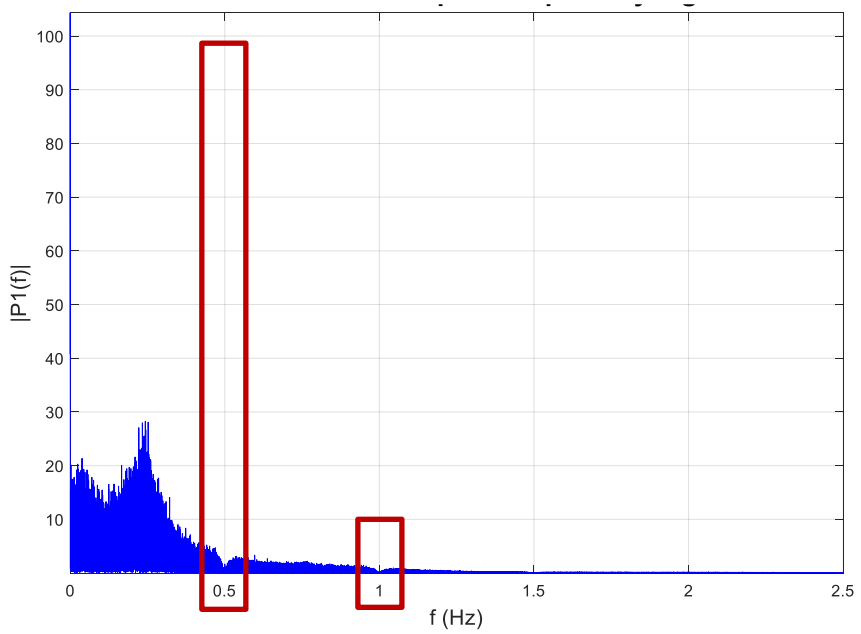

Figure A-3: Fft of resampled respiratory signal with cardiac artefact removed

This cardiac artefact can also be seen in the time domain. Figure A-4 gives an example of this from Lee et al. Note that a) show the RR (black line) and HR (red line) moving into the same frequency band, while b) shows this in the time domain.

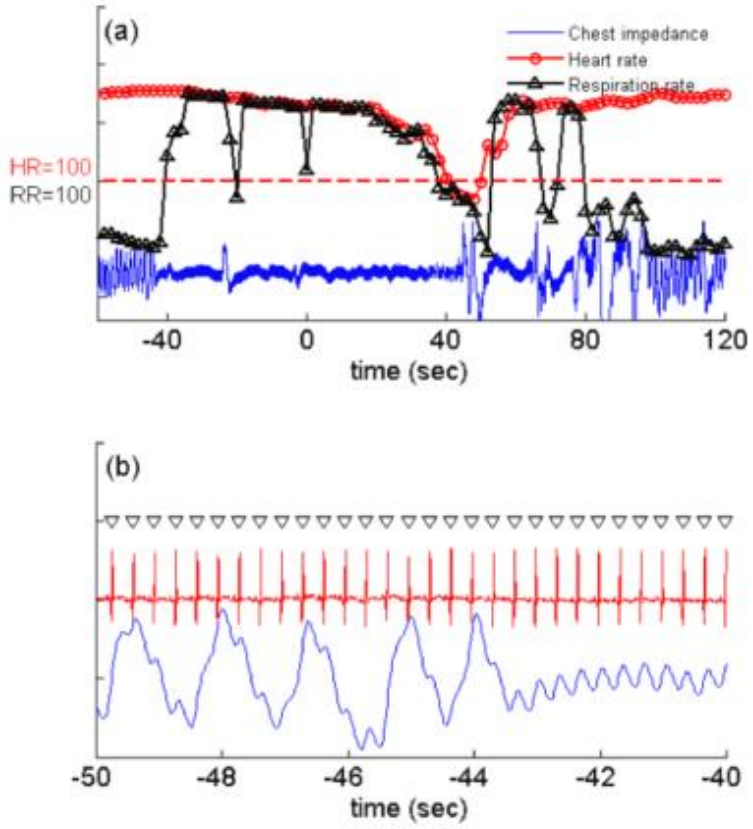

Figure A-4: Cardiac artefact from Lee et al.

Figure A-5 gives an example from this study of the artefact removal in the time domain. Note that activity of a low amplitude throughout the signal at a seemingly similar frequency has been removed between the upper and lower graph.

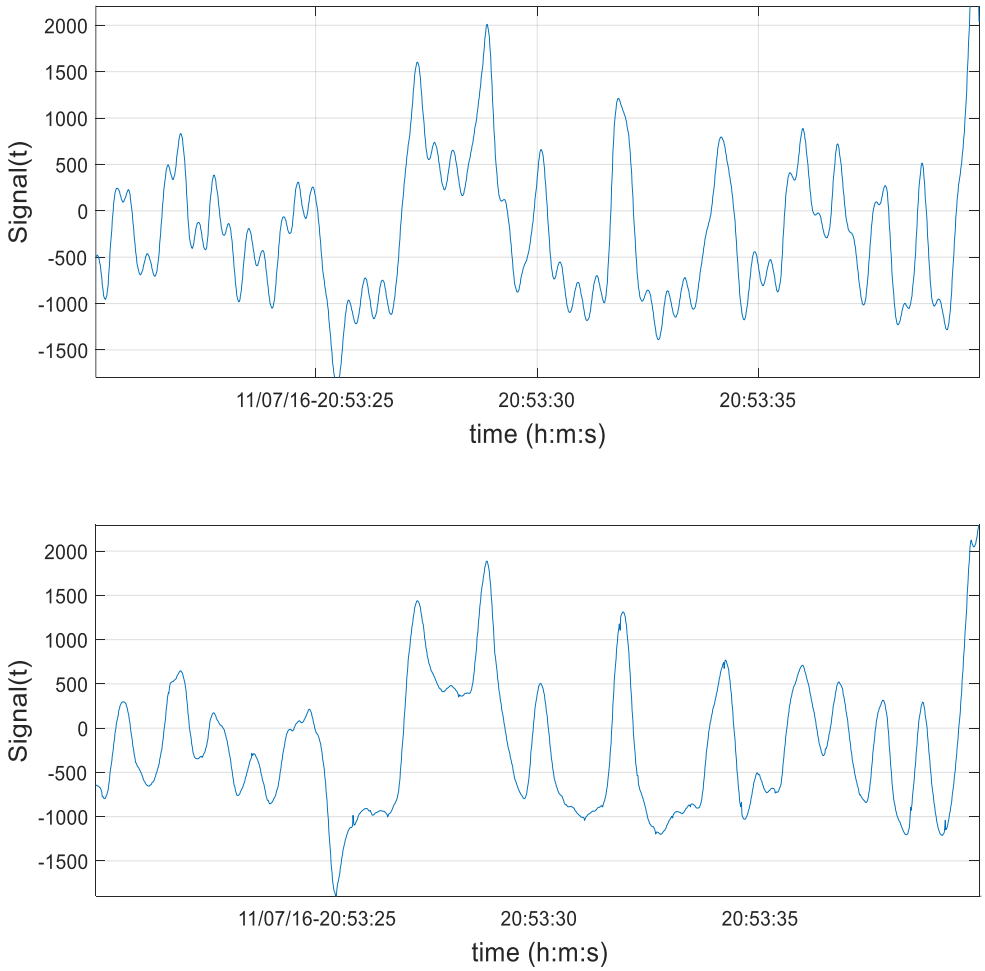

Figure A-5: Top: Original respiratory signal in time domain with cardiac artefact present. Bottom: Respiratory signal in time domain after cardiac artefact removal.

Appendix B Lee et al. algorithm

This study recreated a breathing cessation detection algorithm developed, tested and validated by Lee et al. [12]. The instruction given in their paper was closely followed to ensure that cessation detection is as accurate as possible. Where possible, results obtained during various steps of the process were compared to results outlined in their paper. The cessations detected were also visually expected to see if the algorithm was acting as expected.

When developing the equation to determine the probability of apnea (Equation 4.1), the histogram of the distribution of the variance of the filtered respiratory signal (σ) was studied. The result of this is seen in Figure B-1b. This was a point were clear comparison could be drawn between Lee et al. (Figure B-1a) and this study. Therefore, this same distribution was calculated in this study, and the similarity in results added to the confidence in the recreated algorithms similarity to the original.

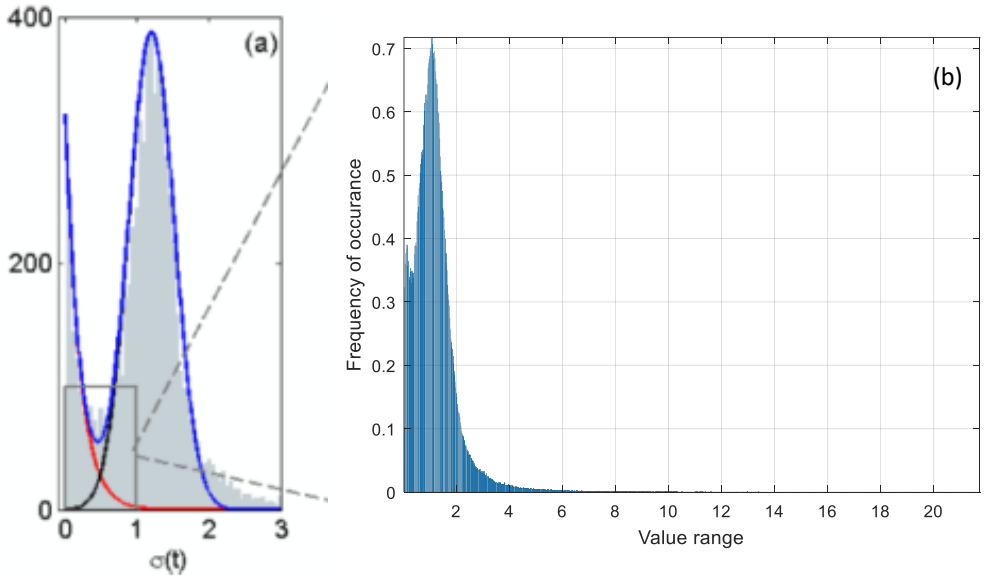

Figure B-1: a) The distribution of the variance filtered respiratory signal (σ) in Lee et al. [12] b) The distribution of the variance filtered respiratory signal (σ) for Infant 2 in this study

Figure B-2 gives a visualisation of this process if it were to be applied to a 22-minute signal.

