Automated Sleep-Wake Cycling Detection in Neonates from Cerebral Function Monitor Signals

By

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Abstract

This thesis presents a link between a clinical need involving the analysis of high frequency physiological data and the informatics and technology designed to automate these specific clinical rules. An algorithmic design for the automated detection of sleep-wake cycling patterns in neonates aged 29-44 weeks gestational age via cerebral function monitor signal is presented in this thesis. The design also includes the automation of impedance levels and background classification of electrical activity via cerebral function monitor signal. The relevance of these algorithms is demonstrated within the neonatal intensive care unit as this monitor is commonly used at the bedside of critically ill infants. The design composition determines analyzable and clinically relevant data through the assessment of impedance levels associated with the cerebral function monitor signal, then the overall background classification of the infant's cerebral electrical activity which indicates whether or not sleep-wake cycling can be present in the signal trace. A third output is the detection of sleep-wake cycling. Current practice in an intensive care setting involves the meticulous and time-consuming process of manual interpretation by a health care professional, subsequently the automation of these processes has the potential to reallocate the use of resources in the form of staff, increase the rate at which the current practice takes place, improve the timing of medical intervention to allow for maximal neurological development in patients as well as facilitate comprehensive analysis with other physiological data streams in unison to deliver enhanced decision making. Performance of the algorithms in comparison to expert clinical annotation resulted in concordance values of 95.70% for impedance, 78.49%, 81.25% sensitivity and 75.32% specificity for sleep-wake cycling and finally 76.34% for background classification. Through this retrospective analysis of de-identified patient data it was determined that this can be applicable to a real-time computer software environment enabled by stream computing.

Publications Related to this Thesis

J. Mikael Eklund, Nicholas Fontana, Edward Pugh, Carolyn McGregor, Paul Yielder, Andrew James, Matthew Keyzers, Cecil Hahn and Patrick McNamara, "Automated Sleep-Wake Detection in Neonates from Cerebral Function Monitor Signals," Computer-Based Medical Systems (CBMS), 2014 IEEE 27th International Symposium, New York, 27-29 May 2014.

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Chapter 1 Introduction

This thesis presents a method for the real-time automated detection of normal and abnormal electrical cerebral activity and the sleep-wake cycling stages in neonates. The research outlines the link between this clinical need and the informatics and technology designed to automate the clinical rules. Through the extensive search of medical literature, algorithms have been designed, evaluated and validated to perform a task that is manually completed frequently in the neonatal intensive care unit (NICU). The retrospective analysis of de-identified patient data will determine whether or not the automated detection of sleep-wake cycling in neonates can be applied in a real-time computer software environment enabled by stream computing.

Cerebral function monitoring is primarily used to aid in the detection of clinical and sub-clinical seizures, as well as to discriminate sleep cycling patterns and associated disorders. The cerebral function monitor (CFM) commonly used in intensive care scenarios displays both an amplitude-integrated electroencephalogram (aEEG) signal trace in microvolts (μV) and the associated impedance in kilo Ohms (kΩ). The CFM requires only one or two channels equating to two or four electrodes to holistically measure the patient's cerebral activity and it can also simultaneously display the raw electroencephalogram (EEG) signal trace with the associated aEEG trace. The current standard practice requires that a health care professional manually annotate and interpret the aEEG and EEG tracings, indicating characteristic patterns within the trace that may be abnormal, when the patient is awake and asleep and offer an opinion on the underlying medical complications that may be occurring. This is by definition a time consuming process. While the automated detection of seizures has undergone continuous and extensive research with limited success, the automated detection of sleep-wake cycling patterns is an aspect that has not been addressed in research to date. This thesis therefore presents original work on the automated detection of the presence or absence of sleep-wake cycling with discrimination and identification of characteristic patterns within the aEEG trace associated with some known medical complications. The motivation for this research was to determine whether online real-time analysis and interpretation of the data from this commonly used bedside tool could accurately automate the annotation of patterns relating to sleep-wake cycling. If possible this would enable more readily accessible brain activity information at the bedside with significant potential to enable earlier detection and diagnosis of certain conditions.

1.1 Application of EEG and aEEG in the Intensive Care of Neonates

Intensive care of neonates has progressed substantially over the last decade as a result of the continuous advancement of technology. Electroencephalography (EEG) is a method that measures the brains electrical activity through the voltage potential difference generated on the scalp between adjacent electrodes (Azzopardi, 2004). This technique utilizes a physiological input/output system and real-time measurement tool valuable in research and diagnostics. EEG has been an extremely useful diagnostic tool for many conditions primarily seizures of all types including both clinical and sub-clinical as well as sleep disorders, stroke, cerebral tumours and neurological disorders such as hypoxic-ischemic encephalopathy and asphyxia (Azzopardi, 2004). The signal generated by EEG is a low pass and spatially filtered which aids in the reduction of noise (artefact) and is displayed at 100 Hertz (Hz) on a CFM monitor (Nunez and Srinivasan, 2005). The clearest results of the electrical activity is in the cerebral cortex are generated by EEG making it the preferred method of signal extraction, amplification and recording in a non-imaging format (Freeman, 2007). This measurement technique is also able to reflect all intracranial currents despite the scalp and skull distorting electric potentials and is transparent for magnetic fields (Freeman, 2007).

Amplitude-integrated EEG (aEEG) is a time-compressed technique, compressing the time scale of conventional EEG by a factor of up to 900:1. It is advantageous for presenting long EEG recordings by using an asymmetrical filter, peak rectifier and semi-logarithmic amplifier to display the signal trace at a slower rate (6cm/hour) (Hellstrom-Westas, 2006). The factors that can be attributed to its widespread application are the reduced number of electrodes, from the 10-20 montage used in standard EEG, to either 2 or 4 depending on whether the set-up is single or double channel (Hagmann et al, 2006). As a result, aEEG is easy to apply, with minimal training required and is easier to interpret than a full, standard EEG (Azzopardi, 2004). Lead application sites have been identified as those areas least affected by artefacts from facial and jaw movements that do not interfere with cranial ultrasound and other clinical procedures regardless of the patient's state of consciousness (Shah, 2010). Additionally, aEEG has the capability to visualize long-term trends and changes in the electrocortical background activity in real-time or retrospectively and can be used in the first few hours of life resulting in a strong long-term

predictor of neurological outcome for infants, requiring less manpower and increased availability of these bedside devices (Hagmann et al, 2006, Randall, 2010).

1.2 Standardization of Trace Characteristic's and the Normal Abnormal Axis of Interpretation

Standardized trace criteria have been established and are used as guidelines when CFM is applied in the NICU and is summarized in Table 1. Conditions for a normal aEEG trace in a term infant include continuous normal voltage without seizure patterns, a lower margin of greater than 5 μV and an upper margin above 10 μV (Figure 1). If a tracing is displayed on CFM and does not possess these characteristics, it is deemed abnormal. It should be noted that in a healthy term neonate, most of the brains electrical activity is around 4Hz with little activity above 10 Hz, as the common usable range is between 2-15 Hz for CFM with activity greater than 15 Hz being considered non-cerebral (Marics et al, 2013). Common background tracings that often occur on CFM include continuous normal voltage (CNV) which consists of continuous and variable activity with minimum voltage of 5–10 μV and maximum voltage of 10–50 μV, and discontinuous normal voltage (DNV) consisting of discontinuous activity with variable minimum amplitude, mainly below 5 μV, and maximum amplitude above 10 μV (Figure 2). Burst suppression (BS) contains discontinuous activity with minimum amplitude without variance at < 5 μV and bursts predominantly with amplitude ≥ 25 μV and is shown in Figure 3; continuous low voltage (CLV) produces continuous and variable activity with maximum amplitude below 10 μV and minimum amplitude at approximately 5 μV. Finally, the last characteristic tracing pattern that can be observed is a flat trace (FT) which is primarily an inactive (isoelectric) trace with both maximum and minimum background activity below 5 μV (Horn et al., 2013).

Table 1. Summarization of micro voltage values for each category of CFM background activity

	Lower Margin	Upper Margin
Continuous Normal Voltage	≥5 – 10 µV	≥10 - 50 µV
Discontinuous Normal Voltage	<5 µV	>10 µV
Burst Suppression	< 5 µV	≥25 µV
Continuous Low Voltage	= 5 µV	<10 µV
Flat Trace	<5 µV	< 5 µV

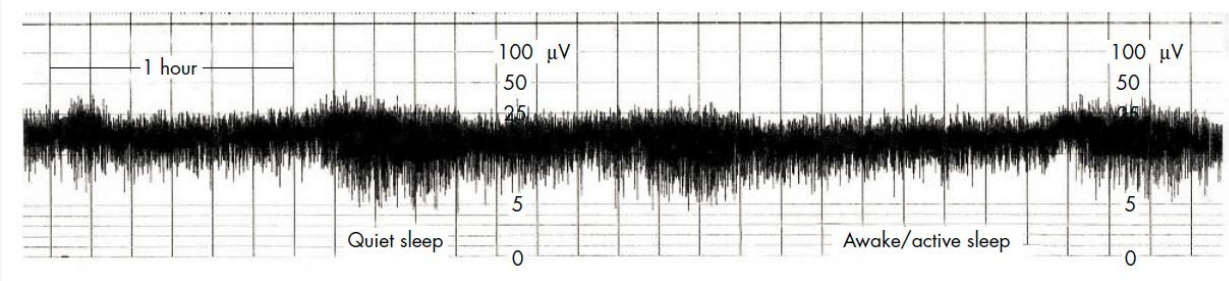


Figure 1. Continuous normal voltage background electrical activity with sleep-wake cycling present (de Vries and Hellstrom-Westas, 2005)

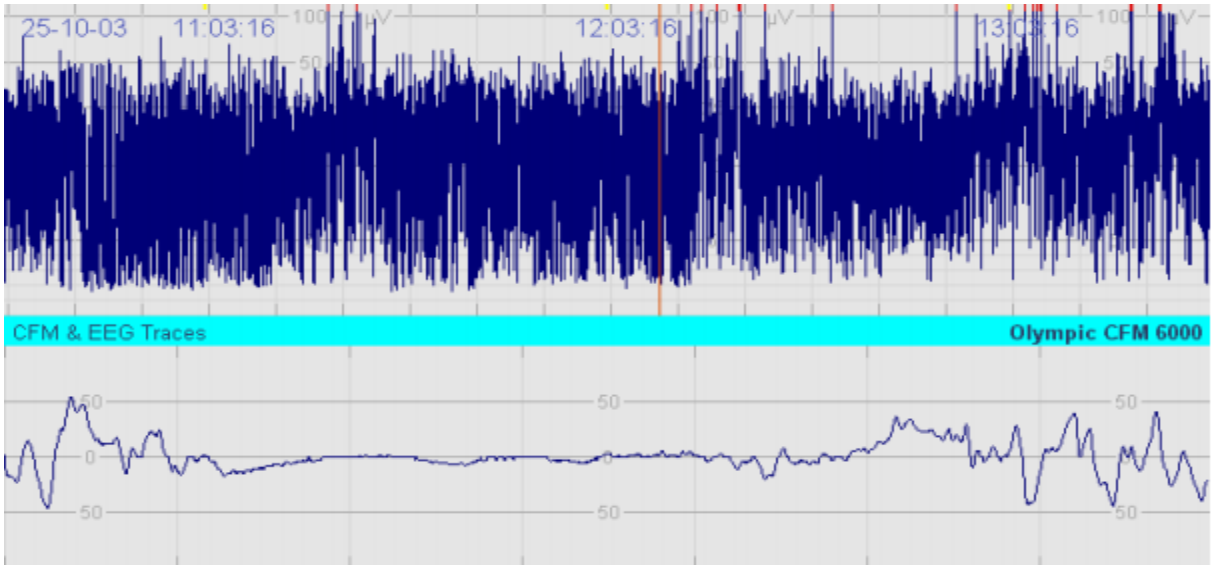


Figure 2. Moderately abnormal CFM trace displaying a discontinuous pattern that is exemplified in the raw EEG trace below (Azzopardi, 2004)

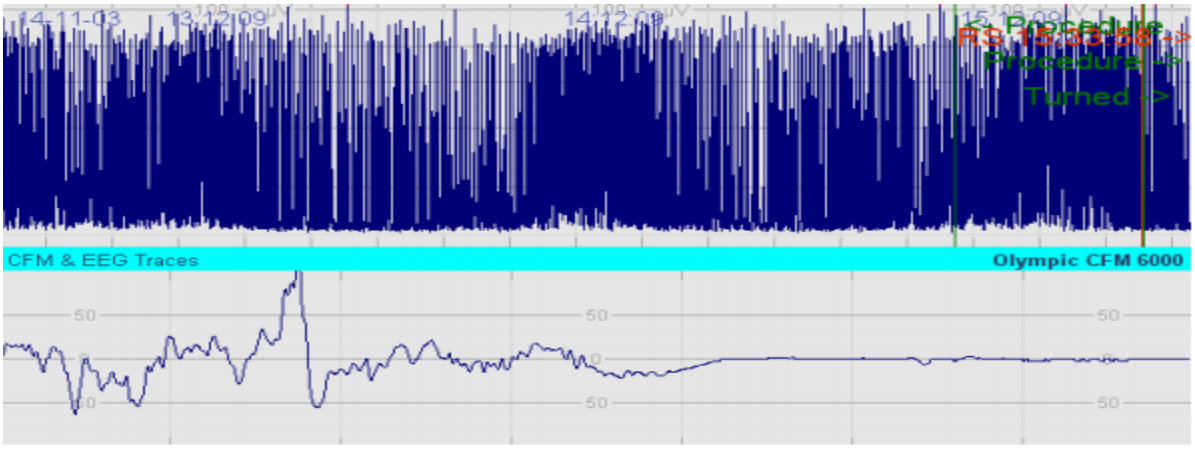


Figure 3. Moderately to severely abnormal CFM trace displaying a burst suppression pattern that is verified by the corresponding raw EEG trace below (Azzopardi, 2004)

1.3 Sleep and the Sleep – Wake Cycle in CFM

Sleep is a complex function of the human body that often requires many different monitors for accurate assessment of the biological processes that are activated. The standard monitoring used during sleep is electroencephalography that measures the production of different wavelengths

corresponding to different sleep states. Additional non-cerebral monitors to detect sleep can include: respiratory monitors for the detection of chest movement, eye monitors for the detection of both horizontal and vertical eye movement, electrocardiogram electrodes to assist in the identification of artifact, electromyography to measure electrical activity generated in skeletal muscle during sleep and cardiographic activity which is often temporally related to QRS complexes ("AASM", 2007).

There are five different stages of sleep which include: wakefulness, stage N1 (non-REM), Stage N2 (non-REM), Stage N3 (non-REM) and Stage R (REM). During these stages of sleep, the human body utilizes the hours of rest to recover from physical exertions required for daily living. The human immune system is also able to work and combat against viruses and infection and of equal importance, maintains mental and emotional health through sufficient sleep (Toh, 2008). In addition to this, sleep has been linked to brain development such as learning, intellectual and physical memory. Critical to the stages of sleep are the natural circadian rhythms that are the mental, physical and behavioural changes in response to light and darkness that are imperative in determining sleep patterns ("AASM", 2007). The suprachiasmatic nucleus, located in the hypothalamus, controls the production of the hormone melatonin that makes humans fatigued or drowsy with the release occurring directly above the optic nerves. This translates information from the eyes to the brain, more specifically in response to light and darkness from the surrounding environment (Toh, 2008). This occurs through the eye's retinal rod and cone cells, which are photoreceptors to distinguish colour, light and darkness. The retina also contains ganglion cells that are photosensitive and directly linked to the suprachiasmatic nucleus (Toh, 2008). This physiological process also relates to the circadian rhythms that are cyclical throughout an approximate 24 hour period, having a significant impact on sleep-wake cycling patterns, the release of hormones, and body temperature regulation (Toh, 2008).

During active sleep, a term infants eyes are often closed with a variety of small and large body movements, as well as sucking and crying with bursts of horizontal rapid eye movement in which EEG is represented by a low voltage trace (Iber et al, 2007, Toh, 2008). In term infants during quiet sleep, the eyes are closed with very little movement and respiration is slower and deeper with the EEG most likely displaying adverse medical or neurological conditions as it is one of the only sleep stages in which these abnormalities may be detected (Iber et al, 2007, Toh,

2008). The majority of sleep in healthy term infants falls into the intermediate stage between wakefulness and quiet sleep.