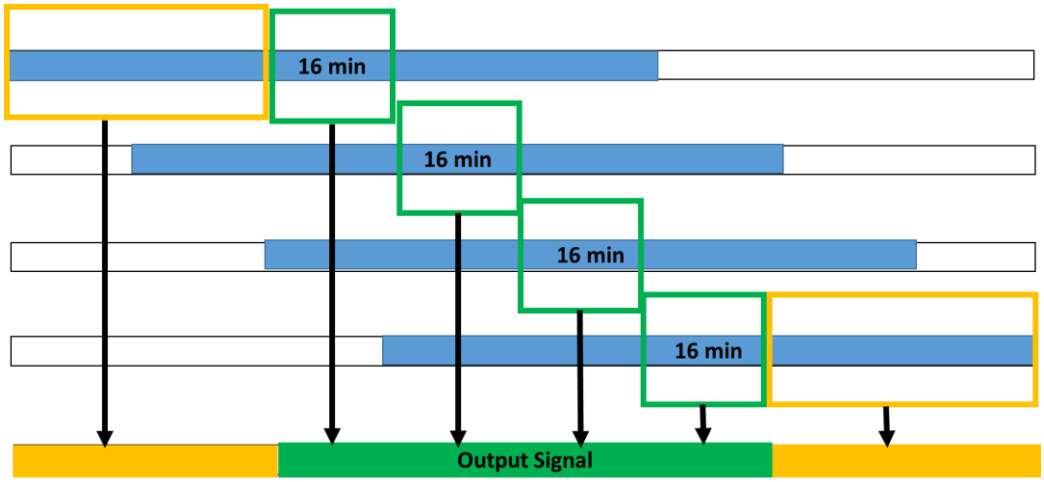

Figure B-2: Visualisation of normalisation of signal using a moving low pass filter envelope

16 minutes of respiratory signal is analysed at a time, represented by the blue segment. As mentioned, the low pass filter is applied to this segment. The respiratory waveform is then divided by the output of this low pass filter. From the now normalised 16-minute segment, the middle two minutes are taken (as outlined in green on Figure B-2) and added to the eventual output of this operation, as suggested by the black arrows. A new 16-minute segment of signal is then selected by means of a moving window of two minutes, and then the process is repeated. The first 7 and last 7 minutes of signal is lost in this process (outlined in yellow in Figure B-2), since there is not both 8 minutes of future and past information available at those stages. Corresponding to these lost segments, NaN values are placed in the output to ensure the signal structure and length is preserved. Note that the shortest signal is 20 hours long, so losing 14 minutes is insignificant to the overall analyses.

Figure B-3 gives an example of the output of this normalisation from the signal of Infant 1. As can be seen when comparing the second halves of the signal, the amplitude is more evenly scaled throughout in the bottom one, which represents the normalised signal.

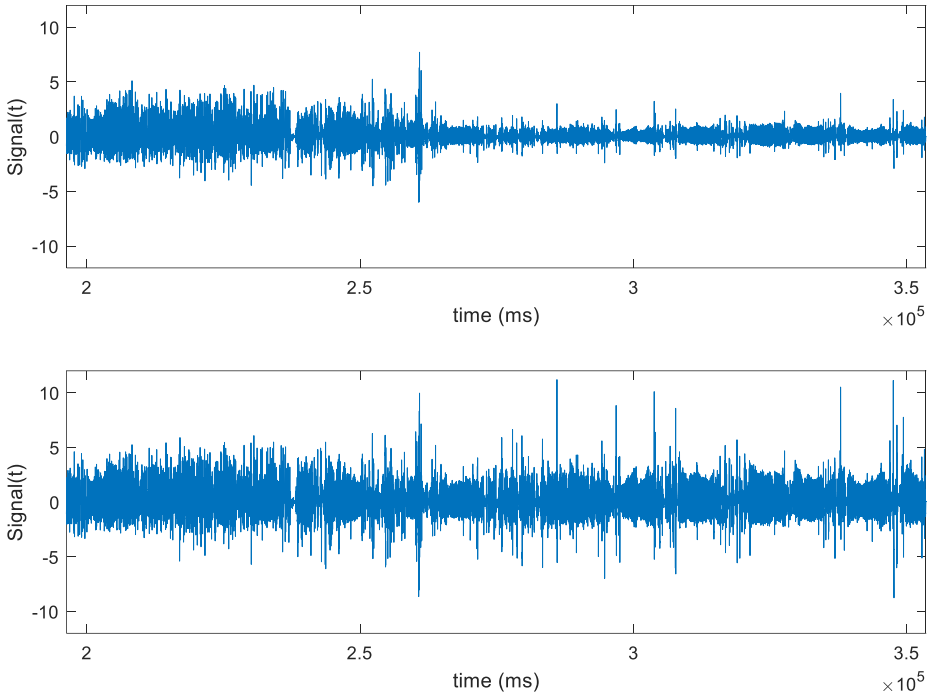

Figure B-3: Respiratory waveform before normalisation had been applied. Bottom: Respiratory signal after normalisation had been applied

This normalisation is important to scale the data. Parts of the respiratory cessation detection algorithm is based on whether values exceed set thresholds, and therefore normalisation is necessary to make adequate comparisons, avoiding false detection of cessations or missed cessations.

Figure B-4 shows the outline of the programming logic followed to recreate the cessation detection algorithm.

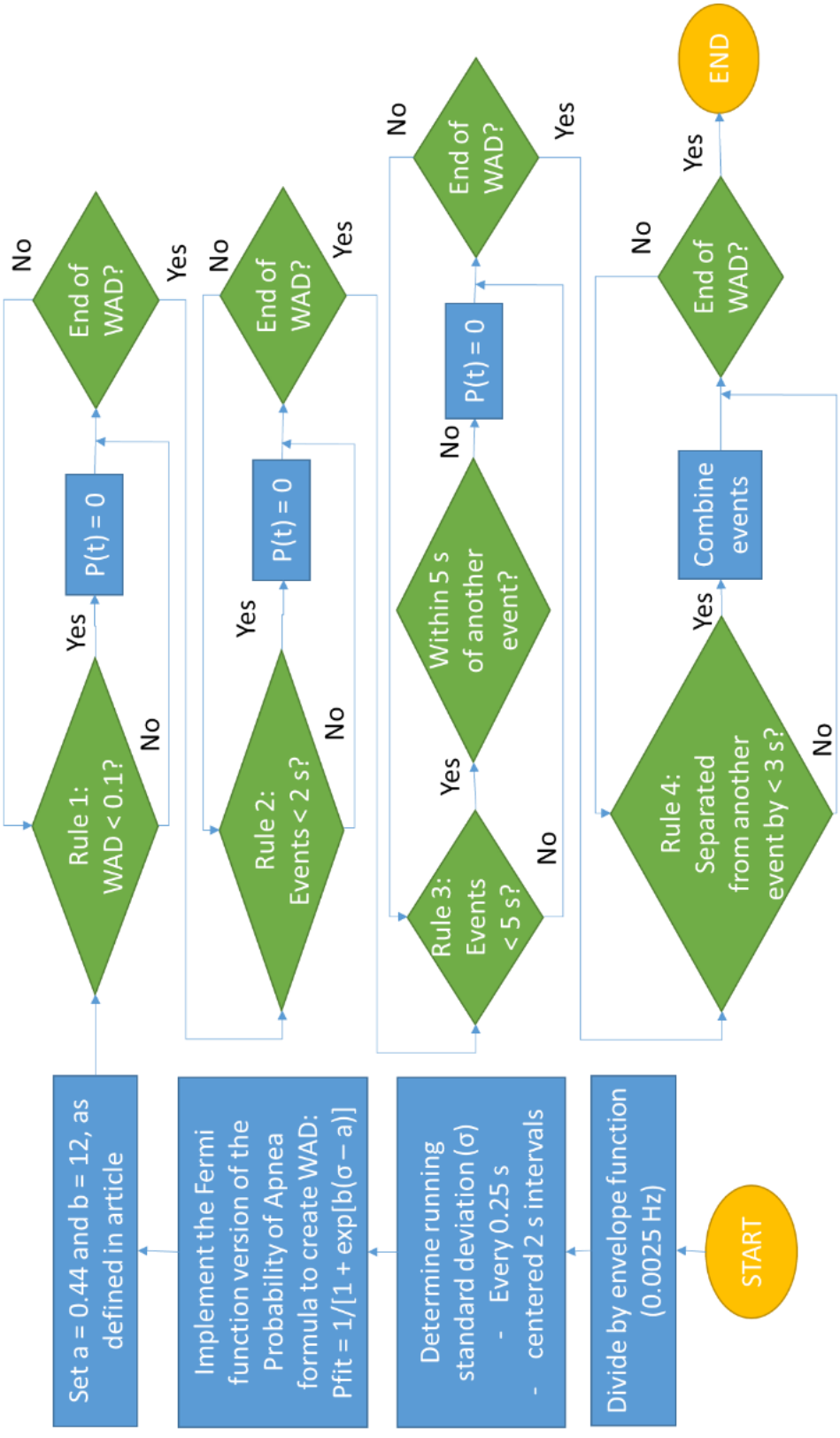

Figure B-4: Programming the logic for Lee et al. cessation detection algorithm

Lastly, Figures B-3 to B-5 give an examples of cessation detected in the respiration signal. The blue signal is the chest inductance signal (representative of the respiratory signal), while the red boxes outlines the areas where a cessation in breathing is detected. As can be observed, wherever reduced activity is detected for a relevant amount of time in the respiratory signal (outlined by the rules in Section 4.2.2) , cessations are noted as occurring.