Sleep-wake cycling is commonly defined and identified using electrophysiological measures such as aEEG, as continuous normal voltage and the presence of both wakefulness or active sleep and quiet sleep with a minimum of two to three consecutive, clear state changes on aEEG lasting for twenty minutes during a 5-6 hour period (Thorngren-Jerneck et al., 2003). The pattern has an approximate frequency between 0.5–1 cycles/hour in both maximum and minimum amplitudes (Thorngren-Jerneck et al., 2003, Osredkar et al., 2005). When displayed by aEEG, sleep-wake cycling is categorised by the smooth sinusoidal variations, primarily of the minimum amplitude or lower baseline microvolt level during recording (Kidokoro et al, 2012,Thorngren-Jerneck et al., 2003, Soubasi et al., 2012). When a broader or expanded aEEG bandwidth is seen, this represents discontinuous background activity during quiet sleep, and a narrow, thinner bandwidth corresponds to a lower voltage, more continuous activity during waking stage and active sleep (Soubasi et al., 2012, El-Dib et al., 2009, Osredkar et al., 2005). Sleep-wake cycling in infants carries great significance as it is often used as a measurement of the infant's neurological development. The absence or delayed development of sleep-wake cycling patterns on aEEG can be the result of hypoxic-ischemic encephalopathy, infection, motor and cognitive impairment, or unilateral brain injury (Kidokoro et al, 2012).

1.4 Automation and the Detection of Seizures and Abnormal Cerebral Function

When considering the informatics perspective of this research, it is apparent that many algorithms have been developed for the automated detection and analysis of seizures and other patterns displayed by EEG and aEEG with minimal success and similarly none has focused on the sleep-wake cycle (Schumacher et al, 2011). They report that there is currently no software program that has been developed for the automatic analysis of sleep-wake cycling. In relation to this, the application of CFM is considered to be very useful when applied in the clinical setting. However the task of the management of these devices and the interpretation of the data shifts from the neurologist to the bedside neonatologist and they become useful in aiding patient management at the bedside only if managed and interpreted accurately. Physicians who are not trained as specialists in electrophysiology must be able to interpret the CFM traces and are often

uncomfortable with this task which is where the application of this algorithm may be successful in aiding health care professionals (Walsh et al., 2011).

Currently the best methods for automated detection of patterns displayed by aEEG are based on computing a running autocorrelation function, rhythmic discharge detection, modeling or complexity analysis, and wave-sequence analysis (Deburchgraeve, 2010). Others have been performed based on the withdrawal of features using entropy, wavelets, frequency content, and then training a classifier on these features to accurately classify the EEG (Lommen et al, 2007).

The characteristics of the complex of neonatal seizures arising focally and then becoming generalized contain a rhythmic frequency activity that can vary significantly from patient to patient (Faul et al, 2005). Limitations in previous research conducted on automated seizure detection include the failure to detect focal and seizures of short duration as well as mistaking artefact for seizures. (Faul et al, 2005). Shifting focus from seizure detection towards automating the detection of sleep-wake cycling patterns in neonates allows for more manageable and straight-forward algorithm metrics and development (Cseko et al, 2013; Klebermass et al, 2011). This research has not been reported in previous literature and has future implications regarding accuracy and classification of neurological complications associated with certain aEEG patterns and predictive measures for these complications.

1.5 The Artemis Platform - Description

The Artemis Platform provides a flexible platform for the real-time analysis of time-series physiological data streams extracted from a range of monitors to detect clinically significant conditions that may adversely affect health outcomes (McGregor et al, 2011). The Data Acquisition component enables the provision of real-time synchronous medical device data and asynchronous clinical data extracted from the NICU's Clinical Information Management System (CIMS). This data is then forwarded for analysis within the Online Analysis component, which operates in real-time. For this real-time component, Artemis employs IBM's InfoSphere Streams, a novel streaming middleware system that processes data in real-time and then enables data storage within the Data Persistency component. It is capable of processing and then storing the raw data and derived data from multiple infants at the rate at which they are generated (Blount et al, 2010). Stream processing is supported by IBM's Stream Processing Language (SPL), which is

the programming language for IBM's InfoSphere Streams middleware. For the Knowledge Extraction component, Artemis utilizes a newly proposed temporal data mining approach (McGregor, 2012). This component supports the discovery of condition onset behaviours in physiological data streams and associated clinical data. New knowledge, once tested through rigorous clinical research techniques, is transferred for use within the Online Analysis through the re-deployment component, which translates the knowledge to a SPL representation.

Through the analysis and extraction of specific components from algorithms related to various different functions, the development of a unique algorithm compatible with the Artemis' infrastructure in the Health Informatics Research Laboratory (HIRL) at the University Of Ontario Institute Of Technology, Oshawa (UOIT) for the detection of variance in sleep-wake cycling in infants could be potentially developed.

1.6 Development of the Research Study and Its Design

Research Question: Can an accurate, reliable, and valid automated algorithm be designed to detect normal and abnormal traces and detect sleep-wake cycling from an aEEG signal in neonates greater than 29 weeks gestational age?

Hypothesis: That the development and application of a robust algorithm for analysis of aEEG data streams captured at the bedside can aid in the diagnosis and determination of variations in the normal sleep-wake cycling patterns in neonates greater than 29 weeks gestational age.

Objective: To design, verify and validate an algorithm to automate the detection of sleep-wake cycling patterns displayed by aEEG, in neonates from 29-44 weeks gestational age, administered to the Neonatal Intensive Care Unit. This algorithm will allow for accurate, rapid detection of the presence or absence of these cycling patterns.

1.7 The Artemis Platform - Process Design and Application

This thesis presents a method of constructive research in which clinicians have identified the use of CFM and the challenges with manual interpretation of the traces and the advancement of the tool through computer analysis. As a result, an original algorithm was designed to enable automated detection of sleep-wake cycling patterns on aEEG in real-time and with the goal of

providing an equivalent or more accurate detection than that performed by physicians. The motivation for this research is to assist physicians in the neonatal intensive care unit to more accurately define the trends and patterns displayed on cerebral function monitors and allow them to spend more time focusing on patient care. This research is the initial step in defining a numerical scale, classifying neurological patterns seen on aEEG.

As previously stated the primary goal of this research is to develop an algorithm that is highly accurate in the detection of when periods of sleep and wakefulness are occurring. The secondary goal is to construct an algorithm that associates particular aEEG traces with physiological dysfunction that are commonly encountered in the NICU. In a study by El-Naggar et al., (2010), high rates if abnormal aEEG tracings were discovered in term infants with cardiorespiratory compromise, more specifically pulmonary hypotension or congenital heart disease, despite having normal neurologic examination. This underlies the significance of aEEG as a complimentary and adjunctive bedside tool in identifying patients at an increased risk for neurological compromise, which otherwise goes undetected through routine assessment. In research conducted by Al Naqeeb et al, (1999) background traces of aEEG in patients with hypoxic-ischemic encephalopathy were positively predictive for abnormal neurologic outcome. Hypoxic-ischemic encephalopathy is often associated with burst suppression and/or discontinuous normal voltage 'low' characteristic background traces, whereas intraventricular haemorrhage in neonates is often associated with discontinuous normal voltage 'low' and continuous/discontinuous low voltage tracing patterns (El-Naggar et al, 2010). Accurately automating the association between these different patterns in aEEG traces and physiological compromise has the potential to provide earlier detection resulting in preventative medical intervention. If successful this will also allow for the comparison of physiological compromise and the effect on sleep-wake cycling patterns in regards to presence/absence, and duration.

The data source sampled specified patients who occupied Artemis bed spaces in the NICU at The Hospital for Sick Children, Toronto, and who also had cerebral function monitors attached to them for at least a six-hour period. A list of patients meeting these requirements was established and the CFM information was obtained from the Hospital. Upon collecting this information the associated aEEG traces were split into three hour time epochs in order to increase the sample size. This time allows for several sleep-wake cycling patterns in term infants as the duration of

these cycles is approximately one hour in length. The data archive required a minimum of 10 patients, however 30 selective data sets were included in the research and processed through the algorithm that was developed for the automated detection of these patterns displayed by aEEG.

1.8 Scope of Thesis

The research that is outlined in this thesis contributes to the larger Artemis Project currently in progress in the Health Informatics Research Laboratory at UOIT. The scope of this thesis includes the design, verification and validation of the algorithms that were developed in order to automate the detection of normal and abnormal aEEG traces and sleep-wake cycling patterns produced by CFM in neonates. Determining how these algorithms could be designed based on the principles of stream based computing as the paradigm within which they were coded fits within the scope of this thesis as well. In relation to this, the question of whether or not EEG analysis proposed in this work is considered a suitable problem for streams computing approaches to solve is also within the scope of this thesis.

The technical coding and development of the algorithm as well as the visualization of the algorithms results are not within the scope of this thesis research. The technical engineering development of the algorithms was conducted in MATLAB by Dr. Mikael Eklund (Department of Electrical, Computer and Software Engineering, UOIT), a key member of the Artemis Project team. Other areas of research within the Artemis team that have most recently taken place include developing ways to visualise data and how to present algorithm outputs to clinicians in the most effective manner (McGregor et al., 2013; Thommandram et al., 2013; Thommandram et al., 2014), the application of automated monitoring techniques for apnoea of prematurity (Catley et al., 2011), seminal work involving the development of a unique and accurate pain profile for neonates (Naik et al., 2013), as well as monitoring conditions related to retinopathy of prematurity (Cirelli et al, 2013). These are just a select few of the myriad of ongoing projects within the HIR laboratory at UOIT under Dr. Carolyn McGregor. To date the current research within the greater Artemis Project has focused on electrocardiogram (ECG) and its derived signals, blood oxygen saturation levels (SpO_2), and blood-pressure in real-time however the clinical signal of EEG has not been used for analysis.

The presentation and visualisation of the algorithms results will be continued by the Artemis team in future research. The output of results within the range of this thesis includes text-based output, concordance and sensitivity and specificity reports in comparison to expert clinical annotations.

1.9 Summary of Thesis

This thesis aims to close the gap between the clinical and technical background for implementing automated technology systems to aid as potential clinical decision support tools. Through an extensive review of medical literature, acceptable standard values were defined for the algorithms that were developed in this research for the automated detection of normal and abnormal traces produced via CFM in addition to the initiation and cessation of sleep and wake stages from the neonatal patient data. The study used a total of 30 de-identified neonatal patient data sets, 15 patients in the algorithm training set and 15 patients for the validation set. In the first algorithm, based on established micro voltage values from the literature, the characteristic background traces identifying good quality and poor quality data were established. These classifications were made during each 30 second epoch of the patient data, which was an arbitrary clinical time selected as a starting point for this Master's thesis. The second algorithm was designed to determine the upper and lower margins of the CFM trace. Once this had been established and verified, a third algorithm was implemented to identify changes in the bandwidth of the trace also known as the paradigm between discontinuity and continuity indicating when stages of sleep and wakefulness are occurring. The output of this algorithm is a binary function of either 1 for sleep or 0 for awake. Finally, the last algorithm was designed to provide temporal analysis, establishing which periods the patient was asleep or awake based on the length of time during each stage. This was determined by matching the output to expert annotations on when these stages were occurring using the first 15 patients in the population. When successful the algorithms output was then validated against the 15 remaining data sets.

1.10 Thesis Structure

This thesis presents the techniques used to measure cerebral activity, as well as a brief physiological and signal acquisition background. An overview of previous work utilizing CFM and medical literature related to sleep-wake cycling in neonates and its clinical significance is

presented in Chapter 2. The third chapter presents a detailed description of the Artemis platform and how this research is situated within the overall project. Chapter 3 also defines the data collection for the research and a high-level study description. Chapter 4 goes into detail on how the algorithm was designed, verified and validated to detect normal and abnormal CFM traces and identifying sleep-wake cycling patterns in neonates. The fifth chapter presents the results of algorithm implementation. Finally chapter six concludes the thesis with a summarization of the findings of the research in support of the questions and hypothesis proposed. Furthermore, suggestions for continued research beyond this thesis are outlined in this chapter as well.

Chapter 2 Literature Review

There continue to be developments in critical care monitoring from both an academic and industry perspective. This chapter presents an in-depth review of previous studies that have been conducted relating to neonates in the intensive care unit and brain monitoring using EEG and aEEG and any attempts that have been made to automate processes within these techniques. These results are presented before describing an innovative methodology for automating the detection of the background trace produced by cerebral function monitor (CFM) and the periods of sleep present within a patient's trace as the initial investigation of applicability within big data and informatics based software as well as in the clinical setting.

To complete this literature review databases including Medline, Scholar's Portal and PubMed were used to search relevant articles pertaining to the study using keywords: aEEG, EEG, Neonates, Sleep-wake Cycling, Cerebral Function Monitor, and Automated Detection. The search date ranged from 1960 to 2013. These searches revealed a strong focus on the use of cerebral function monitors and amplitude-integrated electroencephalogram traces for seizure detection and identification in preterm and term infants. As previously mentioned in the introductory chapter, many attempts have been made to automate the detection of neonatal seizures with limited success, whereas no publications have established a software program or developed algorithms to detect sleep-wake cycling patterns in neonates. This literature review will cover the measurement techniques for electrical cerebral activity including signal acquisition and physiology. The review will also cover sleep-wake cycling and its importance in neonates, the concept of informatics and computer engineering relating to cerebral function monitor signals and finally the clinical significance of this research.

2.1 Cerebral Activity Measurement Techniques

2.1.1 Electroencephalography

Electroencephalography (EEG) is the ideal method for measuring the electrical activity of the brain in adults, children and newborns. A less complex variation, amplitude-integrated electroencephalogram (aEEG) has been developed which is a time-compression technique for long EEG recordings via an asymmetrical filter, peak rectifier and semi-logarithmic amplifier. EEG and aEEG are valuable tools in determining primarily seizures of all types including both

clinical and sub-clinical as well as background electrical activity, periods of sleep, stroke, presence of tumours and neurological disorders such as hypoxic-ischemic encephalopathy (Lommen et al., 200, Nunez and Srinivasan, 2005, Shalak et al., 2003). Sleep wake-cycling patterns can also be visualized and subsequently analyzed from these signals. The absence or presence of abnormalities in sleep-wake cycling of infants can be a long-term indicator of neurological dysfunction.

Electroencephalography (EEG) has been established as the preferred method of signal extraction, amplification and recording which provides the clearest results of cerebral cortex activity in a non-imaging format (Freeman, 2004; Shalak et al., 2003). This method measures the brains electrical activity through the voltage potential difference generated on the scalp between adjacent electrodes. EEG is able to reflect all intracranial currents despite the scalp and skull distorting electric potentials and is transparent for magnetic fields (Freeman, 2004). This technique is a physiological input/output system and real-time measurement tool valuable in research and diagnostics that is measured using an international standard montage of 10-20 electrodes (Figure. 4). An example of the output for neonatal EEG generated from these electrodes is depicted in Figure 5. Using differential data streams normal and abnormal activity can be detected through modeling and extraction of significant data in an attempt to form definitive conclusions (Lommen et al., 2007). EEG is a low pass, spatially filtered signal that aids in the reduction of noise otherwise known as artefact (Nunez and Srinivasan, 2005). The most desirable EEG sampling rate is approximately 500 Hz, with a minimum rate of around 200 Hz. Routinely recorded filter settings possess a low frequency filter for EEG equal to 0.3 Hz and high frequency filter of 35 Hz (Iber et al., 2007).