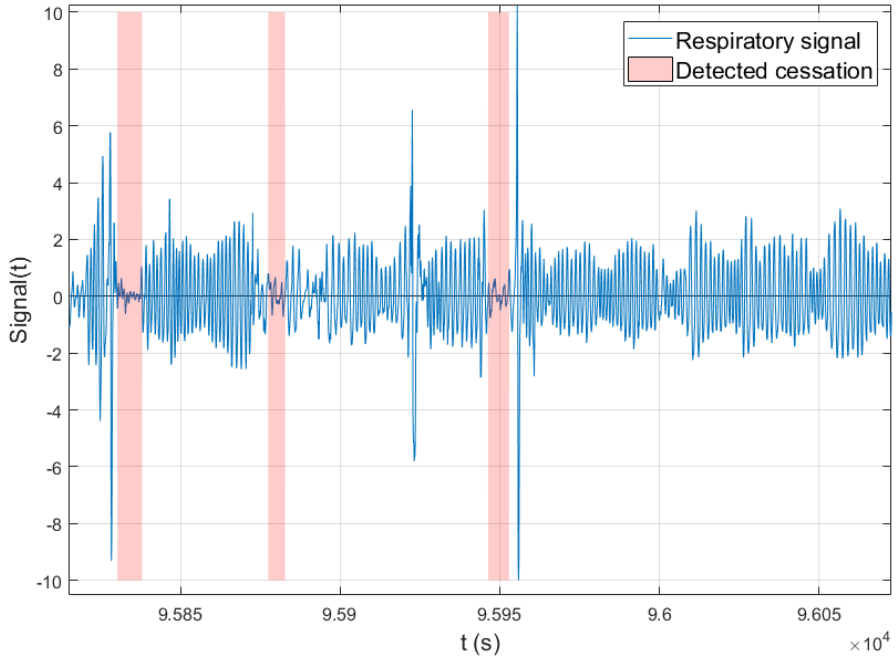

Figure B-5: First example of cessations detected in respiratory signal

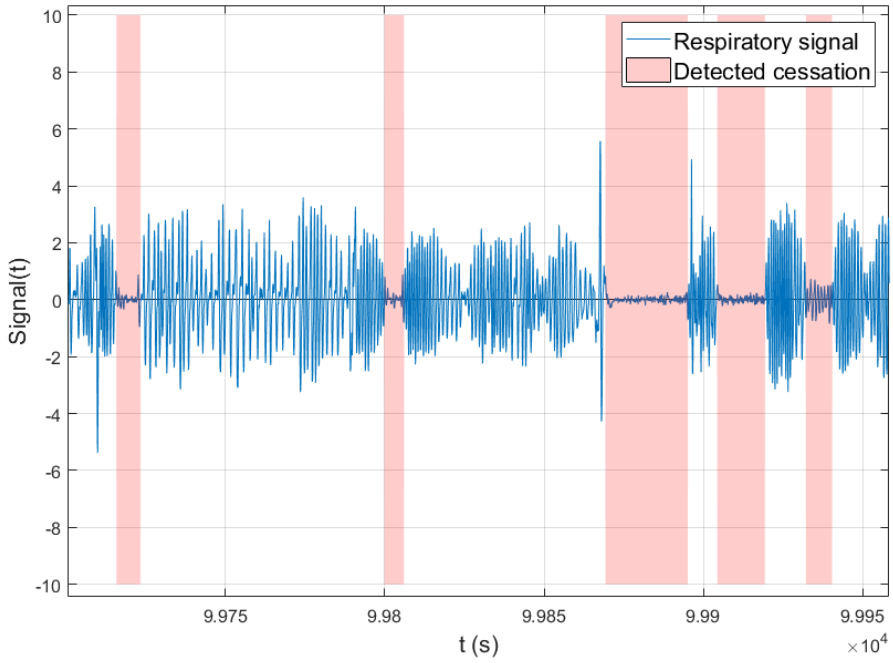

Figure B-6: Second example of cessations detected in respiratory signal

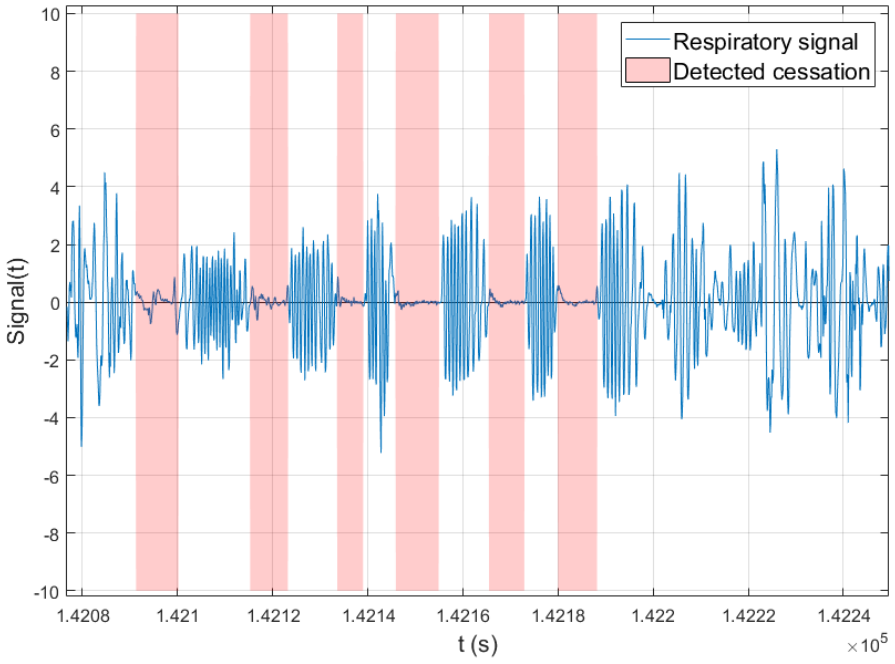

Figure B-7: Third example of cessations detected in respiratory signal

Appendix C Mohr et al. algorithm

This Appendix gives greater insight into the PB detection algorithm described in Section 4.3. In brief, wavelets, designed to adhere to the expected characteristics of PB, are convolved over the WAD signal. (The WAD signal represents the probability that a cessation is breathing is occurring.) It the output of this convolution is higher than the set threshold of 0.6, it is noted that PB is occurring. Figure C-1 gives a visualisation of the wavelet moving across the WAD signal to be convolved. The red arrow indicates the direction in which it is moved.

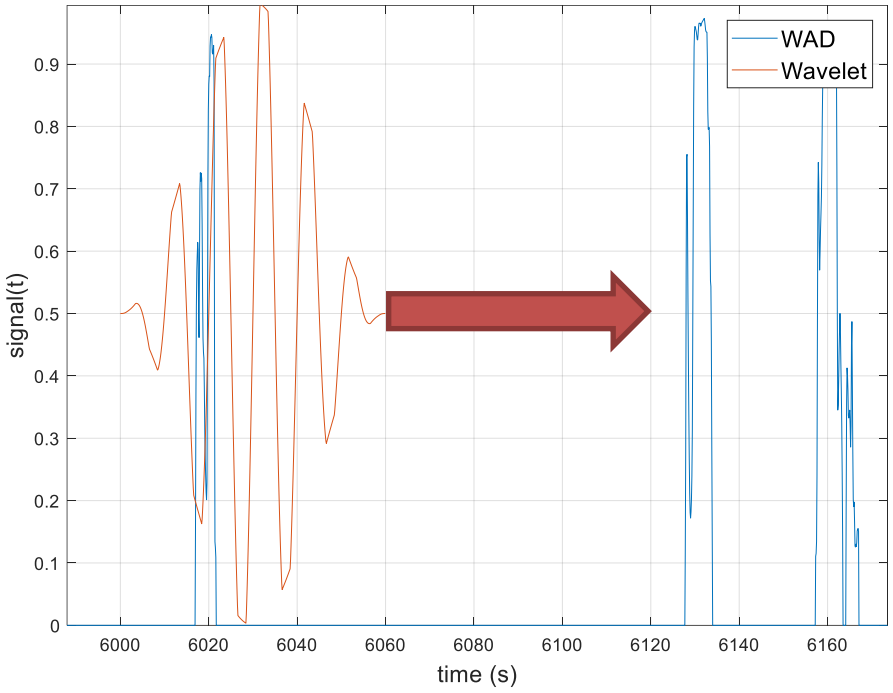

Figure C-1: Wavelet moving across WAD signal representing the probability that a cessation in breathing is occurring

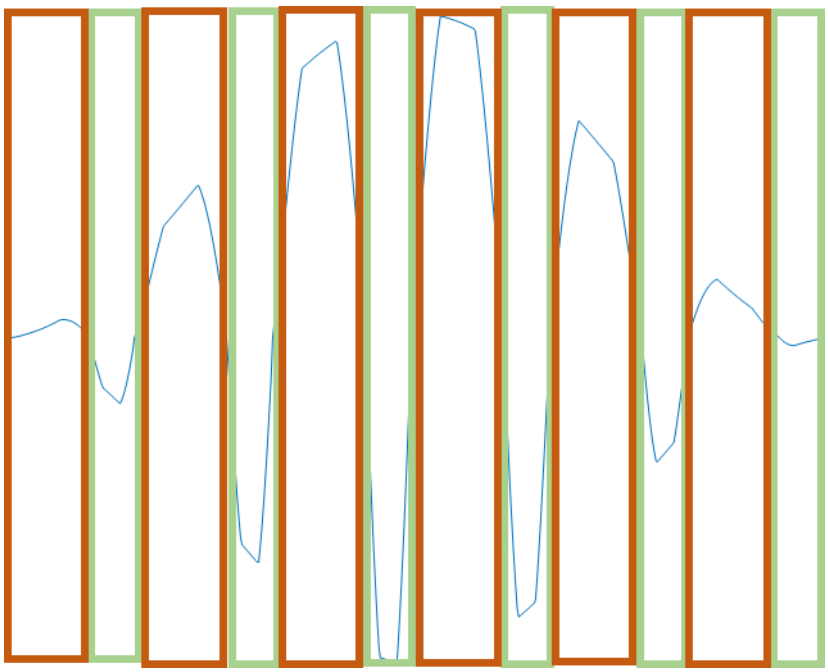

Figure C-2: A wavelet broken in its A:B ratio of 2:1, with the orange frame referring to the A and the green frame referring to the B.