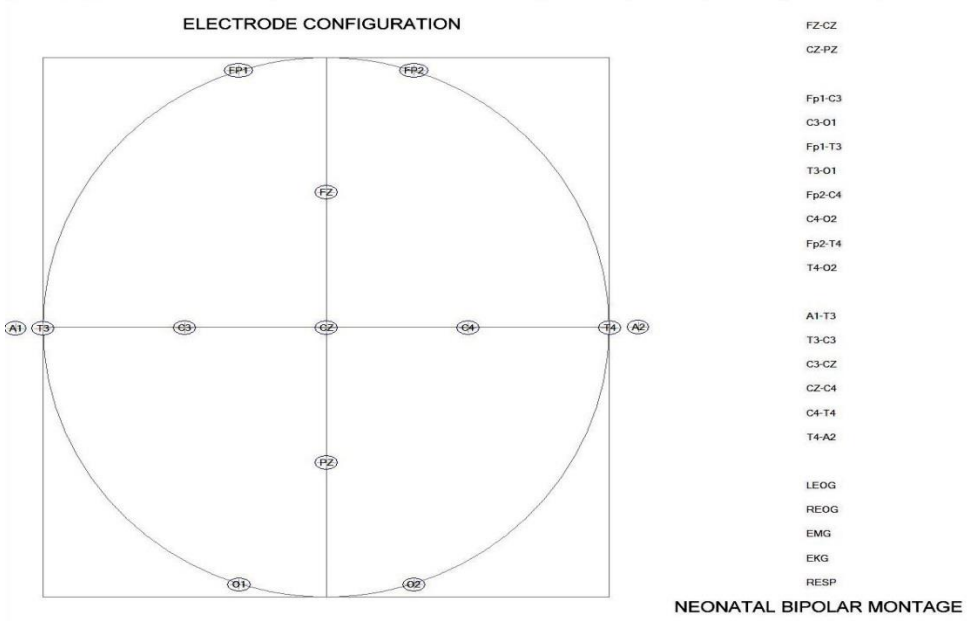


Figure 4. Standard neonatal electrode montage (Vukkadala et al, 2009)

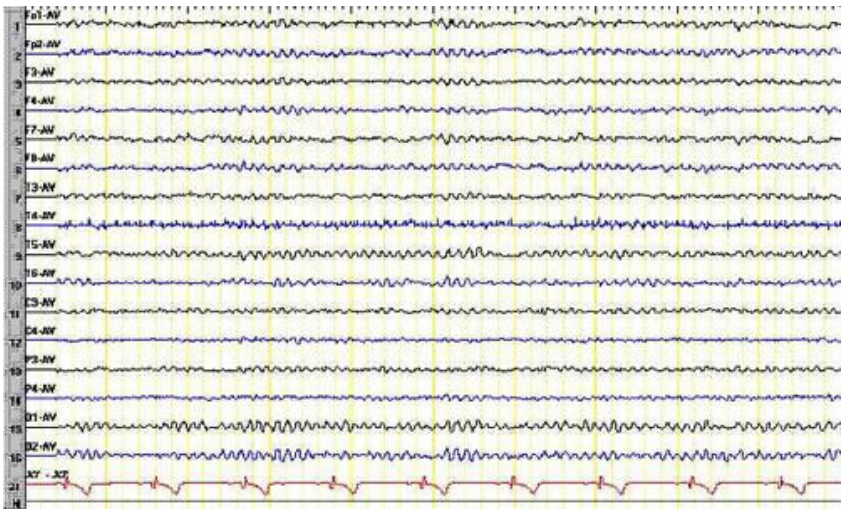


Figure 5. Example of a normal infant EEG (Vukkadala et al, 2009)

EEG is commonly used clinically in adults, children and newborns for determining depth of coma, detecting sleep disorders, stroke, presence of tumours and most importantly detection of seizure. Clinical or sub-clinical seizures may be caused by other neurological disorders such as intraventricular and intracranial hemorrhage, hypoxic-ischemic or metabolic encephalopathies, cerebral infarctions or infections (Nunez and Srinivasan, 2005, Lommen et al., 2007; Shalak et

al., 2003). EEG is also used to potentially look for neurological indicators of epilepsy, certain infectious disease, neurodegenerative disorders, and metabolic disorders (Stjema et al., 2012).

The interpretation of the EEG signal in neonates has been said to be the most challenging in the field of neurophysiology due to the highly developing brain and susceptibility to adverse medical conditions such as those listed above. As a result of this the use of amplitude-integrated electroencephalopathy has emerged as one of the prominent brain monitoring methods at the bedside in neonatal intensive care (Boylan et al., 2010).

2.1.2 Amplitude-Integrated EEG

A variation of the EEG methodology has been developed entitled amplitude-integrated electroencephalogram which utilizes the application of a time compression technique for presenting long EEG recordings using an asymmetrical band pass filter which enhances components of the signal with higher frequency, a peak rectifier and semi-logarithmic amplifier (outlined in Figure. 6) (Hellstrom-Westas, 2006). When aEEG was first developed in the 1960s by Maynard and Prior the aim was to create an instrument to study cerebral activity in patients with suspected brain damage with the basis that the system was simple to use, including automatic operation at a reasonable cost, reliable, noninvasive, vastly applicable and provided direct information about neuronal function that was easily quantifiable (Hellstrom-Westas et al., 2006; Tao and Mathur, 2010). The instrument has continuously developed over the duration of its existence and is commonly applied to both preterm and term infants within the NICU. Shown in Figure 7 is the derivation of aEEG that comes from a reduced EEG of either one pair of bi-parietal electrodes or one channel from each hemisphere using four electrodes, measuring electrical activity between parietal electrodes in the C3 and C4 locations and P3 and P4 electrode locations with one reference or ground electrode (Hellstrom-Westas et al., 2006). Two channel aEEG allows for asymmetrical comparison, which can help determine from which hemisphere the seizure originated, detecting unilateral injury and has been proven that a greater number of seizures are detected using the two channel configuration (van Rooij et al., 2009).

The classification of aEEG is based primarily on pattern recognition of the background activity, however there have been several different approaches generated by prominent figures in the development of the tool which include the use of voltage criteria (Al Naqeeb et al., 1999), the

use of pattern recognition and voltage criteria to describe aEEG patterns (Helstrom-Westas et al., 2006) as well as the application of classification terminology from conventional EEG (Toet et al., 2002). In some instances, inter-observer agreement can vary based on which method is applied (Tao and Mathur, 2010). For inexperienced health care professionals or those who are minimally trained, the process of annotation and interpretation can be a challenging and lengthy process. The difficulty often lies in the distinction between artefact and activity as the range of recorded artefact varies from 12-60% (Tao and Mathur, 2010). As a result non-expert interpretation of events on a neonatal aEEG trace has a tendency to be over or under analyzed (Tao and Mathur, 2010).

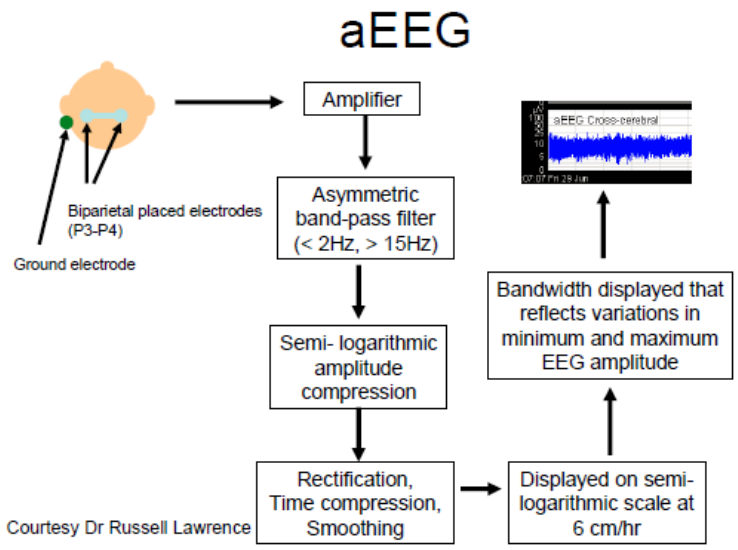


Figure 6**.** Flow chart describing the process of aEEG from signal acquisition to display on a cerebral function monitor (Shah et al, 2010)

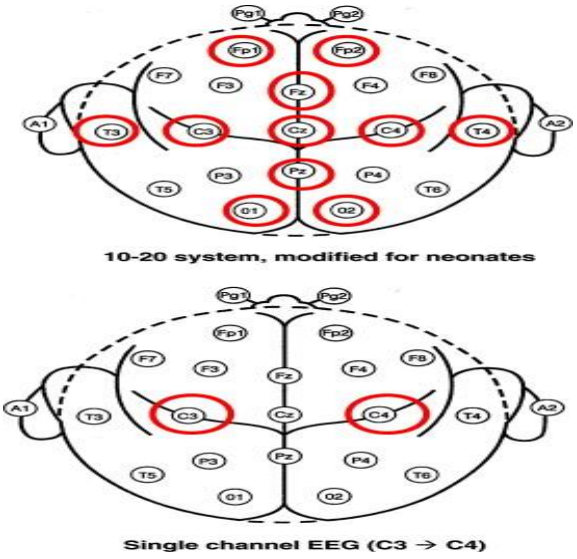


Figure 7. Standard International 10-20 electrode montage for EEG and the C3-C4 arrangement for EEG (Vasiljevic et al, 2012)

2.1.3 Signal Acquisition

The EEG and aEEG signal is electrophysiological based on membrane potentials within the cerebral hemispheres. Essentially EEG is a record of oscillations in electric potential of the brain detected by electrodes on the scalp (Nunez and Srinivasan, 2005). This electrical potential within the brain originates from discrete neuron pools and functional complexes. Ion currents are spread non-uniformly in three dimensions throughout the brain, which acts as the conducting source to allow for the transmission of the signal (Azzopardi, 2004). The ions that comprise the currents within the extracellular space consist mainly of sodium, potassium, calcium and chloride.

Through the negative feedback among excitatory and inhibitory neurons, postsynaptic potentials begin to arise from the firing of previous action potentials within pyramidal neurons, specifically the dendrites (Freeman, 2004). It is these excitations of dendrites within the post-synaptic region of the pyramidal neurons residing in the cerebral cortex that are measured by EEG (Shah, 2010). The summation of postsynaptic potentials from pyramidal cells creates a dipole between the soma and the apical dendrites (Shah, 2010). This dipole is detected by the electrodes on a patient. This is in essence a momentary stored capacitance effect in which it possesses variable spatial and temporal characteristics.

The signal path can be outlined as follows: a single pyramidal cell is activated by an afferent pathway generating electrical activity; the incoming excitatory signal to the synapse causes a postsynaptic potential that generates an inward current of positive ions at the synapse which slows down at the dendrite and moves across the cell membrane. As a result a dipole is formed crating electrical potential via the summation of these dipoles and can be detected by the electrodes.

Background activity is characterized by the uneven distribution of a massive numbers of neurons within the cortex, regulated by the dendritic currents (Freeman, 2004). Normal brain processes that keep patients alive are enough to acquire a background signal on an EEG recording. EEG signals tend to be highly irregular, postsynaptic sites of neurons receive cortical output both temporarily and spatially, which aids in the approximation of the summation of multiple EEG signals in a time window (Freeman, 2004). This allows for accurate signal interpretation in either a resting state or aroused state when receiving stimulus. Stimuli in patients could be the result of medical intervention such as ventilation, administration of pharmaceuticals or surgery in the case of a neonate in an intensive care unit. Resulting firing of the neurons and the signal would translate to different (increased or decreased) voltage output displayed on the digital monitor (Freeman, 2004).

Electrical potentials on the scalp exhibit spatial and temporal patterns depending on the nature/location of the sources and the electrical fields that are distributed through the tissue (Liu et al., 2002). Electrodes are placed on the scalp of the subject, including one reference or ground electrode placed in the frontal region above the nasal bone, which is connected to an input board (Spitzer, 2006). The current travels from the scalp to the input device that can then be controlled by input selector switches (White, 2008). The signal then passes through amplifiers, low frequency filters, high frequency filters, 60 Hz filters and finally to the writing unit which portrays the signal as an EEG tracing (White, 2008). An electrical change towards the negative direction in an electrode is indicated by an upward deflection of the signal and vice versa for the positive direction, before rectification and compression to generate the aEEG output (White, 2008).

When working with devices such as EEG and aEEG, one of the most critical factors is to minimise the signal to noise ratio so that the clearest and most accurate signal is produced.

Impedance and artefact can interfere with the signal from other devices within the intensive care unit such as ECG or ventilators causing respiratory movements. Artifacts can also be the result of crying or coughing in infants, administration of medication, blood draws, intravenous feeding, the changing of diapers, adjustment of masks, suctioning and finally loose leads (Blount et al., 2010). One of the problems with EEG is to relate potentials taken from the scalp to the physiological process within the brain (Nunez and Srinivasan, 2005). Scalp EEGs can become 'contaminated' with non-cerebral artifacts that include movement, muscle and eye-movement occurrences (Shalak et al., 2003).

2.2 aEEG in Neonates

Olishar et al., (2004) conclude that continuous aEEG monitoring can provide information on the infant's sleep-wake status for favorable timing of nursing caregiving, developmental care, and medical interventions. In addition to this, they further state that it can also be used to identify early signs of neurologic compromise, monitor response to treatment, and evaluate responses to environmental stress (Olischar et al., 2004). Amplitude-integrated EEG is used in correspondence with a cerebral function monitor that records the aEEG amplitude at a reduced pace, and displays it on the screen simultaneously with the associated impedance in kilo-ohms (kΩ) or the unfiltered, raw EEG trace (Azzopardi, 2004).

Amplitude-integrated EEG has a useable frequency range between 2Hz and 15Hz and each data sample is rectified and averaged over a time frame, which equates to the aEEG of cerebral function signal displayed on a cerebral function monitor (Azzopardi, 2004; Temko et al., 2011). The voltage fluctuation (y-axis) in relation to time (x-axis) is displayed as the final output of aEEG waveforms (Temko et al., 2011). Recordings are plotted on the y-axis ranging from 1μV and 10 μV on a linear scale and between 10 μV and 100 μV on a logarithmic scale, resulting in lower amplitudes being easier to interpret (Chalak et al., 2011; Hagmann et al., 2006). Amplitude-integrated EEG is generally plotted as 6cm per hour and has a compression ratio up to 900:1 (Chalak et al., 2011; Hellstrom-Westas, 2006).

The specific placement of frontal-parietal electrodes for aEEG is due to the fact that it is the area least affected by artefacts from facial and jaw muscle movement, has the least interference with medical treatment, provides maximum comfort for the neonate and generates the maximum

amplitude of cerebral activity whether awake, sleeping, sedated or unconscious (Shah, 2010). Generally, the degree of electrical impedance ranges from 0-25 kΩ, which is often a measure of the quality of the signal being received and if this impedance exceeds 20 kΩ,, alarms will sound on the devices used indicating inaccurate signal detection and consequently causing results to be inaccurate (Spitzer, 2006; Soubasi et al., 2012).

When considering the digital output of the aEEG signal, a standard tracing in premature newborns based on the degree of cerebral maturation contains discontinuity where short bursts of electrical activity are followed by lulls or low voltage activity (Shah, 2010) With an increase in age, the digital output transitions from discontinuous to an increase in continuous activity (Randall, 2010).

The most common aEEG patterns (Figure 8) seen in the NICU are as follows:

- Continuous Normal Voltage (CNV) displays a narrow bandwidth minimum voltage above 5 µV and a maximum voltage above 10 µV (Randall, 2010).
- Discontinuous Normal Voltage (DNV) is represented by a moderately wide bandwidth a minimum voltage below 5 µV, but variable and a maximum voltage above 10 µV,
- Burst Suppression (BS) displays an extremely wide bandwith maximum and minimum voltages both very low and very high, and without variability to the lower margin (1 µV to greater than 25 µV), which often indicates seizure activity in neonates (Randall, 2010). Normally the episodes of suppression are longer (5-10 seconds) than the bursts of activity (1-3 seconds) (Randall, 2010). Bursts are defined as amplitudes reaching 100 µV or greater (Olischar et al., 2004).
- Continuous Low Voltage (CLV) with an output of a narrow bandwidth the maximum and minimum voltages below 10 µV and finally inactive recordings that have a very narrow band with all activity below 5 µV (Randall, 2010). These values can be used for determining neurological disorder as the assessment of encephalopathy can be defined as moderately abnormal corresponding to an upper margin >10 µV and lower margin <5 µV or severely abnormal, corresponding to an upper margin less than 10 µV (Takenouchi et al., 2011).