As was mentioned in Section 4.3, wavelets have different A:B rations, with A referring to breathing cessations and B referring to non-cessations, therefore regular breathing. Figure C-2 shows a wavelet with an A:B ratio of 2:1, with its A parts framed in green and its B parts framed in orange. In reference to Table 4.2, if the wavelet were to be set up to detect PB of cycle 15 s, it would aim to detect 10 s of cessation and 5 s of regular breathing. However, if for example a cycle of 40 s is to be detected, this A:B ratio of 2:1 would not be applied. In the case of a 40 s cycle, this wavelet would search for cessations of around 26.7 s, which fall outside of the definition for PB. Therefore in this case only the A:B ratios of 1:2 and 1:1 would be employed.

Figures C-3 to C-5 give examples of PB detected. The blue lines represent the chest inductance respiratory signal. The orange areas show where cessations in breathing were detected. Encompassing the red areas are yellow areas. This yellow represents the PB detected. As can be seen, PB is detected where a sustained pattern of cessations is detected. It is important for this algorithm to be able to discern between PB and simply clustered apneas [49]. In Figure C-3 it seems like the left side could also be PB, but when studying the lengths of the cessation it becomes apparent that there are discrepancies. Therefore the algorithm does not determine it to be PB. Similar situations can be seen in Figures C-4 and C-5.

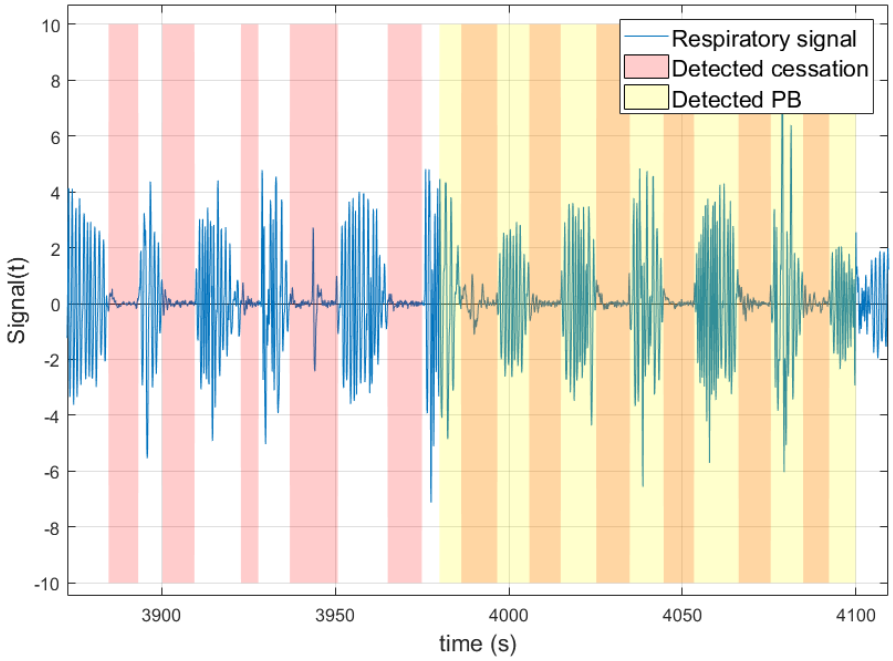

Figure C-3: First example of detected PB

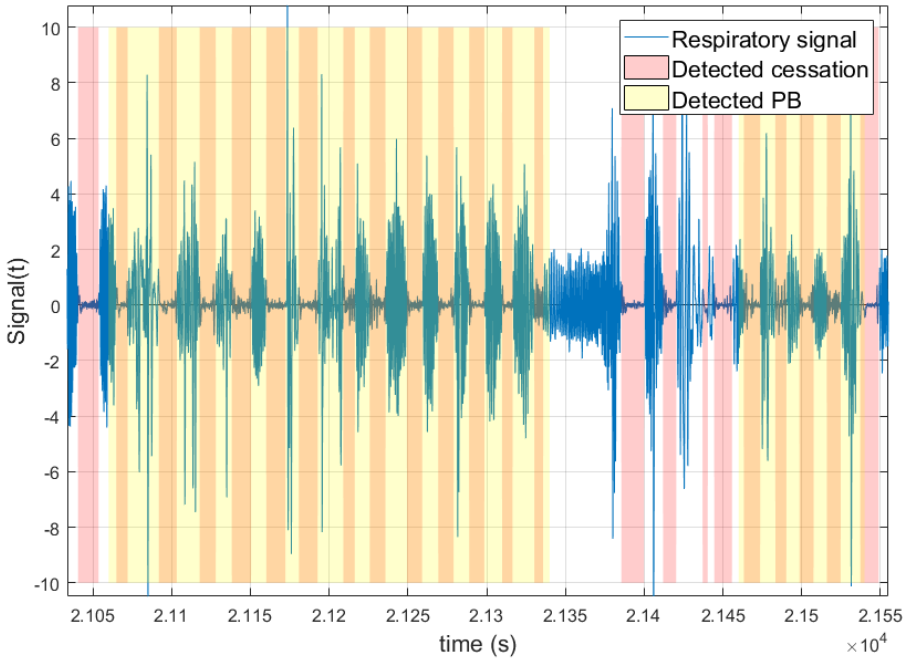

Figure C-4: Second example of detected PB in respiratory signal

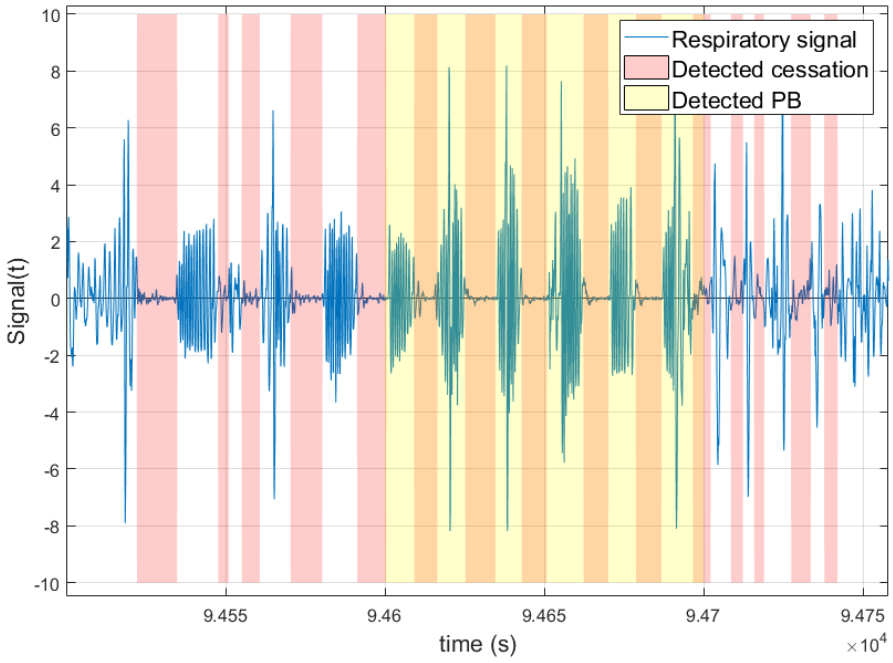

Figure C-5: Third example of detected PB in respiratory signal

Appendix D PRSA and BPRSA

A set of PRSA and BPRSA graphs were calculated for each infant, as explained in Sections 4.6 and 4.7. Section 5.6 outlines the results with focus on Infant 1 and the overall average, while Section 6.4 discusses the results. As mentioned in Section 4.6, at least 1000 anchor points are needed for accurate analysis. Table D-1 gives the anchor points for all infants.

Table D-1: Number of anchor points for each infant

Infant	Anchor points for deceleration	Anchor points for acceleration
1	344 666	471 334
2	338 630	411 260
3	344 803	414 178
4	379 065	461 550
5	163 188	210 976
6	370 205	499 796
7	160 180	202 793
8	164 664	216 611
9	563 850	674 242
10	347 214	394 781

Figure D-1 gives the PRSA and BPRSA graphs for Infant 1, with *T* set to one for the left graph, and *T* set to ten for the right graphs. Note the differences in the graphs. With *T* set to one, it is much more sensitive, as is evident in the fine detail visible in the signal. For *T* set to ten, the signal appears smoother, demonstrating how increasing *T* acts like a low pass filter.

Figure D-2 to D-11 give graphs for all ten infants respectively, with both acceleration and deceleration plotted against each other. As indicated in Section 5.6, there is a common behaviour in the second graphs, namely the BPRSA with the RR signal as trigger and the WAD as target signal. In addition, the behaviour for the acceleration and deceleration are noticeably symmetrical. These trends hold true for all infants apart from Infant 5, which shows no coupling between any of the trigger and target signals.