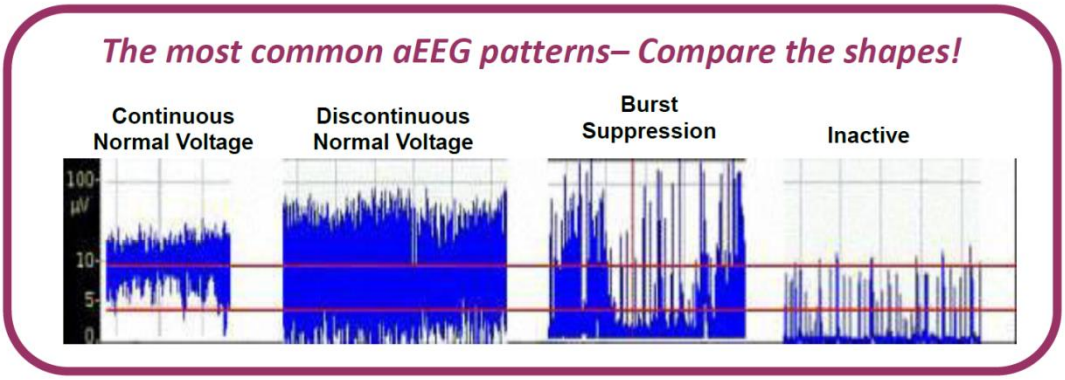


Figure 8. The most common aEEG traces found in neonates (White et al, 2009)

In extremely preterm infants the prevailing background pattern is discontinuous activity and is referred to as "trace´ discontinue", which has relatively long inter-burst periods of latency mixed with superimposed short bursts of electrical activity (El-Dib et al., 2009). The length of the suppressed intervals between the bursts or inter-burst intervals decreases with increasing postmenstrual age (Hellstrom-Westas et al., 2006). The upper and lower margins of the aEEG tracing form two envelopes that follow the maximum and minimum peak-to-peak amplitudes of the EEG signal (El-Dib et al., 2009). The difference between these upper and lower margins, is called bandwidth which reflects the variance in aEEG amplitudes (El-Dib et al., 2009). The value of the aEEG voltage envelope for term infants (without complications) is >5 μV peak to peak for the lower border and > 10 μV peak to peak for the upper border. If there is a decrease in both the minimum (<5 μV peak to peak) and maximum (<10 μV peak to peak) amplitudes, then this designates significant amplitude suppression of the EEG signal (Hellstrom-Westas et al, 2006; El-Dib et al., 2009).

The aEEG trace that appears is dependent on the condition of the neonate, as during sleep a wider trace is produced, while during active sleep or while awake a narrow band is seen. When a wider distance between the upper and lower margins of the aEEG trace are seen, this represents discontinuity in the cerebral activity, while a narrow trace represents continuity of the electrical activity (Azzopardi, 2004). Generally the range of the aEEG trace varies approximately from 1 to 40 microvolts (Hagmann et al., 2006). The CFM however does not provide information about the EEG frequency of cerebral function as it is more concerned with signal voltage (Hagmann et al.,

2006). Amplitude-integrated EEG is a useful tool in predicting long-term neurological outcome in high-risk infants and for future neuroprotective protocols and the timing of medical intervention (Spitzmiller et al., 2007).

In regards to neonates residing in intensive care units, they are often subjected to medication to treat complications that can affect background electrical activity (Chalak et al., 2011). Another downfall of aEEG is the fact that standard EEG used in combination with aEEG is far more accurate than aEEG alone (White, 2008). Helstrom-Westas et al. (2006) also found that short electrical seizures under 30 seconds in duration went undetected by the aEEG system, and that when using only one or two channels, focal seizures that originate at a distant site from the electrodes such as the centroparietal region may go undetected (Shah, 2010). Limited channels also limit visualization of spatial evolution compared to multiple channels as well as the duration and focus of the seizures (Freeman, 2004). As with all medical imaging and diagnostic equipment, the signal output is the computer systems interpretation and representation, meaning that it may not be 100% accurate all the time. Despite this EEG and aEEG are proven techniques that are highly reliable in the clinical setting.

Additional strengths of aEEG include the fact that it is a non-invasive technique and safe, especially for neonates who are extremely delicate and underdeveloped. The technique is easy to use which allows for greater repeatability regarding set-up and placement of electrodes along with subsequent recording of the signal (Hagmann et al., 2006; Shah, 2010).

2.3 Sleep-Wake Cycling In Neonates

This next section begins an in-depth analysis on the critical component of this research which is the sleep-wake cycling patterns of neonates. Sleep-wake cycling is commonly defined as having continuous normal voltage and the presence of both wakefulness or active sleep and quiet sleep with a minimum of two to three consecutive, clear state changes on aEEG during a 5-6 hour time epoch with an approximate frequency between 0.5–1 cycles/h in both maximum and minimum amplitudes (Thorngren-Jerneck et al., 2003; Osredkar et al., 2005). When displayed by aEEG (Figure 9), sleep-wake cycling is categorized by the smooth sinusoidal variations, primarily of the minimum amplitude or lower baseline microvolt level during recording epochs (Thorngren-Jerneck et al., 2003; Soubasi et al., 2012). Sleep-wake cycling on aEEG, in term infants is

categorised by semi-periodic inconsistencies in bandwidth that represent the changing variance in peak-to-peak amplitude in the altered states of wakefulness and sleep (El-Dib et al., 2009; de Vries and Hellstrom-Westas, 2005). When a broader or expanded bandwidth is seen, this represents discontinuous background activity during quiet sleep, and a narrow, thinner bandwidth corresponds to a lower voltage, more continuous activity during waking stage and active sleep (Figure 10) (Soubasi et al., 2012; El-Dib et al., 2009; Osredkar et al., 2005). These patterns are state-dependent, representing the physiology of complex interactions among cortical, basal forebrain, thalamic, and hypothalamic neurons, which receive a significant input from the ascending arousal system also known as the reticular activating system localized in the dorsolateral aspect of the brainstem below the tegmental region (Takenouchi et al., 2011).

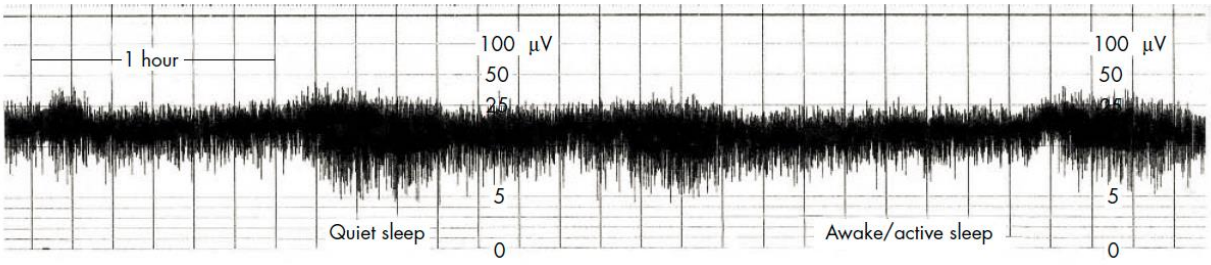


Figure 9. Continuous normal voltage background pattern with sleep wake cycling present (de Vries and Hellstrom-Westas, 2005)

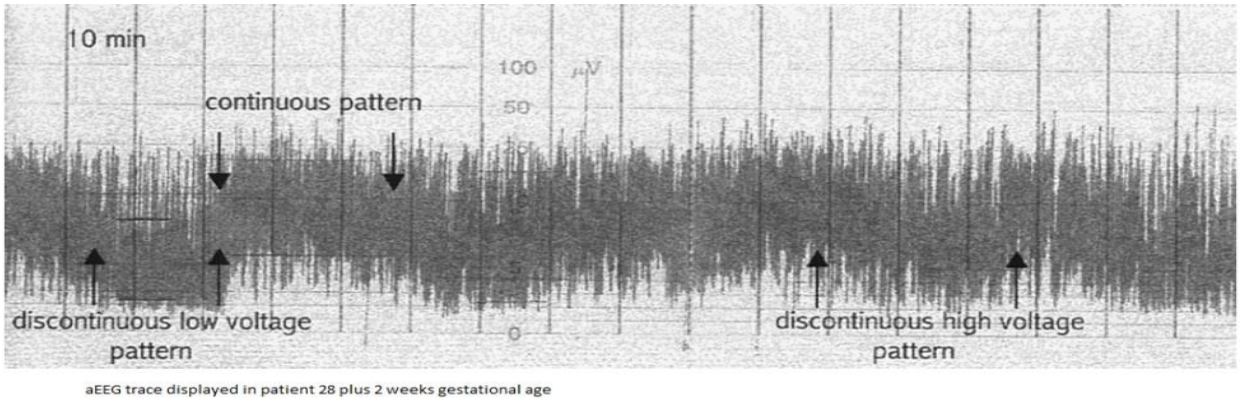


Figure 10. aEEG trace displayed in a patient 28 plus 2 weeks gestational age (Liu et al., 1992)

When discussing an infant's age classification in relation to sleep, the associated signal traces must also be outlined. Postmenstrual age (PMA) is equal to the gestational age, measured from the time of the last menstrual period plus the infant's postnatal age at the time of recording. Term infants range in age from 37 up to 44 weeks PMA, preterm infants are less than 37 weeks PMA, and post-term infants are 44 to 48 weeks PMA (Tsuchida et al., 2013). The EEG pattern in preterm infants is characterized by bursts of high voltage (50-300 μV from peak to peak) activity that is often interrupted by low voltage inter-burst periods (< 25 μV from peak to peak). At 27-34 weeks PMA, 40-45% is spent in active sleep, 25-30% in quiet sleep, and 30% in indeterminate sleep (Tsuchida et al., 2013). Beyond 35 weeks PMA, 55-65% of time is spent in the active sleep stage, 20% is spent in quiet sleep and 10-15% is spent in indeterminate sleep. The duration of a sleep cycle: first active sleep, then transitional sleep and finally quiet sleep, is 30-50 minutes for neonates <35 week PMA and increases to 50-65 minutes beyond 35 weeks PMA and it can be expected that the cycling will not disappear once acquired (Tsuchida et al., 2013).

Active sleep in infants is represented by combined theta and delta frequency waveforms with intermixed low-amplitude irregular segments of alpha and faster rhythms, while quiet sleep is the combination of high amplitude slow waves, predominantly in the delta band, and ‘‘tracé alternant" segments which includes beta and theta activity mixed with delta activity (Korotchikova et al., 2009; Thornberg and Thiringer, 2008). Pattern changes in the brain's electrical activity that leads to the cycling of sleep and wake stages can be attributed to neuronal firing in an oscillating network between the thalamus and the cortex (Thorngate et al., 2013). As the brain matures, processes become more organized and activity begins to consistently cycle between periods of continuity and discontinuity which ultimately reflect the changes in sleep states (Thorngate et al., 2013).

With the emergence of cycling on aEEG at approximately 28-29 weeks gestation shown in Figure 11, the lower baseline of continuous activity in the tracing is commonly evaluated and classified as: severely depressed (<3 μV); somewhat depressed (3-5 μV) and elevated as (>5 μV) (Palmu et al., 2010; Soubasi et al., 2012). The upper margin of the aEEG trace is generally not analyzed to the extent of the baseline, however upper margin amplitude in infants with neurological disorder is significantly higher compared to controls or healthy infants (Soubasi et

al., 2012). Abnormal sleep-wake cycling (SWC) contains the presence of SWC on a discontinuous background pattern with corresponding lower margins of the narrowest and broadest bandwidth continuously <5 μV (Osredkar et al., 2005). Sleep-wake cycling generally appears by the gestational age of 29–30 weeks on aEEG (O'Reilly et al., 2012).

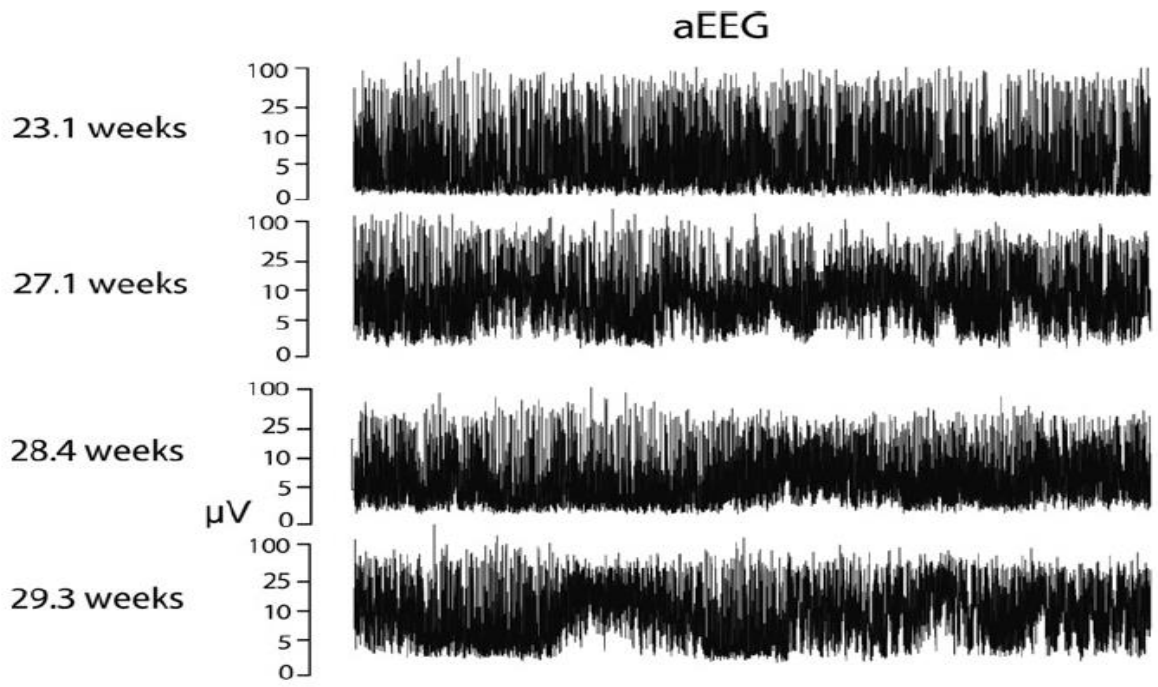


Figure 11. Patterns of aEEG at different gestational ages - the signal exhibits a wider, more discontinuous trace at a younger age and narrower trace with increased age. The emergence of cycling is seen with an increase in age (O'Reilly et al, 2012)

Sleep-wake cycling is often recoded via polysomnography, which is considered to be the gold standard for sleep testing. This test records continuous pulse oximetry and nasal respiration during sleep as well as many other biophysiological factors such as eye movement, muscle activity and skeletal activation (Kushda et al., 2005). Polysomnography is conducted in ideal setting within a sleep laboratory and can also determine which state of sleep or wakefulness the patient is in, as well as apnoea events and oxygen desaturation (Kushda et al., 2005).

It has been commonly noted that as postmenstrual age advances, the presence of continuous activity increases relative to discontinuous activity. Additionally, as gestational maturity progresses, the lower margin amplitude increases, the bandwidth decreases, and sleep-wake cycling appears (O'Reilly et al., 2012). In late preterm babies, sleep-wake cycling can be detected on EEG by increased discontinuous activity during quiet sleep. Babies born at term display a less discontinuous, alternating trace in quiet sleep, up to a postmenstrual age of 45-46 weeks (El-Dib et al., 2009). The alternating tracing describes the appearance of quiet sleep in which the discontinuous EEG alternates between higher-voltage bursts and lower-voltage inter-bursts (El-Dib et al., 2009). The burst suppression pattern on neonatal EEG is linked with poor outcome and a patient displaying predominant inter-burst interval duration of more than 30 seconds has a 100 % probability of experiencing severe neurologic disabilities or death and an 86 % chance of developing subsequent epilepsy (Deburchgraeve, 2010).

When premature infants experience hypoxic-ischemic encephalopathy, they can display either moderately abnormal traces on aEEG (upper margin >10 μV and lower margin <5 μV) or severely abnormal (upper margin less than 10 μV) (Takenouchi et al., 2011). The median time of onset of sleep-wake cycling in infants with normal outcome is 72 hours with a range of 12 to 132 hours, in comparison to greater than 132 hours for infants who suffer from profound motor and cognitive impairment and do not acquire sleep and stages (Takenouchi et al., 2011). The transition to sleep-wake cycling in neonates has been shown to be preceded by changes in the background EEG activity, from a discontinuous to continuous pattern (Takenouchi et al., 2011). Examples of normal and abnormal sleep wake cycling can be seen in Figure 12.

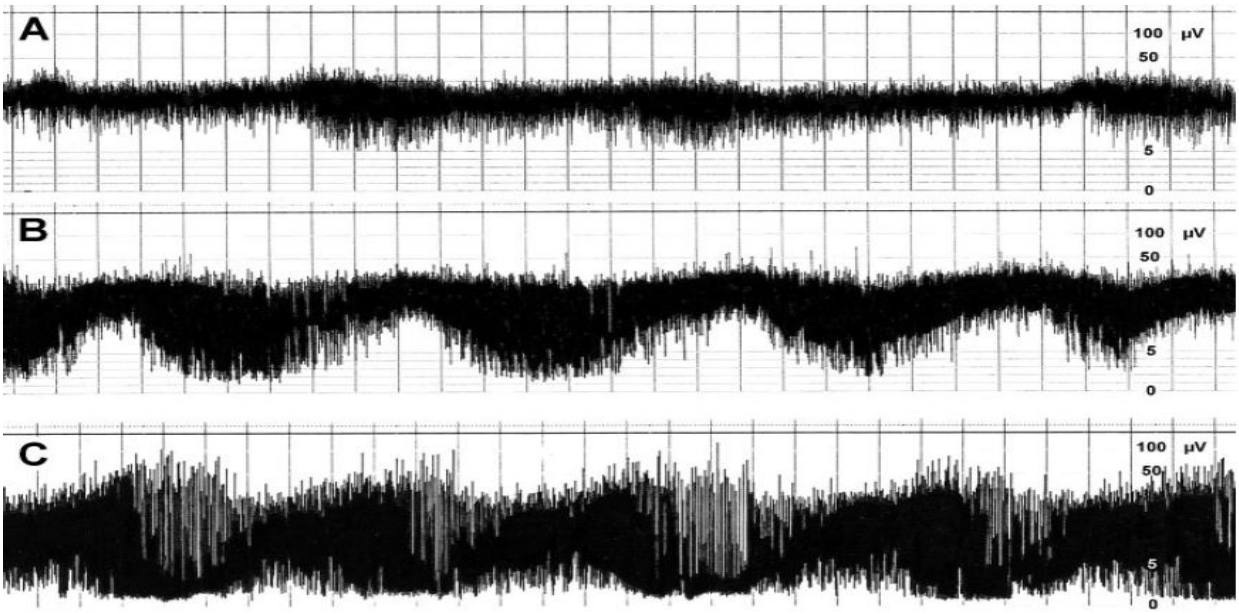


Figure 12. A) Normal SWC with Continuous normal voltage, with an unusually long cycle period B) Normal SWC during quiet sleep C) Abnormal SWC, discontinuous background trace (Osredkar et al, 2009)

Despite what has been outlined thus far, there is an argument that has been put forth regarding the currently used definition of sleep-wake cycling on aEEG. This definition is frequently used by clinicians and researchers, and has been suggested that 'cyclicity' should be used to describe this sinusoidal alternation between continuous and discontinuous activity (Kidokoro et al., 2012). SWC is a technical term that refers to the biological pattern of alternating sleeping and waking states, which is difficult to define with only aEEG and the absence of other physiological parameters (Kidokoro et al., 2012). Furthermore, the absence of cyclicity on aEEG is a stronger reflection of the sequence of the subdued background activity of an aEEG following cerebral injury or dysfunction than sleep/wake states. Consequently, aEEG bandwidth exhibits the difference in voltage between maximum and minimum amplitude activity and in a short period of time the EEG activity repetitively changes from high to low amplitude and back, giving aEEG bandwidth a wider appearance (Kidokoro et al., 2012). In contrast, when the EEG activity does not fluctuate, the aEEG bandwidth appears narrower. Hence, cyclicity in aEEG is the derivation of repetitive changes between continuous and discontinuous EEG activity (Kidokoro et al., 2012). In premature infants, the relationship between EEG patterns and sleep states is more

complicated because of the immaturity in the organization of each physiological parameter leads to an increase in immature sleep (Kidokoro et al., 2012).

Recent studies have suggested that unprompted motor activity has an important role in the promotion of cortical development, organization and cyclical sleep rhythms. Cyclical cerebral activity on aEEG appears to be equivalent to the intrinsic and extrinsic rhythms in the brain (Kidokoro et al., 2012). Discrepancies arise between EEG- defined and behaviourally or physiologically defined sleep and wake states when there is an absence of cyclicity on aEEG due to asphyxiation experienced by the neonate (Kidokoro et al., 2012). An asphyxiated term infant with extended discontinuous background activity displayed on EEG/aEEG may be categorized as quiet sleep according to the EEG-based definition however this is not the case as infants with this condition show decreased quiet sleep (Kidokoro et al., 2012). An additional example is those infants with unilateral brain injury who demonstrated an absence of cyclicity only on the aEEG recorded on the affected hemisphere. The disassociation between hemispheres suggests that the lack of cyclicity on aEEG reflects uncharacteristically suppressed EEG activity and therefore, does not guarantee the lack of sleep/wake functioning in the brain. As a result, the absence of cyclicity on aEEG is a reflection of the sequence of the suppressed background activity of aEEG following cerebral injury or dysfunction, and is considered as a part of background activity (Kidokoro et al., 2012).

Different neonatal sleeping states are defined according to body movement levels, eye opening and closing, eye and facial movements, consistency of respiration, vocalizations, and reaction to internal and external stimuli (Foreman et al., 2008). Sleep states are categorized as either quiet or deep sleep and active or light sleep. The awake state is characterised by four stages: drowsy, quiet alert, active alert, and crying. The drowsy stage is often observed as the alternation between sleep and wake states (Foreman et al., 2008). Infants with a higher birth weight also display more prominence in the organization of their sleep patterns, primarily during quiet sleep (Foreman et al., 2008). These four different EEG background patterns are normally displayed during one sleep cycle lasting between 40-60 minutes, which on aEEG trace includes: low voltage irregular, mixed, high-voltage slow and trace alternant (Kidokoro et al., 2012). In infants with normal

SWC, the cycle period range is 30–110 minutes and the duration of the quiet sleep phase ranges from 18–43 minutes (Osredkar et al., 2005).

Research has identified active sleep as one of the primary states during the preterm period, which is consistent with the current knowledge of active sleep in this stage of brain development. Literature has also shown that premature infants exemplify a tendency to increase the amount of quiet sleep, drowsiness, and wakefulness, while decreasing active sleep, and more distinct and less diffuse states over increased age (Foreman et al., 2008).

There are relatively significant differences between term and preterm infant traces displayed on EEG or aEEG which include a shorter sleep cycle, prominent EEG delta rhythms, intra- and inter-hemispheric electrographic asynchrony, discrete neonatal waveform patterns, a high proportion of sporadic respiration, a greater random assortment of rapid eye movements and unique motor patterns (Scher, 2004). These characteristics are more indicative of fetal rather than postnatal movements seen during infancy (Scher et al., 1995). Through the analysis of sleep-wake cycling patterns, aEEG will produce the most distinct changes in state in term infants ranging from 37-44 weeks gestational age and is a strong basis for this research's study population age range.

2.4 The Automation and Informatics of CFM Signals

When considering the informatics perspective of sleep-wake cycling, many algorithms have been developed for the automated detection and analysis of seizures and other patterns displayed by EEG and aEEG however none have focused on the automated detection of changes in normal sleep-wake cycling patterns. Extensive research pertaining to automatic seizure detection has been conducted which will be outlined in the following section along with the potential application of certain components to the automated analysis of sleep-wake traces.

Algorithms that have been attempted for the automated detection of aEEG and EEG trends and can be summarized in the following categories:

- **Inverse Filtering:** Normal EEG is the output of a filter with fixed parameters where this is revered in an inverse filter and the input is considered stationary and the output is noise;
- **Wavelet Transform:** Involves time frequency analysis;
- **Artificial Neural Networks:** Raw EEG or some parameters of the EEG are weighted and combined to form specific criteria from which output is compared with thresholds established in pervious training of an established algorithm;
- **Template Matching:** Templates of specific waves are created and when cross correlation eclipses a threshold an alarm will signal (Liu et al, 2002). This can be a challenging method due to the variety of waves in a trace and the balance between false detection and omission of critical patterns within the trace;
- **Expert system:** Attempts to mimic human visual analysis, calculating parameters and thresholds of the of the trace along with temporal and spatial context to detect spikes and minimize false detection of artifacts and finally
- **Orthogonal Transform:** For example, fast Fourier transform, captures rhythmic changes of traces, and uses averaging while sacrificing some of the temporal details (Liu et al., 2002).

Currently the best methods for automated detection of any form of trend or output from these signals are based on computing a running autocorrelation function, rhythmic discharges detection, modeling/complexity analysis, and wave-sequence analysis (Figure 13) (Deburchgraeve, 2010). Others have been performed based on the withdrawal of features using entropy, wavelets, frequency content, and then training a classifier on these features to accurately classify the EEG (Deburchgraeve, 2010). Figure 14 illustrates another method involving band pass and high pass filtering, phase synchrony, and smoothing of amplitude fluctuations which is performed on a raw EEG trace to smooth these signal traces to ease the analysis of trends (Tokariev et al., 2012). When analyzing seizure patterns on aEEG, the first distinction is a clear change comparative to the background EEG and aEEG that in many cases involves an elevation of both the minimum and maximum amplitudes (Deburchgraeve, 2010). The second and most important characteristic is the repetitiveness of the signal, as the majority of seizures exhibit some form of recurrent pattern (Deburchgraeve, 2010). These patterns can be detected by the

methodology stated above however limitations and complications that have arisen include the high rate of false detections indicating that the level of performance still isn't suitable for clinical application (Faul et al, 2005).

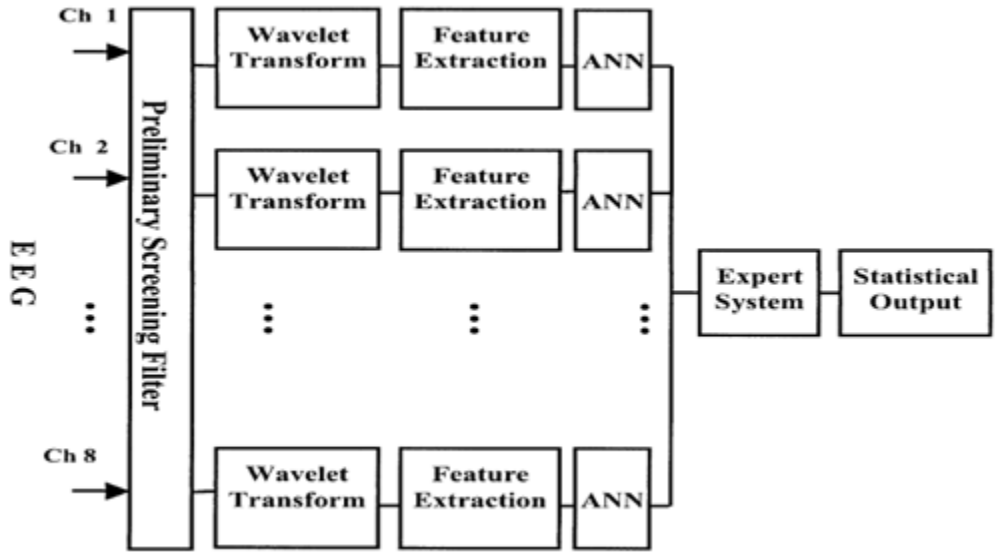


Figure 13. Shows a schematic of an algorithm developed for the screening of different patterns to reduce the amount of data analysed followed by computing a running autocorrelation function, rhythmic discharges detection, modeling/complexity analysis, and wave-sequence analysis (Liu et al, 2002)

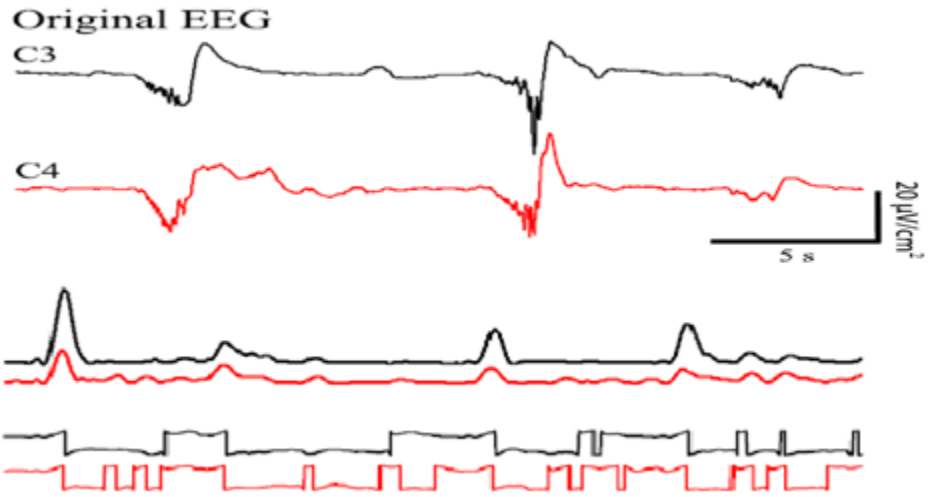


Figure 14. Band pass and high pass filtering, phase synchrony, and smoothing of amplitude fluctuations is performed to a raw EEG trace (Tokariev et al, 2012)

Another option for analysis apart from the autocorrelation of the complete EEG is to limit the analysis to specific parts of the signal that represent an important increase of low-frequency activity compared to the background (Deburchgraeve, 2010). One can also break down the trace into small intervals of time and average maximum and minimum values to create simplified continuous representations of the EEG trace for automated analysis (Figure 15) (O'Reilly et al., 2012). The combination of these improvements results in a lower false positive rate compared to previously published algorithms without altering the sensitivity (Deburchgraeve, 2010). When analyzing results and performance of automated detection in both measurement techniques, sensitivity needs to be high when detecting both seizures and sleep-wake cycles minimizing the number of seizures and sleep or wake stages missed. Specificity must also be high to limit the number of false positive detections (Deburchgraeve, 2010).

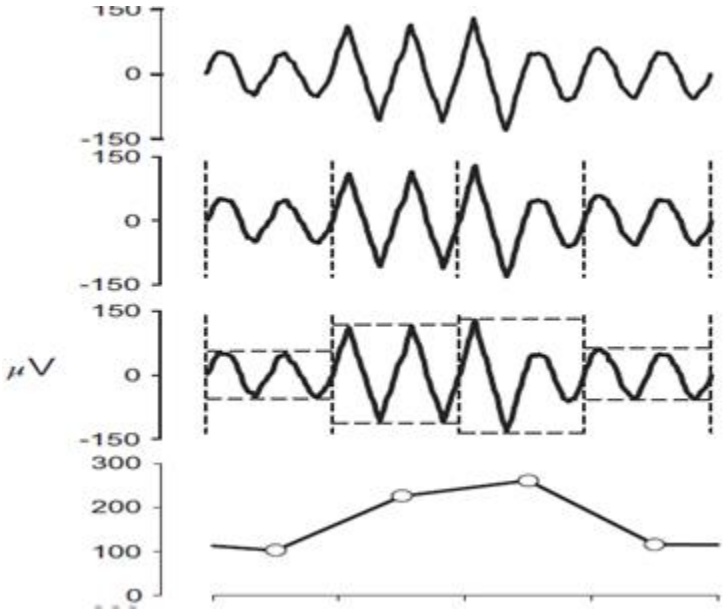


Figure 15. Partitioning of original trace into two second intervals, followed by amplitude measurement and construction of a continuous representation of the EEG amplitude. Points are the averaged min and max values for each interval (O'Reilly et al, 2012)

When awake and during active sleep, respiration is much more irregular and the absence of sleep-wake cycles is one of the earliest abnormalities in an irregular brain (Deburchgraeve, 2010). In opposition to this, the presence of sleep wake cycling is a good prognostic sign of a

healthy neurological condition. Earlier onset of sleep wake cycling is related to better outcome as Osredkar et al, (2005) found that with each increase in time interval from birth to onset of cycling for one hour, there is a 0.96 fold decrease in the odds of a positive outcome. In order to measure the consistency of the respiration, the signal is divided into epochs of 30 seconds and then the autocorrelation function of the signal is calculated (Deburchgraeve, 2010). The standardization of this autocorrelation function can be quantified by calculating the normalized area under the curve and if the area is larger, the stronger the correlation in time. The autocorrelation function will rapidly fall to zero for uncorrelated signals but remains high for repeating signals (Deburchgraeve, 2010).