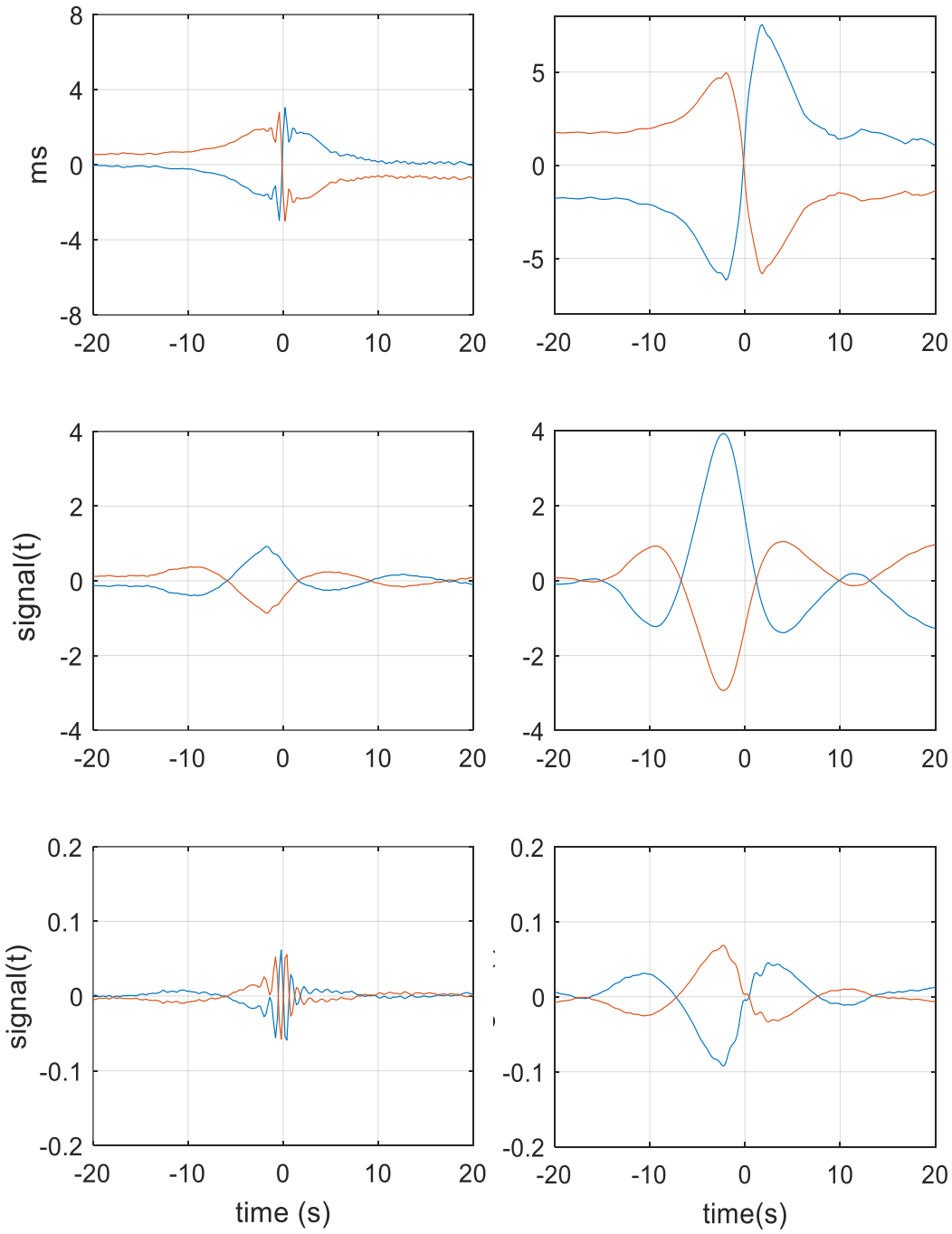

Figure D-1: Decelerations and acceleration graphs for Infant 1. All the left graphs have T = 1, and the right graphs have T = 10. Top: PRSA of RR signal. Middle: BPRSA with RR signal as target signal and WAD as target signal. Bottom: BPRSA with RR signal as target

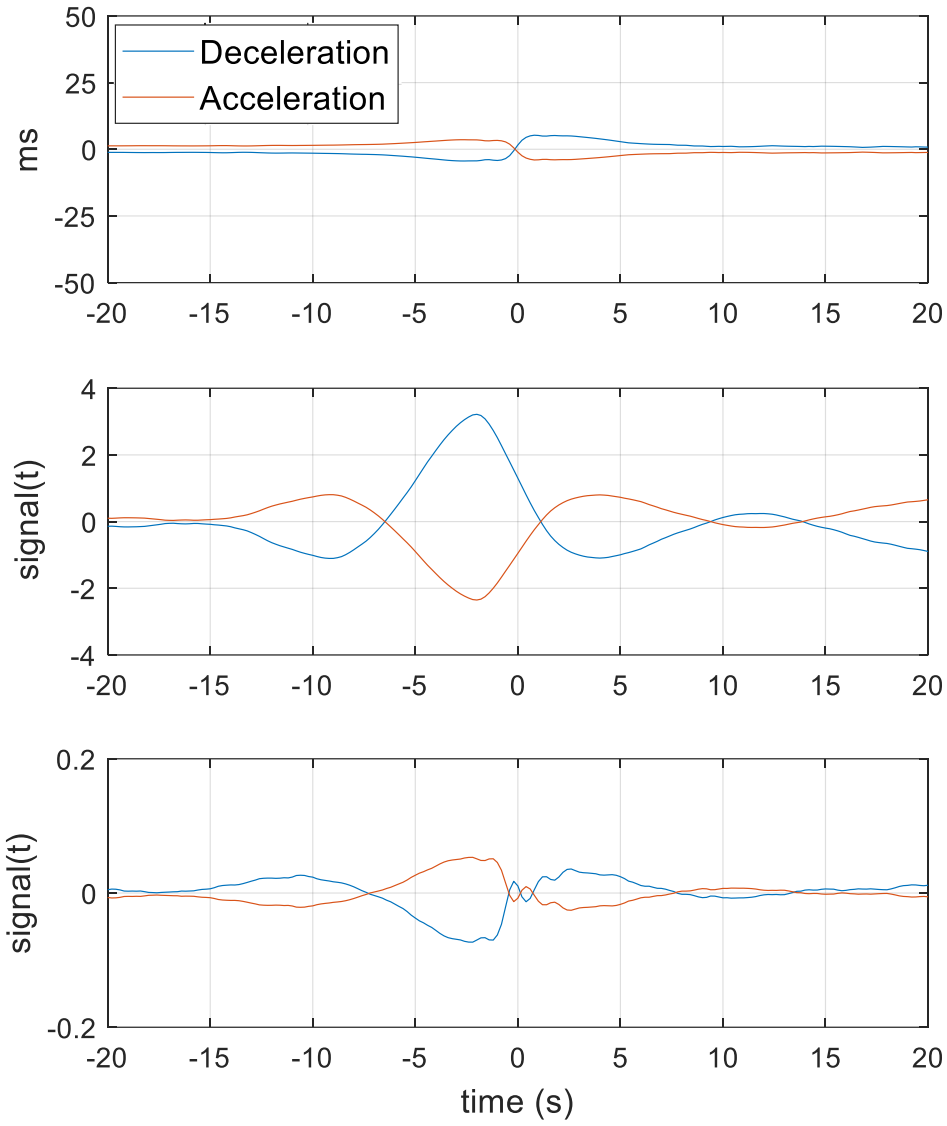

Figure D-2: Decelerations and acceleration graphs for Infant 1. Top: PRSA of RR signal. Middle: BPRSA with RR signal as target signal and WAD as target signal. Bottom: BPRSA with RR signal as target signal and respiratory signal as target signal

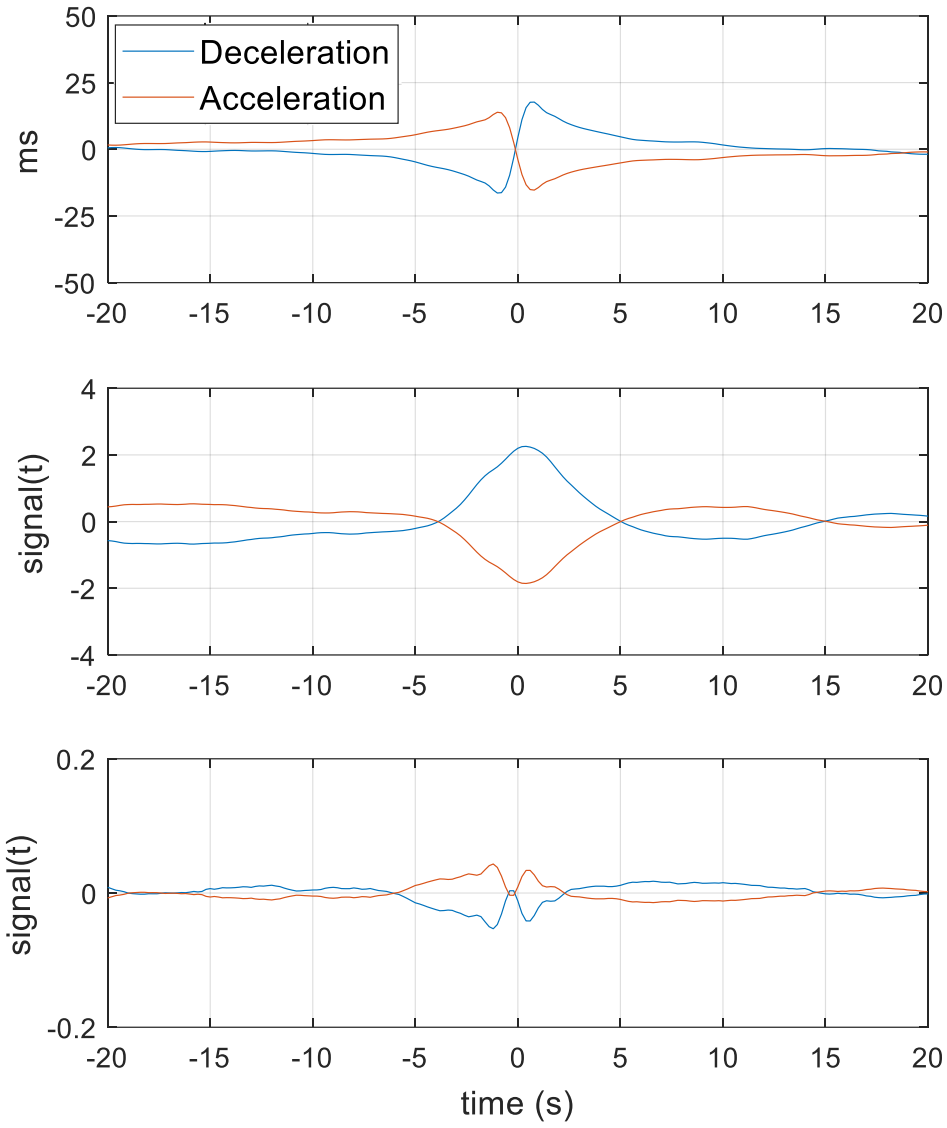

Figure D-3: Decelerations and acceleration graphs for Infant 2. Top: PRSA of RR signal. Middle: BPRSA with RR signal as target signal and WAD as target signal. Bottom: BPRSA with RR signal as target signal and respiratory signal as target signal

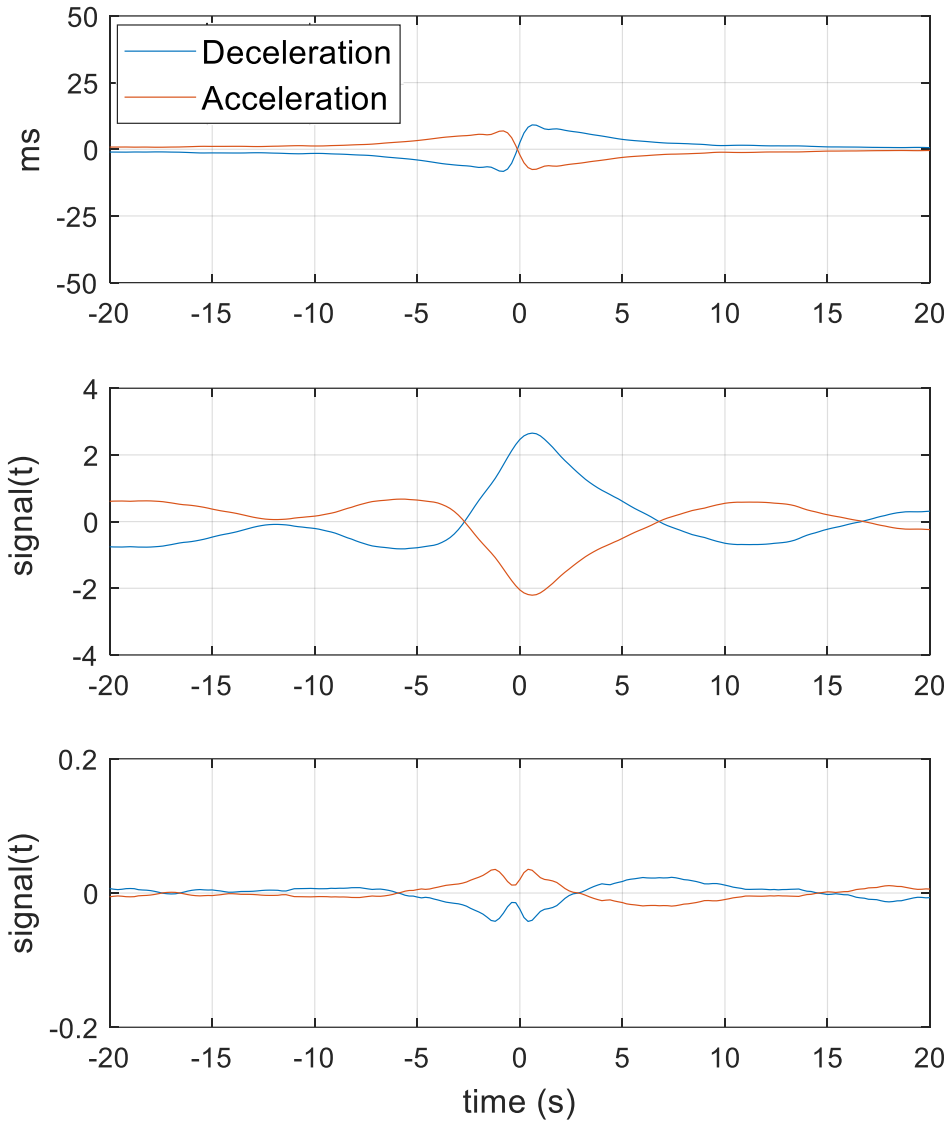

Figure D-4: Decelerations and acceleration graphs for Infant 3. Top: PRSA of RR signal. Middle: BPRSA with RR signal as target signal and WAD as target signal. Bottom: BPRSA with RR signal as target signal and respiratory signal as target signal

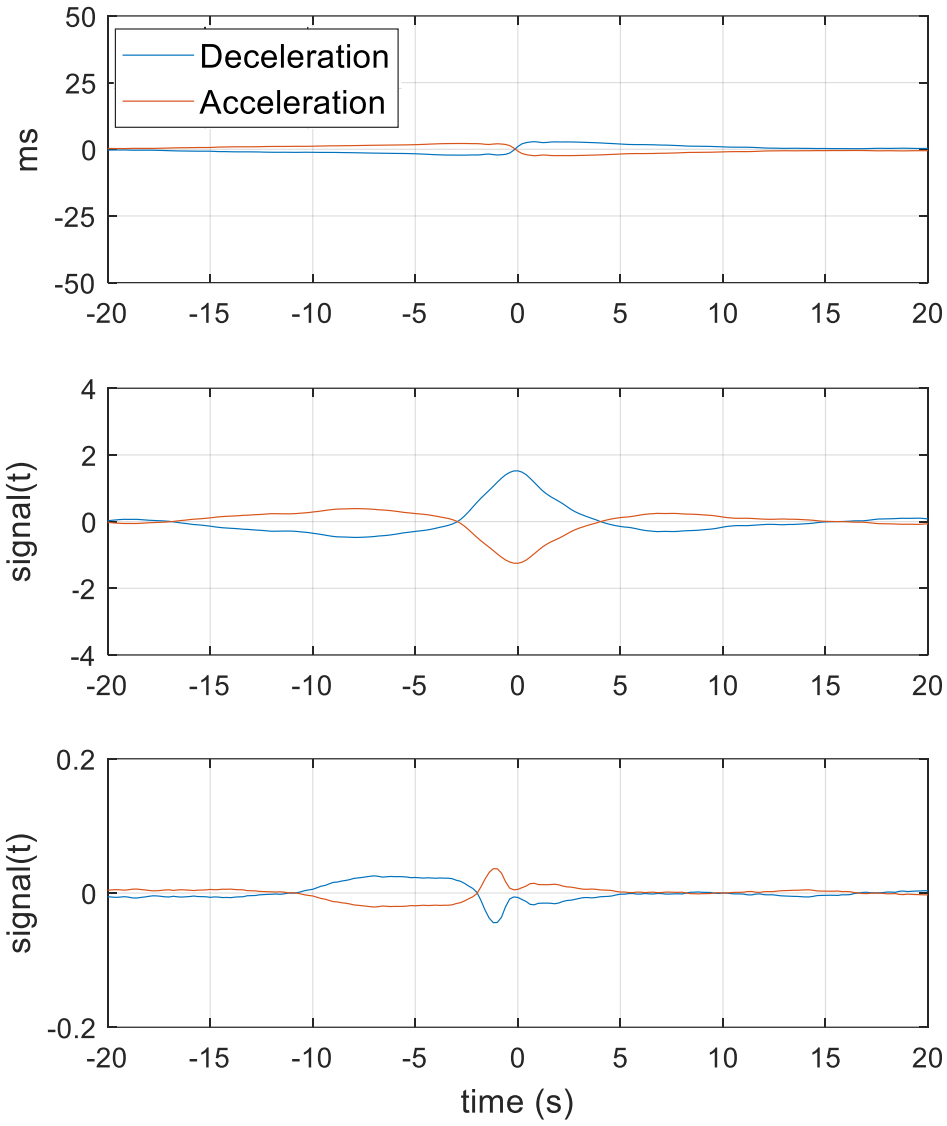

Figure D-5: Decelerations and acceleration graphs for Infant 4. Top: PRSA of RR signal. Middle: BPRSA with RR signal as target signal and WAD as target signal. Bottom: BPRSA with RR signal as target signal and respiratory signal as target signal