Other algorithms for automated EEG signal trace analysis have been developed to calculate inter-burst interval ratios that are related to adverse outcome and abnormalities displayed via cranial ultrasound (Liu et al., 2002). This is done by finding the percentage of time the EEG signal is in a depressed state over a moving window of time and based on percentage has had success in determining changes in maturation of EEG derived parameters (Liu et al., 2002). The automated detection of spontaneous activity transients or bursts has been utilized when attempting to detect seizures and the associated feature recognition/extraction using fast Fourier transform (Liu et al., 2002).

Other automated systems attempt to automate seizure detection uses a probabilistic neural networks, encompassing a time frequency domain feature of the EEG signal called entropy (Murugavel and Ramakrishnan, 2011). The Input signal is initially detected, then wavelet transformation occurs, features are extracted, features are specifically selected, then the signal enters the trained probabilistic network and finally detection occurs. In addition to this, seizure detection algorithms have used spike-train detectors that run in parallel detecting high energy segments of the EEG and analyses the correlation between the two as well as oscillatory detection of low frequency activity between 1-8 Hz for seizures (Cherian et al., 2011).

Nicolet One is a software program that is used frequently in the analysis of EEG data that involves fast Fourier transform for trend analysis. It has been proven that both a frequency-only technique and an amplitude-only technique can miss EEG changes, so it is recommended that a

technique encompassing both frequency and amplitude is used for optimal results (Cherian et al., 2011).

In research published by Palmu et al., (2010) the authors noted in their methodology regarding algorithm development for automated EEG analysis that avoiding using amplitude and/or frequency criteria can be detrimental for two reasons. The first being despite their numerical accuracy, they are always arbitrary, and they cannot take into account the inter-individual variations in EEG amplitudes (Palmu et al., 2010). A visual criterion via expert analysis or other method is easily normalized in this respect. Second, the use of numerical criteria prevents a valid comparison between visual and automated detection (Palmu et al., 2010).

Similar to what Palmu et al., (2010) indicated in their research, another challenge with the use of CFM is that comprehensive interpretation is limited by the lack of reliable quantification and summarization of the output. The current best practice is through trained or expert visualization or annotation that provides clinically significant information, however numerical statistics are not produced or readily available. In relation to this, the classification systems that have been developed thus far still rely on an element of qualitative analysis to determine characteristic tracing patterns including cycling between continuity and discontinuity. Other methods use the raw reduced channel EEG signal produced by CFM and conduct transformations and signal analysis in frequency domain (Thorngate et al., 2013).

In order to successfully develop an automated detector of trace changes for infants from a CFM signal, techniques that can capture the unique neurological expressions of state transitions in infants is ideal. These include the recognition of shorter sleep cycles, prominent EEG delta rhythms, intra-hemispheric electrographic asynchrony, discrete neonatal waveform patterns, and a high percentage of periodic breathing, increased arousals and unique fetal reflexes (Sher, 2008). Automated analysis methods of neonatal EEG sleep traces using both cerebral and non-cerebral measures can more comprehensively detect and quantify linear and nonlinear behavioral relationships. Assessment of multiple cerebral and non-cerebral measures better define neonatal state in addition to spectral analyses of EEG, cardiorespiratory behavior, arousal behavior, and rapid eye movements all indicate important physiological differences during sleep between healthy preterm and full term infants (Sher, 2008).

As a result of the findings there are several important factors that must be considered for the research conducted in this thesis. It is clear that a mixed methodology of algorithm components will be required in order to accurately detect and classify the start and end points of sleep and wake stages in neonates. A moving window, which classifies periods of trace, whether continuous or discontinuous based on time to identify sleep or wake stage as used in the algorithm developed by Liu et al., (2002) will be a crucial component to the algorithm developed in this research. This will act as a relative change feature. Using a threshold value as in the algorithm developed by Deburchgraeve, (2010) will also be applied as a percentage change feature from the upper margin to the lower margin and determining which state the patient is in. Finally, as a method of quality control like in many of the algorithms outlined, data will be group into poor and good quality based on particular impedance levels.

2.5 Clinical Relevance

Amplitude-integrated EEG is becoming more useful in the NICU because of the ability to analyze long-term trends and changes in the electro-cortical background activity of patients through pattern recognition (Hellstrom-Westas et al., 2006). Amplitude-integrated EEG can be used in the first few hours of a neonate's life which acts as a strong predictor of long term neurological outcome as it can be left on for days to monitor trends (Randall, 2010). Amplitude-integrated EEG and sleep-wake cycling can also aid in the recognition of IVH and other activity or lack thereof within the brain.

The overall background of a CFM trace as well as the presence of sleep-wake cycling in aEEG and EEG traces holds great significance in the long-term outcome of developing infants. Osredker et al, studied 171 term infants with hypoxic-ischemic encephalopathy and found that using aEEG, a linear correlation between the onset of sleep-wake cycling, the severity of encephalopathy, and neurodevelopmental outcome was discovered. In addition to this, the time of onset of sleep-wake cycling was indicative of neurodevelopmental outcome, with an onset of sleep-wake cycling less than 36 hours associated with a favorable result (Takenouchi et al., 2011). It has also been shown that the occurrence, time of onset and quality of sleep-wake cycling reflects the severity of the hypoxic-ischemic injury to which newborns have been exposed to (de Vries and Hellstrom-Westas, 2005). As a result this device can be very useful for

the detection of medically significant conditions that precede the onset of medical complications. Through the work of this research the goal is to make the initial steps in automating this detection of the sleep periods and classifying background tracing in an attempt to improve the current manual methodology that is in place.

The automated detection of sleep-wake cycling also holds significance in regards to the timing of medical intervention for these newborns patients. Often in the NICU treatment is provided at the convenience of the health care professional, which is frequently not the ideal time for these neonates as they are in a deep sleep or have just fallen asleep. During these stages, it is optimal for neurological development that is hindered by the interventions that take place. If an automated system were developed to conveniently display when sleep and wake stages are occurring and when they are predicted to occur based on the trends in the data, this can have a significant impact on the timing of the procedures around these developmental stages. In addition to this one of the goals is to improve on the current practice of manual interpretation of the CFM traces. If the algorithm can become accurate and consistent enough then it can become a faster and more accurate method for the detection of presence or absence of cycling patterns. In relation to this, through the Artemis platform storage of this information is possible for future online data mining and analysis contributing to making the platform a robust, applicable clinical decision making tool.

2.6 Summary

Progression in this field of research has begun to look for ways of automatic detection of seizures using aEEG. This can be done in two ways: using threshold methods that analyze aEEG output using a limited number of descriptors and numerical thresholds (Temko et al., 2011). The second using a classifying method based on pattern recognition in order to categorize features based on data-driven decision rules (Temko et al., 2011). One of the primary shortcomings of the threshold, numeric based method is that often time it results in a single-fixed operating point, which translates to minimal control over a good detection rate and the number of false detections per hour (Temko et al., 2011).

In contrast to this, the use of a classifier approach results in a continuous or probabilistic output allowing the system to be effortlessly adapted to the chosen performance or to meet the

requirements of an application more effectively (Temko et al., 2011). The most successful features of such a method for the detection of seizures in neonates are those that encompass frequency, energy and structural content of the signal (Temko et al., 2011). Most of these components can be applied and utilized in the development of algorithms for sleep-wake cycling detection as many of the criteria are similar in both cases. One dimensional signals are divided up into segments called epochs, in which a specific set of features is extracted to denote the characteristics of the signal in each segment (Temko et al., 2011). This approach will also be considered for this research project for the annotation process by the expert health care professionals. Each patient data set contains screenshots of CFM trace that will consist of three-hour epochs, for a total of up to 8 epochs per patient or 24 hours of data. Both the annotations and algorithm will be broken down into analysis of these three-hour epochs of data. The algorithm design, methodology and subsequent experiments of the study will be described in the next chapters of the thesis.

As previously mentioned, extensive work has been performed by others in an attempt to automate seizure detection and other patterns displayed by EEG and aEEG in infants, however there is a gap in literature regarding research performed in the automation of analysis of sleep-wake cycling. Through the Artemis framework in place, the goal is to design an algorithm to fill this void and make the first steps in automating the detection of normal and abnormal CFM traces, sleep-wake cycling patterns and the feasibility of implementing an algorithm of this nature into Artemis.

In conclusion, this literature review has thoroughly examined different types of brain monitoring techniques, sleep-wake cycling in neonates, and the concept of informatics based on CFM signals. Informatics and Big Data tools have come to the forefront of medical research as these techniques are starting to be used for real-time diagnosis of other signals like ECG and pulse oximetry. The integration of all these signals together for composite real-time clinical diagnostic tools such as the research taking place within the Artemis research team relating to neonatal spells holds great promise to give advanced clinical decision support in real-time at the bedside. As a result of this review, it has been revealed that there is a lack of automation using big data informatics tools with regards to the detection of sleep-wake cycling patterns displayed on CFM, which could have significant implications on the exposure of current inefficiencies during

medical practice relating to this diagnostic tool. Classification of normal and abnormal CFM traces in the NICU as well as the identification of the presence or absence and onset/cessation of sleep-wake cycling patterns can make the manual tasks of annotation far less tedious; requiring fewer healthcare providers and far less time to complete these tasks. In addition to this, the timing of medical intervention has been exposed and can be addressed through an algorithm of this nature to base care around sleep stages to optimize neurological development in such fragile patients.

Chapter 3 Artemis Framework

In this chapter the Artemis platform is presented. The Artemis system, depicted in Figure 16, may be categorised as an extensive and sophisticated Big Data informatics platform within which compatible algorithms such as the one designed in this thesis for sleep-wake cycling modelling can be functionally deployed. While the focus of this research is on the processing of the single aEEG stream, the strength of Artemis possesses a unique ability to ingest in real-time data and synchronise multiple signals. With this capability, it is possible to demonstrate how the algorithm unique to this research can be deployed within Artemis and also demonstrate how the sleep-wake cycling classification may be integrated within the platform in association with other signals to support the potential for higher level diagnostic support at the bedside.

3.1 Artemis Platform

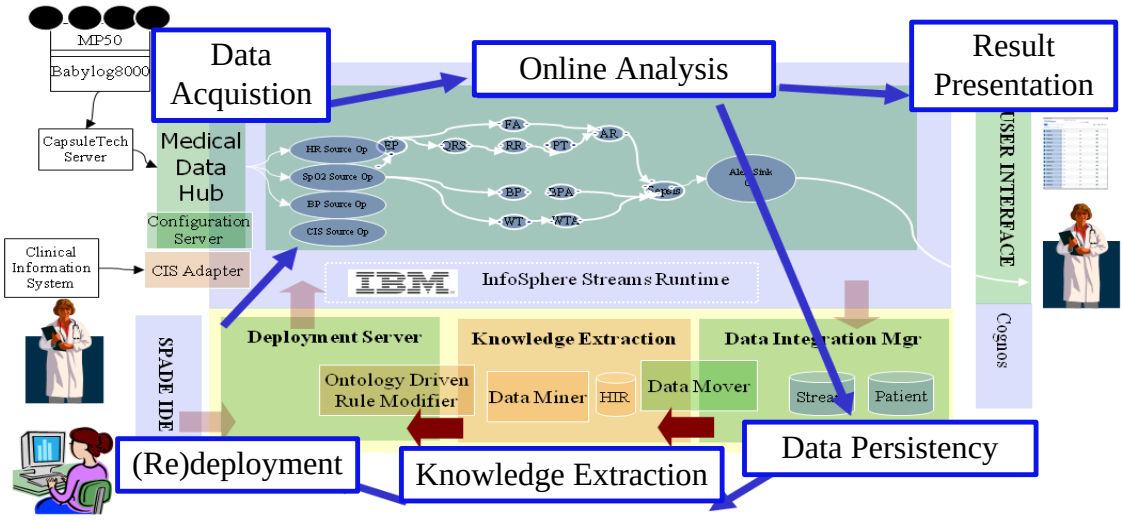


Figure 16. Artemis Framework (modified from McGregor C., 2011)

Artemis is a flexible platform supporting online health analytics inclusive of retrospective knowledge discovery from multiple patients and multiple conditions with a unique ability to ingest multiple streams of physiological and other medical 'device' generated data. This data is merged and matched to other clinical information supporting advanced clinical decision making in order to detect clinically significant conditions that may adversely affect health outcomes

(McGregor et al., 2011). The data acquisition component enables the provision of real-time synchronous medical device data and asynchronous Clinical Information Management System (CIMS) data to be refined, formatted and standardized. This data is then forwarded for analysis within the Online Analysis component that operates in real-time (McGregor et al., 2011). For this real-time component, Artemis employs IBM's InfoSphere Streams, a novel streaming middleware system that processes data in real-time and then enables data storage within the Data Persistency component (McGregor et al., 2010). It is capable of processing and then storing both the raw data and derived data from multiple infant sources at the rate at which they are generated (Blount et al., 2010). Stream processing is supported by IBM's Stream Processing Language (SPL), the system specific programming language for IBM's InfoSphere Streams middleware (Blount et al., 2010). For the Knowledge Extraction component, Artemis utilizes a newly proposed temporal data mining approach (McGregor, 2012). This component supports the discovery of condition onset behaviours in physiological data streams and associated clinical data. New knowledge, once tested and derived from rigorous clinical research techniques, is transferred for use within the Online Analysis component through the Re-deployment component, which translates the knowledge to an SPL representation.

The Artemis Platform has been developed to provide a flexible platform for real-time and offline analysis of patients data streams with the capability to store raw, physiological data such as electrocardiogram, heart rate/variability, respiratory rate, blood oxygen saturation level and other physiological sources, from the bedside of multiple infant sources at the rate the data is generated (Blount et al., 2010). Artemis also has the ability to access static asynchronous patient information including lab results and other test results for holistic patient analysis. In our research work at The Hospital for Sick Children, Toronto (SickKids) this information is accessed through a CIS adapter, so that clinical data can be de-identified to preserve the anonymity with the data sets tabulated and populated from the NICU's Clinical Information Management System (CIMS) (McGregor et al., 2010). Artemis has been used to collect clinical and physiological data since August 2009 from a cohort of babies initially in two beds that has now increased to 16 beds connected to the Artemis within the SickKids NICU, aided by CapsuleTech drivers to access data from hundreds of medical devices (McGregor, 2013).

Currently, the Artemis platform (previously demonstrated in Figure 13) captures ECG signals at 1024 samples per second; with a profile including respiratory impedance at 62.5 Hz, continuous invasive blood pressure measurements, when connected and blood oxygen saturation plethysmography at one Hz. Heart rate and respiration rate derived from the ECG and respiratory impedance respectively are also collected at one Hz being the rate they are generated (Thommandram, 2013).

The aim of algorithm development within the Artemis framework is to detect medically significant conditions that precede the onset of pathophysiological changes and medical complications. The long-term goal is to confirm the capability of Artemis as a robust decision support tool that provides insight into multiple streams of data, normally too large to asses using traditional methods (Blount et al., 2010).

Traditionally adopted methods involving Clinical Decision Support Systems (CDSS) primarily encompasses synchronous, patient centric data from medical devices, with little information coming from readings taken at the bedside or in the lab from those caring for the patients; thereby not directly supporting clinicians decision making capability or exploiting the full extent of the CDSS's capability. In the past updating clinical rules has been restricted in modern CDSS, however the storage of electronic medical knowledge has drastically increased over the past decade (Kamaleswaran et al., 2013). These issues of concern have been addressed in part through the engineering and conjunction of the Artemis platform and InfoSphere Streams runtime. Artemis uses the programming language Streams Processing Language (SPL) for the processing of data streams within the platform and is able to support the ingestion and storage of multiple real-time data streams from multiple patients to identify multiple medical conditions. As a result this system has the potential to aid physicians in the modification of guidelines or the testing of new diagnosis hypotheses, a decrease in interactivity between clinician and the system, simplifying its use and finally creating a simple user interface in which clinicians can model different rules and the code can be easily generated to implement them (Kamaleswaran et al., 2013).

It is the hope that Artemis can make a significant contribution to clinical diagnostics with physiological data related to research implicit of the various themes that have been developed under the Artemis project such as apnoea (Thommandram et al., 2013; Thommandram et al.,

2014; Catley et al., 2011), retinopathy of prematurity (Cirelli et al., 2013), and anemia of prematurity (Pugh et al., 2013), in addition to other areas such as infection (McGregor, Catley & James, 2012; McGregor, 2013), pain thresholds in association with pharmacokinetics and pharmacodynamics (Naik et al., 2013; Bressan et al., 2013).