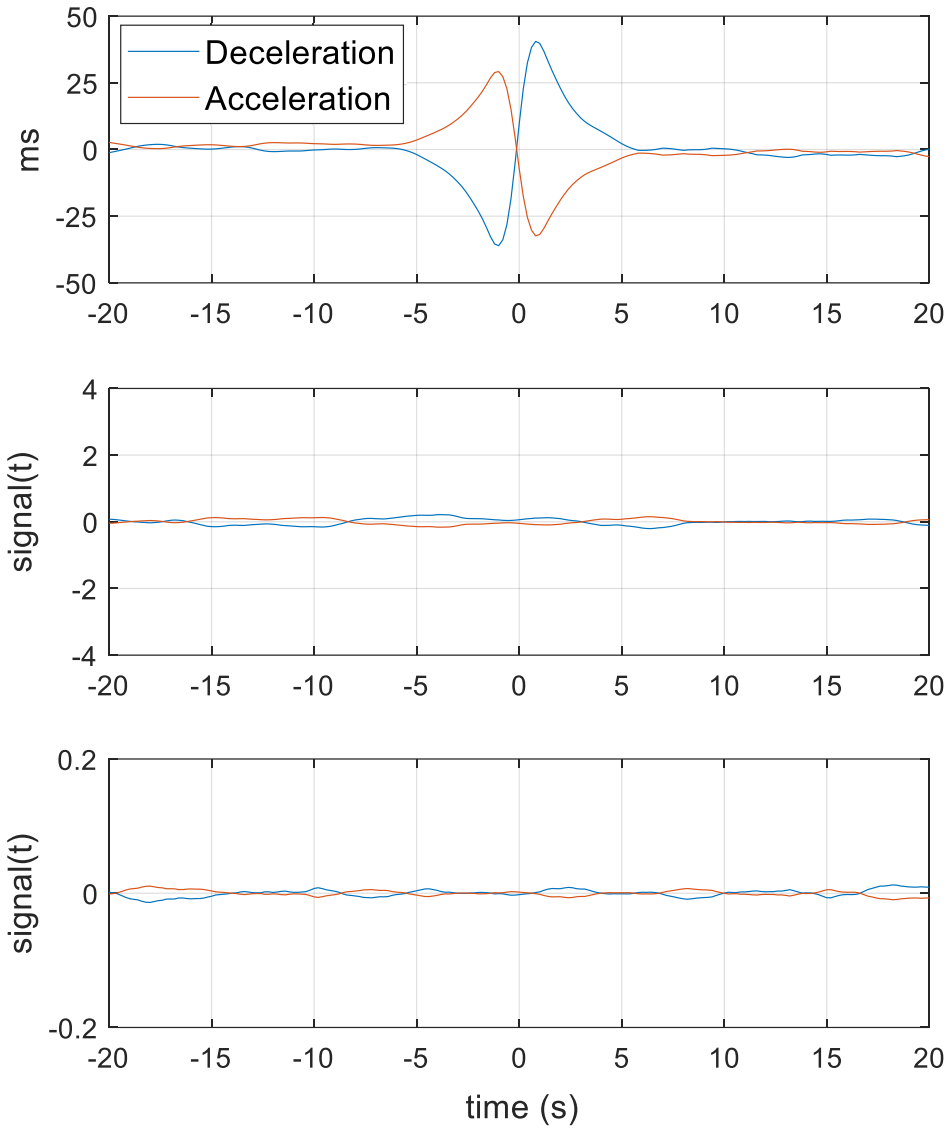

Figure D-6: Decelerations and acceleration graphs for Infant 5. Top: PRSA of RR signal. Middle: BPRSA with RR signal as target signal and WAD as target signal. Bottom: BPRSA with RR signal as target signal and respiratory signal as target signal

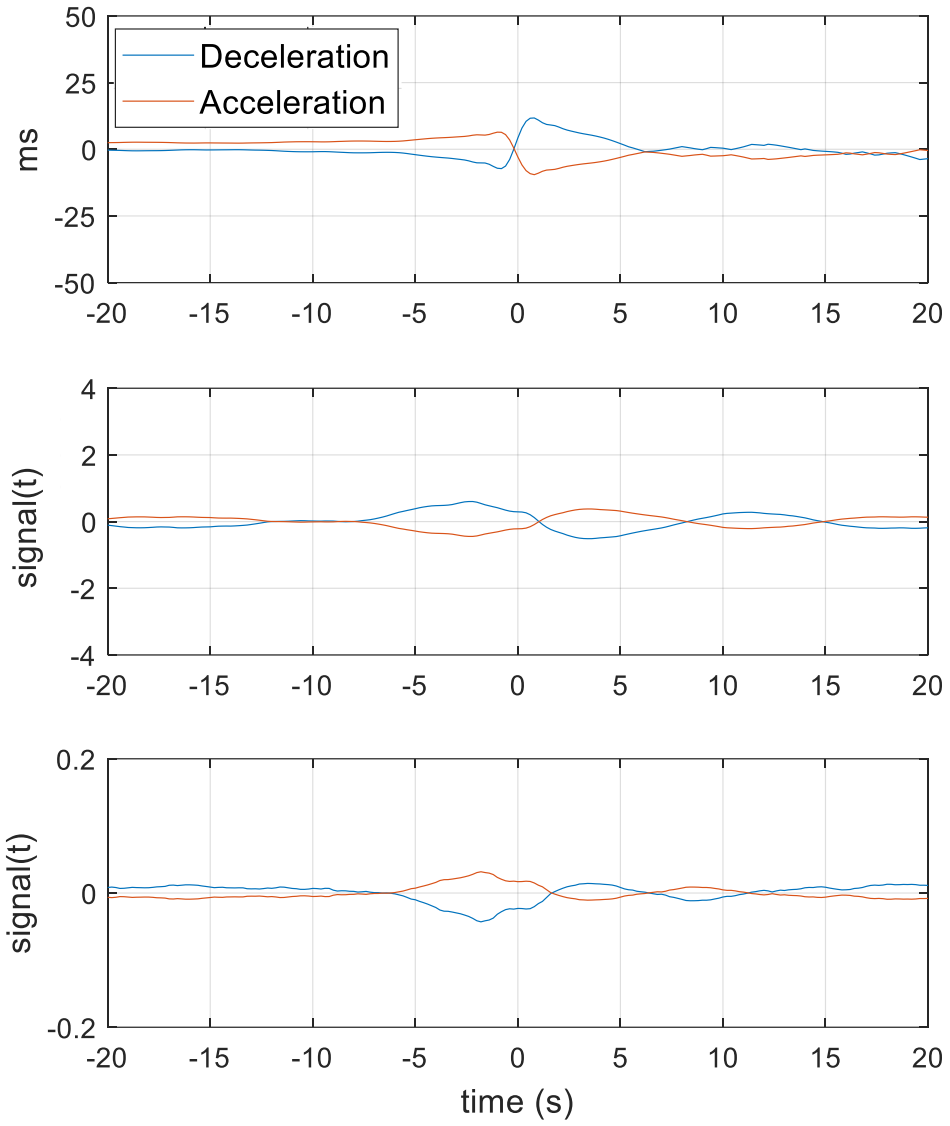

Figure D-7: Decelerations and acceleration graphs for Infant 6. Top: PRSA of RR signal. Middle: BPRSA with RR signal as target signal and WAD as target signal. Bottom: BPRSA with RR signal as target signal and respiratory signal as target signal

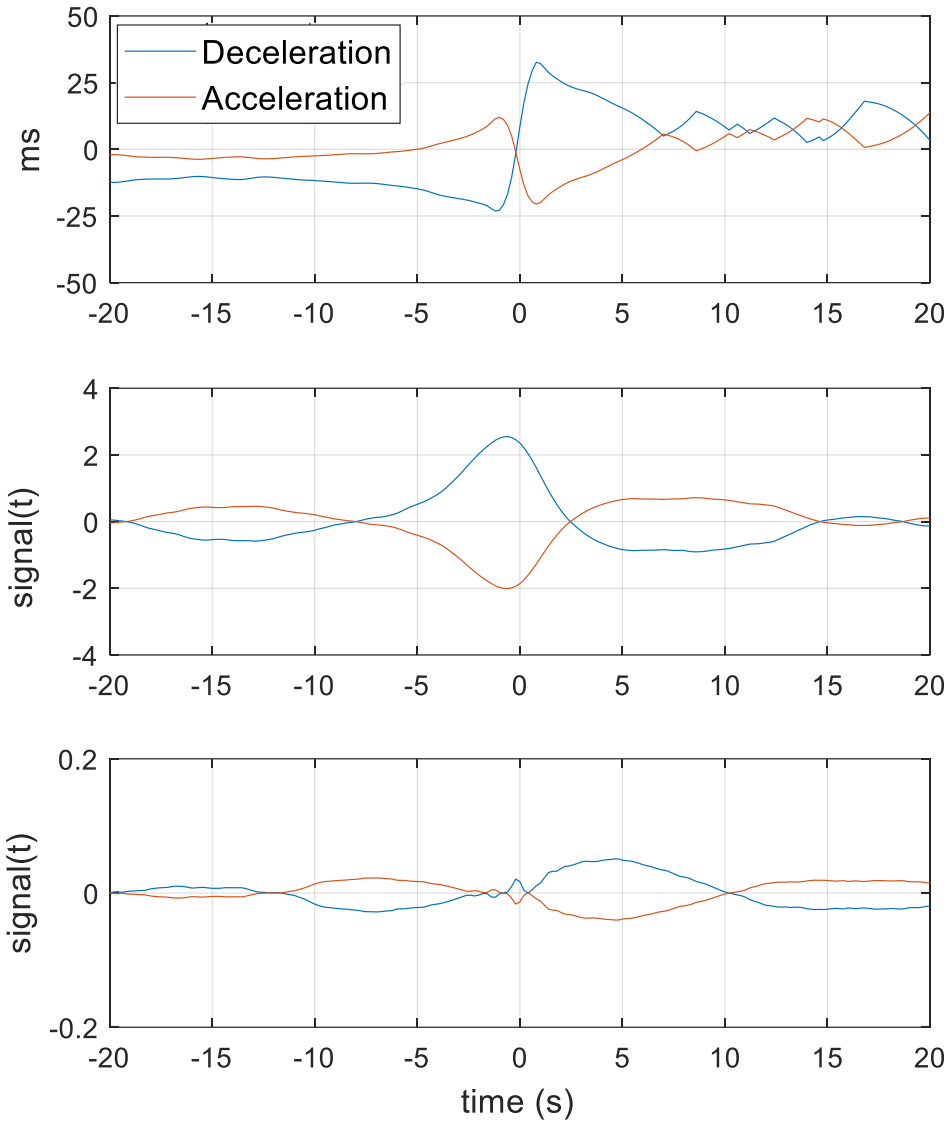

Figure D-8: Decelerations and acceleration graphs for Infant 7. Top: PRSA of RR signal. Middle: BPRSA with RR signal as target signal and WAD as target signal. Bottom: BPRSA with RR signal as target signal and respiratory signal as target signal

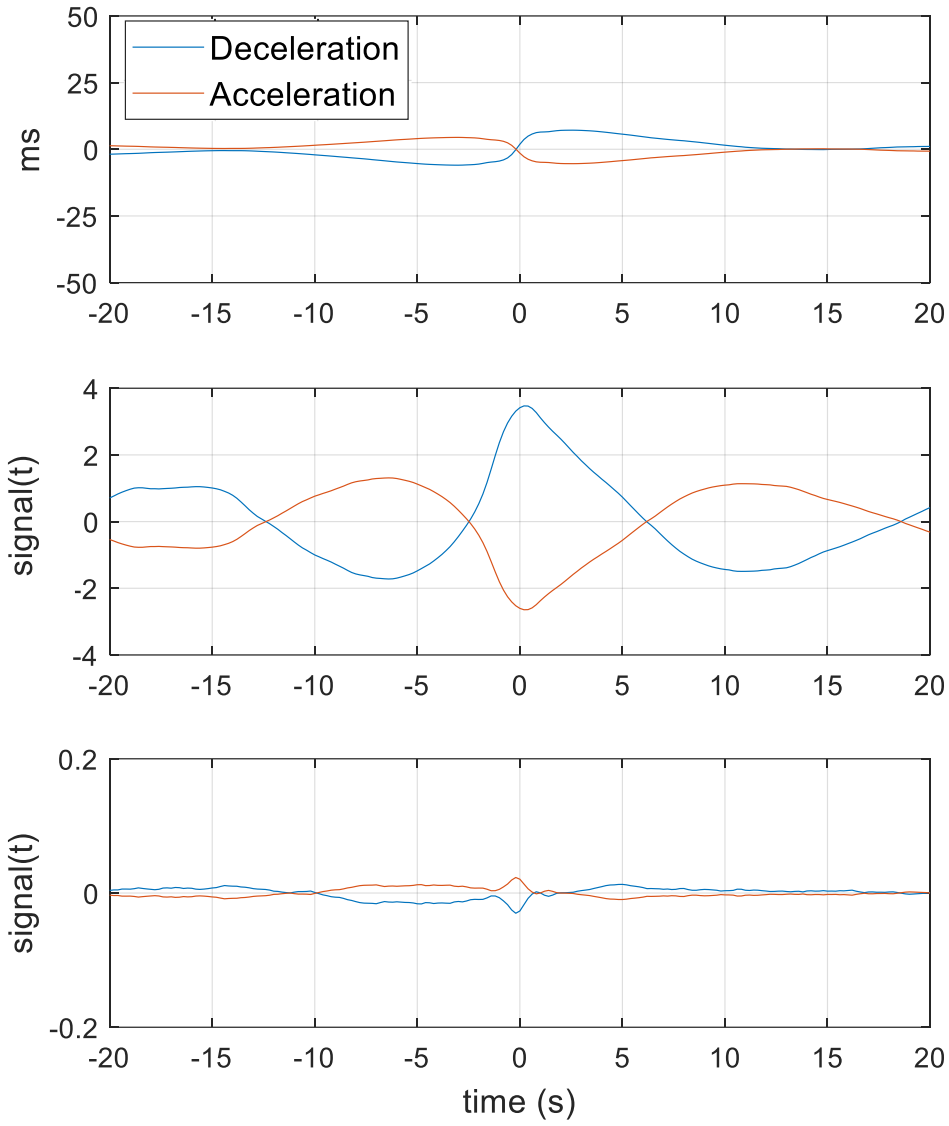

Figure D-9: Decelerations and acceleration graphs for Infant 8. Top: PRSA of RR signal. Middle: BPRSA with RR signal as target signal and WAD as target signal. Bottom: BPRSA with RR signal as target signal and respiratory signal as target signal

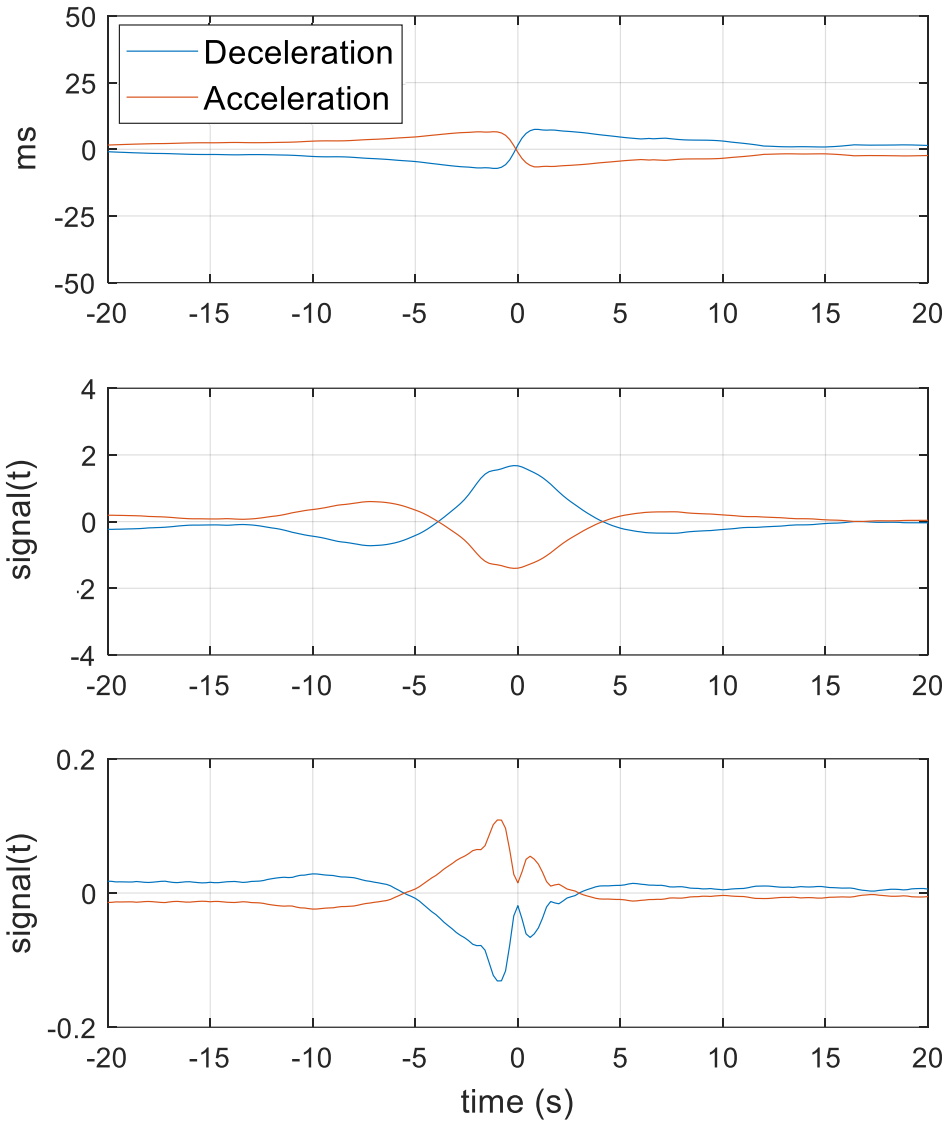

Figure D-10: Decelerations and acceleration graphs for Infant 9. Top: PRSA of RR signal. Middle: BPRSA with RR signal as target signal and WAD as target signal. Bottom: BPRSA with RR signal as target signal and respiratory signal as target signal

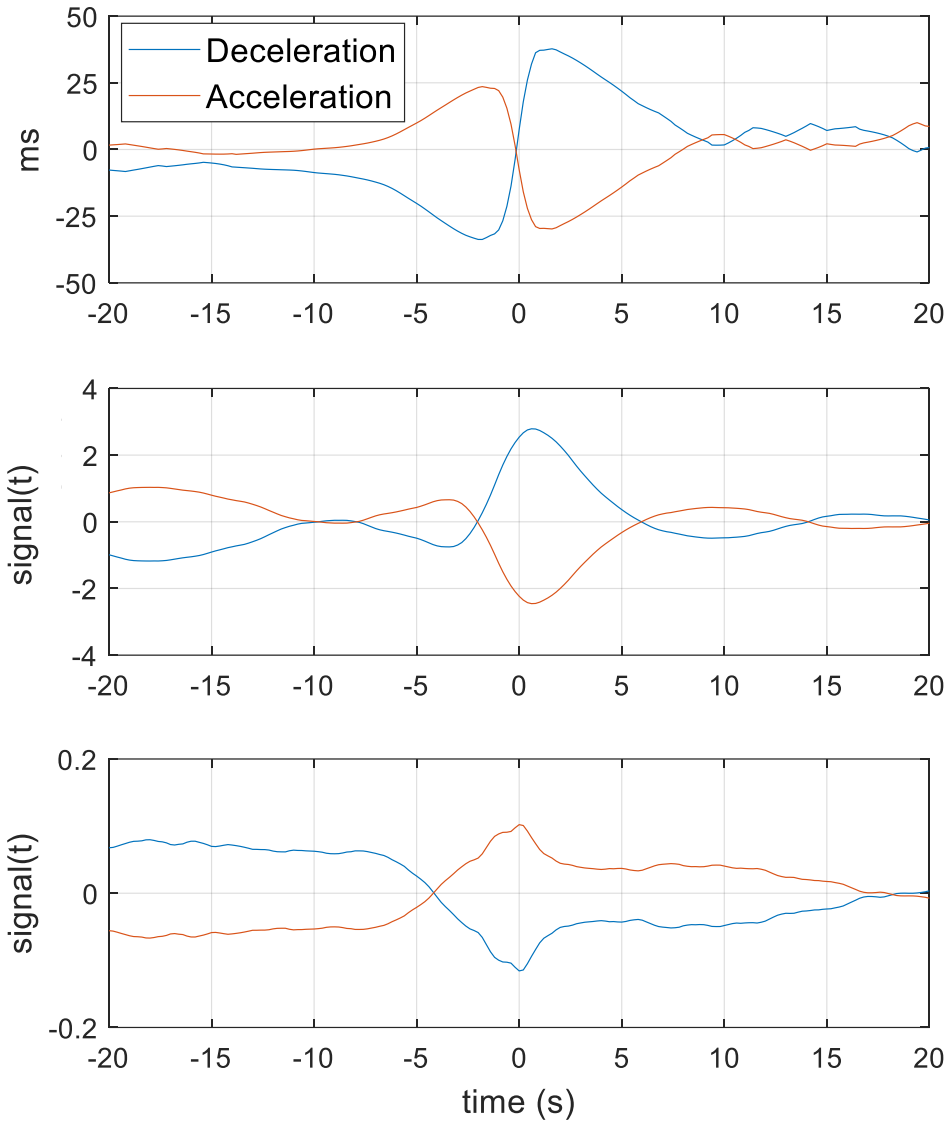

Figure D-11: Decelerations and acceleration graphs for Infant 10. Top: PRSA of RR signal. Middle: BPRSA with RR signal as target signal and WAD as target signal. Bottom: BPRSA with RR signal as target signal and respiratory signal as target signal