To date, research utilising the Artemis platform has not been conducted on the brain and the brain and neural substrates with potential to stream physiological data from a patient's brain through Artemis to not only deploy algorithms using the signals in isolation, but to correlate these signals with the other data already being collected by Artemis. Contextually this research proposes an algorithm for the classification of background aEEG patient traces as well as sleep-wake cycling patterns for analysis that can be deployed in the future within Artemis to analyse electrical cerebral activity through data from CFM monitors in the NICU.

Chapter 4 Experimental Design

This chapter presents a detailed review of the design and application of the algorithm inclusive of its various design characteristics and application of the inherent processes in the overall data processing chain. The overall algorithm contains "discrete" data management sequences to ensure standardisation and reproducibility of signal categorisation, quantification and scaling of measurable indices, with signal processing interventions designed to select and label significant data units. Supporting graphics have been developed to demonstrate the processed signal characteristics.

The algorithm design was influenced by two main themes reported in the literature specifically the potential for automation and the selectivity of data sourced from manual observation and work practices in the NICU. In combination these contribute to the diagnosis and discrimination of normal and abnormal traces and periods of sleep and wakefulness in term infants. These themes influenced the operational development of the algorithm for temporal analysis of aEEG data streams captured at the bedside and contribute to CFM. Cerebral function monitoring has proven to be a useful tool for predicting the severity of hypoxic-ischemic encephalopathy. When applied during the first 6-12 hours following perinatal asphyxia, it has also proven useful in identifying sleep-wake cycling and infants experiencing clinical and subclinical seizures and has also been useful in determining significant neurological dysfunction, post cardiac arrest (McNamara and Keyzers, 2006). Within the NICU It is usual that all designations of staff caring for patients participate in some aspects of CFM monitoring. It follows therefore for optimal treatment and effectiveness of the process that each health care professional have a clearly defined role. With regard to role definition and the scope of practice of staff in the SickKids NICU the respiratory therapist or nurse will usually set-up and operate the equipment, troubleshot technical difficulties and aid in the interpretative process (McNamara and Keyzers, 2006). The registered nurse is required to be a system observer for indicators of clinical complication, to track and record times when procedures and administration of medication takes place, and also to communicate issues to the respiratory therapist and inform the respiratory therapist of alarms or any major changes (McNamara and Keyzers, 2006).

In context the role of the physician or nurse practitioner is to order the commencement or discontinuance of the CFM using standard medical order sheets (McNamara and Keyzers, 2006). They are also incumbent to interpret the tracing and manage any medical abnormalities detected via CFM. They are also expected to inform ancillary staff and other physicians and concurrently document abnormal traces and corresponding medical treatment in patient's chart.

As previously mentioned, in most instances CFM traces are annotated by registered nurses who attach labelled markers on the device screens if any clinical symptoms of seizures are observed. Labels are also attached to indicate the presence or absence of sleep-wake cycling or if the administration of anti-convulsants or sedatives occurs. Labelling is also marked if repositioning or stimulation of the patient causes disturbances in the tracing. Actual marking on the CFM monitors is conducted by pressing a 'MARKER' button on the device, followed by tapping the screen of the CFM tracing at the appropriate time and selecting the desired marker from the window that appears indicating what has occurred in the trace.

This manual process has led to the design of algorithms to perform automated detection of sleep-wake cycling patterns as well as the determination of normal and abnormal traces based on the background characteristics of the trace. The purpose of the design of this algorithm is essentially to reduce the number of staff involved in the monitoring of the CFM, and aid in the timing and precision of medical interventions to maximize patient growth, health and neurological development

4.1 Three Stage Algorithm Design

The algorithm for this thesis was developed in three stages:

The first was in the form of a quality assurance algorithm that separated aEEG traces with impedance greater than 10 kilo ohms, which was deemed poor quality data and aEEG traces with impedance less than 10 kilo ohms which was considered good quality data. The two types of trace, "good and poor quality" were then are separated into different pools and subsets and analysed further.

Stage two of the development of the algorithm was to design a "percentage change" function determining continuity and discontinuity to characterise sleep and awake states with the capability to detect and calculate individual values to establish the sleep and awake baselines.

Stage Three of the development of the algorithm was to design a function able to discriminate and calculate the magnitude of change between the different periods when the patient was asleep and when awake over varying lengths of time windows, displayed by the aEEG trace. A general overview of the algorithm design is outlined in Figure 17.

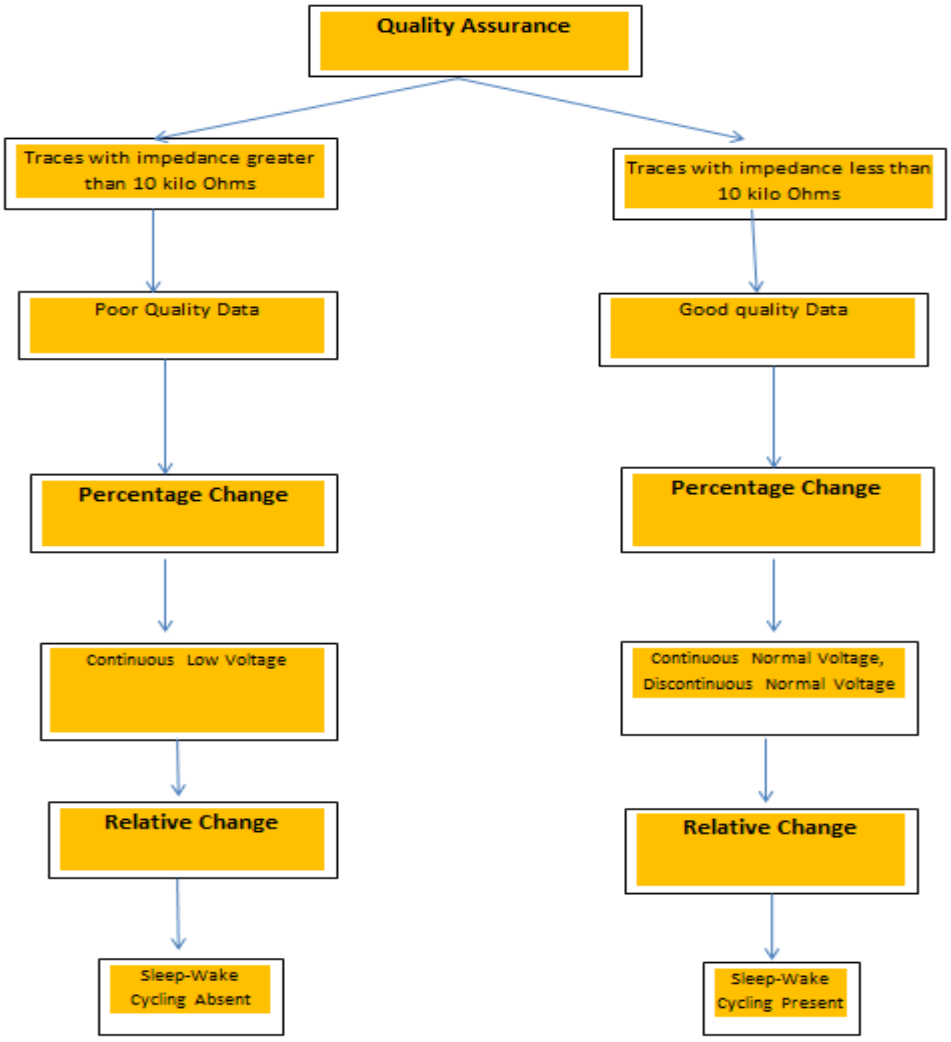


Figure 17. Summary of the algorithm design

The goal of the combination of these algorithms was to automate the process leading to determination of whether or not the traces were normal or abnormal both when the patients were awake or asleep and also to record the timing of when these events occur. A critical consideration is the interval of how long the patient is in each stage. The overall validity and accuracy of the algorithm will be compared to three standardized expert annotations.

4.2 Classification of Background Trace

The original microvoltage values establishing the five categories of background classification were generated from Table 2, which was published by the Department of Pediatrics at Mount Sinai Hospital, Toronto (Azzopardi, 2004). These involve categories of 'burst suppression' and 'flat traces'. To reflect clinical practice within the NICU, these five categories were reduced to three in a more generalized format of Continuous Normal Voltage, Discontinuous Normal Voltage and Continuous Low Voltage. The resultant three categories of voltage encompass both categories eliminated from the five stage classification model previously mentioned.

Table 2. Terminology and voltage criteria for background classification of CFM traces. Table also includes whether the corresponding background tracing is considered normal or abnormal for both term and preterm infants (Azzopardi, 2004).

Term infant	Specific Terminology	Upper margin	Lower margin	SWC	In preterm
Normal	Continuous	> 10 μV	> 5 μV	±	Normal
Mildly abnormal	Discontinuous Normal Voltage (DNV) 'High'	> 10 μV	2-5 μV (VARIABLE)	±	Normal
Moderately abnormal	Discontinuous Normal Voltage (DNV) 'low' *OR* Burst suppression (BS) 'plus' (i.e. high burst frequency resulting in a thick trace)	> 10 μV	0-2 μV (No VARIABILITY)	-	Abnormal
Severely abnormal	Burst suppression (BS) 'minus' (i.e. low burst frequency resulting in thin trace)	bursts of > 10μV	0-2 μV (No variability)	-	Abnormal
Severely abnormal	Continuous or discontinuous low voltage (CLV/DLV)	≤ 10μV Narrow bandwidth (≤5 μV)	~ 5μV; no variability; few or no bursts	-	Abnormal
Severely abnormal	Flat trace (FT)	<5μV Inactive trace	<5μV Inactive trace	-	Abnormal

Data that is considered both good and poor quality based on levels of impedance are analysed as to whether or not the associated traces are normal or abnormal indicating the paradigm between continuity and discontinuity. If the background trace displays activity falls into the categories of continuous normal voltage corresponding to an upper margin microvoltage value greater than 10 and a lower margin micro voltage greater than 5 or alternatively if a discontinuous normal voltage displays an upper margin greater than 10 µV and a lower margin less than 5 µV this is classified as normal. A background tracing that falls into the categories of continuous low voltage (upper margin less than 10 µV and lower margin less than 5 µV), is considered abnormal. This classification is outlined in Table 3 Background tracing that is considered abnormal in term infants corresponds to an absence of sleep-wake cycling whereas if the signal trace is normal sleep-wake cycling can occur.

Table 3. Breakdown of the voltage criteria for each classification category

Classification	Upper Margin	Lower Margin
Continuous Normal Voltage	>10 µV	> 5 µV
Discontinuous Normal Voltage	>10 µV	< 5 µV
Abnormal Voltage	< 10 µV	< 5 µV

4.3 Classification of Sleep-wake State

The development of these the various algorithmic stages and the automated system to detect when sleep and wake cycling is occurring in term infants has significant clinical implications. As previously stated, during an infant's sleep phases the majority of neurological development occurs. However in the NICU an infant may be about to enter a period of deep sleep when awoken by a medical professional for some form of clinical intervention inclusive of medication, intubation, or routine check-ups on rounds.

Consequently if a system were in place that could tell the health care professional that the patient is in a deep sleep and for how long the infant has been in this stage this has the potential to aid in the development of the patient thus providing a useful mechanism in the NICU.

Currently boundary detection of CFM data is routinely interpreted by observation using established clinical guidelines (Azzopardi, 2004). This interpretation is often based on the upper and lower thresholds of the CFM traces. This is represented in Figure 18 which displays standard annotations on a CFM tracing for sleep and wake state changes. These thresholds are in actuality artefact of the resolution of the CFM display, as the aEEG data is in fact discrete 100 Hz samples that form a continuous, but highly compressed in the time axis, line. When expanded to a higher scaling the waveform becomes apparent.

For a computer program to perform similar analysis on the CFM waveform, it cannot take advantage of this visual artefact and must process the signal to get the upper and lower boundary that the observing eye can easily pick out from the CFM display. To develop this function, a boundary detection algorithm was employed that auto searches for the local minima and maxima over a sliding window of the data. These local minima and maxima are then interpolated to produce a new waveform of the same resolution as the original CFM waveform, representing the boundaries detected by the human eye.

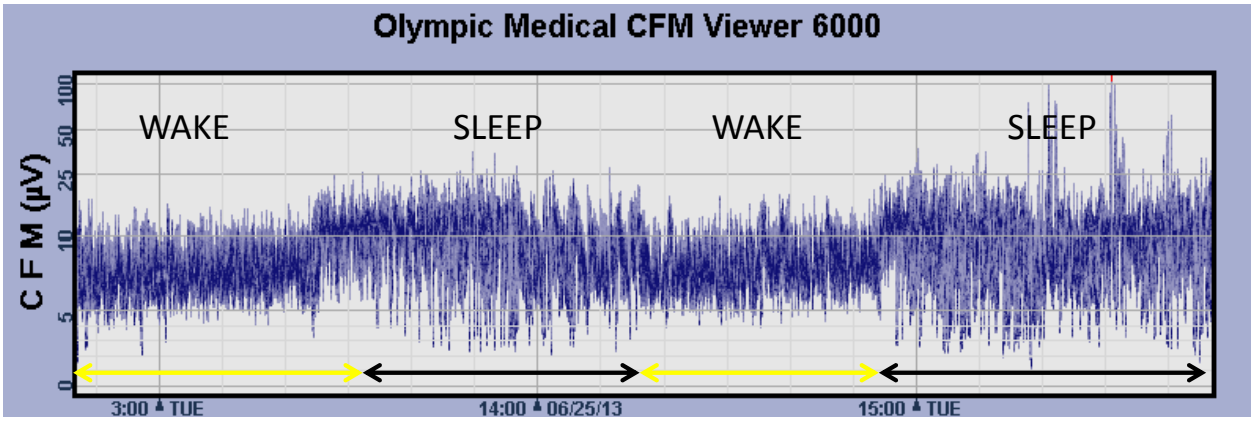


Figure 18. Plot with sleep-wake annotations. Yellow arrow indicates the length of the wake stage and the black arrow indicates the length of the sleep stage.

This is repeated for each of the upper and lower boundaries, maximum and minimum respectively. In this case the window size is set to 3000 samples, or 30 seconds. A sample of the boundary detection is shown in Figure 19. These two boundaries in Figure 19 are the computational interpretation of the band thresholds observed by the eye on the CFM plots of the dense data, such as seen in Figure 18.

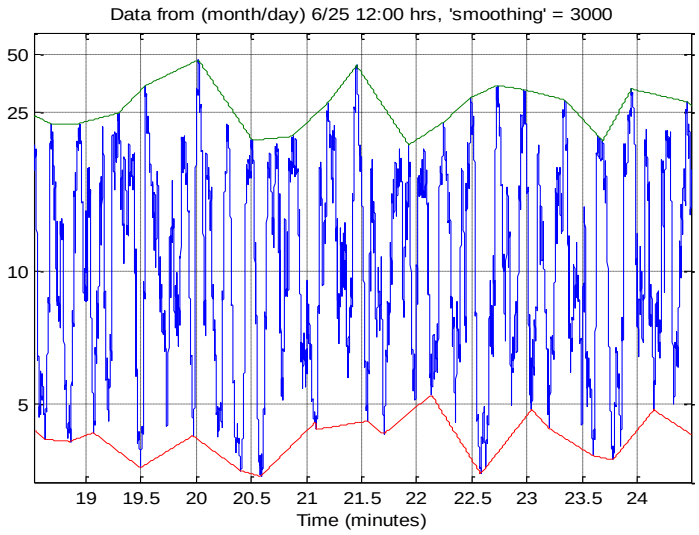


Figure 19. Detection of CFM signals at every time scale

The second stage of algorithm development for this study involved determining the upper and lower thresholds to determine the width of the CFM trace practically achieved by a filtering process using a fourth-order, low pass Butterworth filter to smooth out the boundaries. This created a green outline if the upper margin and a red outline of the lower margin, both of which matched the CFM patient trace. The difference between these bands is then used with a threshold detector to determine if the neonate is awake or asleep.

An example of the output is shown in Figure 20 where it can be seen that the sleep and wake condition is correctly identified, however, the onsets of each do not precisely match the annotated onsets. This may be attributed to the fact that the compression and filtering methods for the aEEG trace produced by the Olympus 6000 monitor nay not be exactly the same as the

compression and filtering done to mimic the upper and lower margins of the trace. Upon in-depth investigation the precise methodology of the transformation from the raw EEG trace cannot be determined.

Currently the algorithm has two output capacities which include the detection of when sleep and wake stages begin and end, in addition to the classification of the patient data background tracing as either continuous normal voltage, discontinuous normal voltage, continuous low voltage. These classifications are based on established literature norms as discussed in previous chapters and are based on values that have been accepted as the gold standard for CFM use. The algorithm has been designed to classify the background trace every 30 minutes and can be easily adjusted to sample these traces more or less frequently from every second to every twenty-four hours. Initially the 30 minute sampling rate was selected as an arbitrary value based loosely on the timing of sleep and wake stages for neonates which cycle approximately every 20-30 minutes or 0.5 to 1 cycle between sleep and wake states per hour (Thorngren-Jerneck et al., 2003, Osredkar et al., 2005). Annotations for the classification of these background traces are based on each three hour screenshot or epoch of CFM patient trace data, making the algorithm more thorough in its analysis of the trace and potentially more accurate than the manual interpretation.

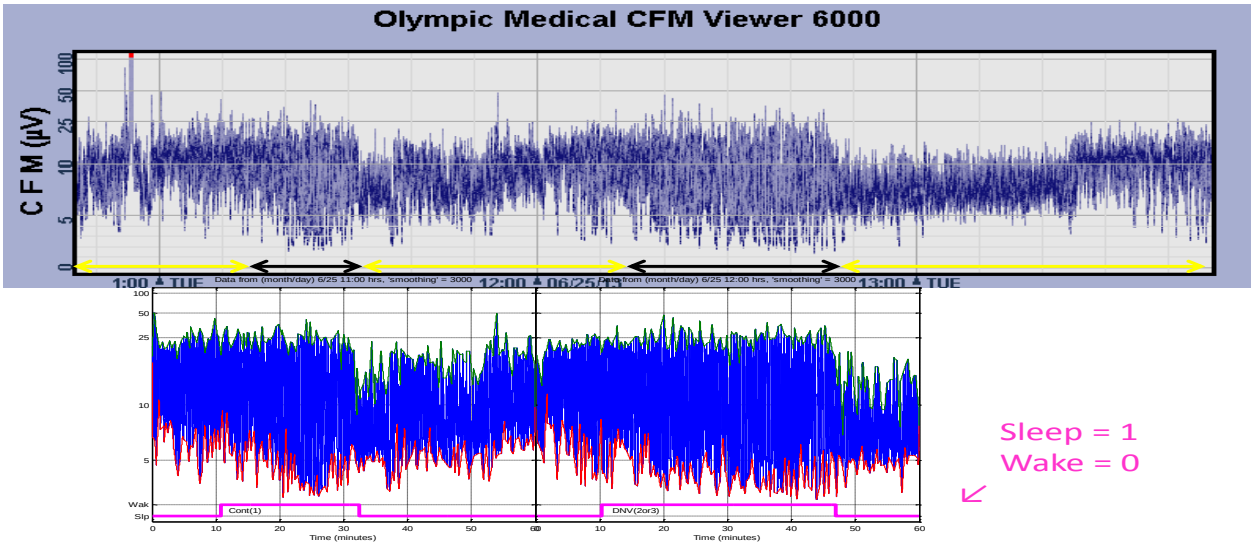


Figure 20. Example of sleep-wake detection output shown in the lower graph, aligned with the CFM data in the upper graph. Note the magenta line in the lower graph which represents sleep for the high value and wake for the low value.

In order to refine the sleep-wake cycling algorithm during testing on the training set data, 45 different experiments were performed. This involved slight changes to the algorithm in every experiment. Changes involved the development of three different versions of the algorithm relating to the identification of sleep-wake cycling. These three different groupings of fifteen versions of the algorithm were developed and broken down in V1-0 through 4, V2-0 through 4 and the same for V3. Version 1 and its variants used a methodology in which the algorithm attempted to identify the peaks of the upper and lower margins closely mimicking the trace with a line of best fit. Version 2 used statistics and the 90th and 10th percentile values or standard deviations over various lengths of time for rolling windows to identify the upper and lower bounds applying essentially a smoothing technique more to mimic the overall trend of the trace thus making classification more accurate. Version 3 used the 80th and 20th percentile values for the upper and lower bound and also used windows of varying lengths of time The difference between the dashed versions, for example V2-3 and V2-4 is the size of the time windows used to classification and identification purposes.

4.4 The Standardized Annotation Scoring System

A standardized annotation scoring system was developed for the experts to use on the CFM traces for all of the patient data sets. The scorecard includes the patient's Artemis I.D. number, with three-hour time epoch's listed in the top row starting from 0 through twenty-four hours. Along the left column includes categorical measurements of impedance ranging from good = 0-5 kilo ohms, marginal = 5-10 kilo ohms or poor being greater than 10 kilo ohms.

This column also includes the presence or absence of sleep-wake cycling and the classification of characteristic background traces which were defined as: Continuous Normal Voltage (CNV), Discontinuous Normal Voltage (DNV), Continuous Low Voltage (CLV), Burst Suppression, and finally a flat trace based on gold standard microvoltage specifications previously mentioned in the design of the algorithm. In addition to the standardized scorecard, the annotators also indicate on the traces the start and end times of each sleep and wake stage.

Through the application of these algorithms, it is suggested that an accurate system to automate the detection of when an infant patient is asleep or awake can be developed and applied. All data sets are then analysed to measure the algorithms accuracy and significance. Once this has been

completed with aEEG data traces, the analysis of the two lead, one channel EEG trace takes place if time permits. This provides a comparison test to the rendered aEEG file against the raw EEG signal that is also produced on the same cerebral function monitor. This provides depth and comparison between the two signals and their output.

4.5 Data Collection

The data in this study has been collected previously as a component of the neonate's clinical care and archived in a secure database maintained within the Division of Neonatology at The Hospital for Sick Children, Toronto. The primary and selected physiological data retrieved for this study includes single lead EEG and aEEG signals generated by CFM. This can be classified as retrospective, de-identified and quantitative aEEG patient data.

In addition, the data included secondary de-identified physiological data, already captured in an REB approved, previous study performed in conjunction with UOIT and the SickKids NICU entitled: "Real-time, multidimensional temporal analysis of complex high volume physiological data streams for the identification of condition onset predictors for nosocomial infection in the neonatal intensive care unit" (REB File Number: 1000013657). Additional data elements to be captured from the SickKids NICU Clinical Information Management System were the patient's gestational age, birth weight, sex and admission diagnoses. These elements were included to provide perspective for the analysis of the sleep-wake cycling data and prefigure some expectations of trace patterns in addition to the potential medical complications that may be evidenced in the associated CFM data. While not used within this initial research component the Artemis data extracted can be used in the future to help demonstrate clinical significance when all the signals are combined to make more thorough clinical decisions through the use of this technology.

4.6 Acquisition Protocol

Standard procedures for acquiring the CFM data were followed including the electrode placement and skin preparation of the patients. The aEEG and EEG data was collected in the SickKids NICU from the Olympic CFM 6000 (Natus Medical, San Carlos, CA), which samples the EEG signal 100 times per second and displays the aEEG signal at 6cm/hour. Data is quality assured via the alarms and detection system programmed into this monitor in association with selected patient data from those who meet the inclusion criteria and also by selective algorithm processing which discards traces with high impedance values.

The algorithm designed during this thesis was translated into MATLAB code by Associate Professor Dr. J. Mikael Eklund as a first step to determine whether automation was possible and was used to accomplish descriptive stats, percent concordance compared to the gold standard annotations, inter-rater reliability between algorithm output and the annotations, sensitivity and specificity. The presentation of the study's results will be in chart and graphical form showing the algorithm's performance relating to impedance levels, sleep-wake stages, and background classification in comparisons to visual analysis and expert annotation as well as physiological parameters based on the patient's condition.

4.7 Study Description

This study involves multi-dimensional research combining disciplines from computer engineering, computer processing, informatics, biosignalling, physiology, and clinical applications. The data for this research project comes from the Division of Neonatology at The Hospital for Sick Children. The neonatal intensive care unit shares a unique technological relationship with UOIT in which real-time and retrospective data from the NICU can be streamed to the HIR lab at the university for analysis.

A patient list of 30 was used for the research project all of whom met the inclusion criteria. The inclusion criteria for this study includes: patients who were previously enrolled in the study "Real-time, multidimensional temporal analysis of complex high volume physiological data streams for the identification of condition onset predictors for nosocomial infection in the intensive care unit." (REB File Number: 1000013657). This study was previously conducted in

conjunction with UOIT and the SickKids NICU. Additional criteria includes patients in Artemis bed spaces who underwent CFM as a component of their critical care, and the patients must be greater than 29 weeks gestational age so that sleep-wake cycling patterns are evident. Further ineligibility criteria for analysis include impedance in the aEEG trace greater than 10 kOhms, unexpected presence of gross movement or electrical noise artefact from other devices in the NICU, loss of amplitude due to extremely low impedance whether that be the result of poor electrode attachment or a severe decrease in the patients well-being and finally, asymmetry of voltage in one channel due to electrode migration. Criteria for the exclusion of neonates also included those with active infection, necrotising enterocolitis, congenital cardiovascular malformation, cardiac arrhythmia, and patients requiring respiratory support. A summarization of the inclusion and exclusion criteria can be seen in Table 4.

Table 4. Summary of the inclusion and exclusion criteria for the study

Inclusion	Exclusion
Patients previously enrolled in study REB File Number: 1000013657	Impedance in the aEEG trace greater than 10 kOhms
Artemis bed spaces	Unexpected presence of gross movement or electrical noise artefact from other devices in the NICU,
Underwent CFM as a component of their critical care	Loss of amplitude due to extremely low impedance
Greater than 29 weeks gestational age	Asymmetry of voltage in one channel due to electrode migration
	Active infection
	Necrotising enterocolitis
	Congenital cardiovascular malformation
	Cardiac arrhythmia
	Requiring respiratory support

All patient information was extracted from the SickKids clinical information systems including: electronic patient charts, KidCare, the Picture Archiving and Communication System (PACS)

and the Clinical Information Management System (CIMS). A total of 30 de-identified patient data sets and one test file were used in this study to design, refine and validate the algorithm developed for this thesis. Screenshots of these patient data sets were taken from the CFM viewing software and display three hours of aEEG trace per screen shot for a maximum of 24 hours per patient with the minimum amount of patient data being 12 hours. These CFM screen shots were then annotated together by three experts from SickKids, creating a gold standard. These experts included a neonatologist, neurologist and respiratory therapist who were able to provide standard annotations that would occur within the NICU, marking the beginning and end of sleep and wake periods, in addition to categorising the overall background trace during each three hour period as either normal, moderately, or severely abnormal and the impedance levels. Three experts were chosen so that in the event of discrepancies a tie break would be possible.

Using a sample de-identified patient test data set and corresponding screen shots of the patients CFM data, annotations indicating when the patient was asleep and awake throughout the 20 hours of aEEG tracing were performed by a respiratory therapist from SickKids. The respiratory therapist is experienced in the use and analysis of CFM data for patients in the NICU. This data for the test patient file and the annotated screenshots are those for which the original algorithm for the automated detection of the sleep-wake cycling patterns was tested. The data are processed in a multiple step automated process as shown in Figure 21 that incorporates a boundary detection step, filtering and a threshold classifier.

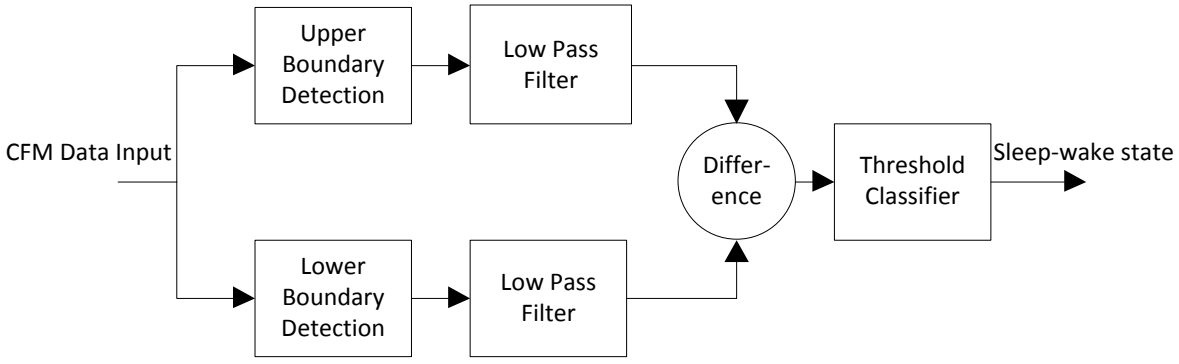


Figure 21. Overview of the sleep-wake classification process

Once this output was verified through comparison to the traces and annotations five patient data sets were used as the training set for the algorithm. Upon the completion of the same process, verification that the output performed the expected analysis and was validated based on a high level of concordance with the expert annotations, a final 15 patient data sets were used as the validation set for the algorithm. Analysis of the concordance between the algorithms output and the expert annotations will complete this thesis.

The strengths associated with this research include the fact that it is seminal and pilot work involving automated analysis compared to expert annotation. The algorithm has the capability for retrospective and real-time automated detection, it also has the ability to detect normal and abnormal CFM traces and sleep-wake cycling patterns quicker and more accurately than physicians manual interpretations. This research continues the development of the Artemis platform for a more holistic diagnostic tool, continuing its potential to contribute to clinical decision support structures through improving medical care, reducing costs, eliminating of redundant testing, and minimizing the workloads. This research also has the potential to aid health care professionals in the timing of their medical interventions and treatment of neonates in the NICU.

4.8 Ethics

Ethics for this study was required by both SicKids and UOIT which were successfully approved. Both research ethics board (REB) applications fell under the category of secondary data usage which made the application processes less complex however the SickKids REB application was far more extensive than the UOIT REB application package. Consent was not required for each patient due to the large number of pariticipants and the complete de-identification of the patient data. This research relies on the secondary usage of retrospective data that has already been de-identified in previous SickKids REB approved research and no sensitive personal health information will be collected. All data was collected from archived CFM records in a database maintained by the Division of Neonatology. After use electronic data residing on UOIT's Health Informatics Research Laboratory secure server will be destroyed in accordance with both SickKids and UOIT policies.

4.9 Streams Processing Language

Another alternative to the methodology proposed using MatLab for the development of the algorithms for the identification of impedance levels, detection of sleep-wake cycling and classification of the background trace is the use of a data stream processing environment such as InfoSphere Streams which is the middleware used in the Online Analysis component of the Artemis platform. InfoSphere Streams is a novel streaming framework that uses a library of operators programmed in Streams Processing Language (SPL) to support the analysis of continuous data streams such as physiological signals and their association with clinical conditions. The InfoSphere Streams framework was developed using InfoSphere Streams Studio created by IBM (Ballard et al., 2012). SPL is the specific programming language that enables streams based applications. Applications within streams are commonly called graphs and are deployed to run operators allowing for the processing of the streams in parallel to one another as they enter the system (Thommandram, 2013). Each operator signifies a step in the logic of an SPL graph and communicates with other operators through packets called 'tuples' using a simple message format. Streams is able to allocate processing over multiple computing elements through the itemization of a program into steps and operators (Thommandram, 2013). This system is highly scalable and effective at handling large amounts of data. Through the use of Streams, algorithms can be developed in a distributed manner and linked together to perform multifaceted classifications such as those desired in this research work (Thommandram, 2013). Independent low level alerts can be channeled to any algorithm requiring them which allows for the expansion and broadening of analysis (Thommandram, 2013).

Proposed is a framework in Streams for the design of the algorithms required for the detection of sleep-wake cycling in infants via the use of operators programmed in SPL. This allows for the support of analysis of electrical activity in the cerebral cortex associated with clinical conditions. Similar work performed by Thommandram (2013) and Catley et al., (2011) have utilized these methods for the detection of apnoea and spells events in premature infants and is feasible for its application to sleep-wake cycling in infants greater than 29 weeks gestational age. Figure 22 displays the overall architecture of the streams framework in which the theoretical design for this thesis will be modelled after.

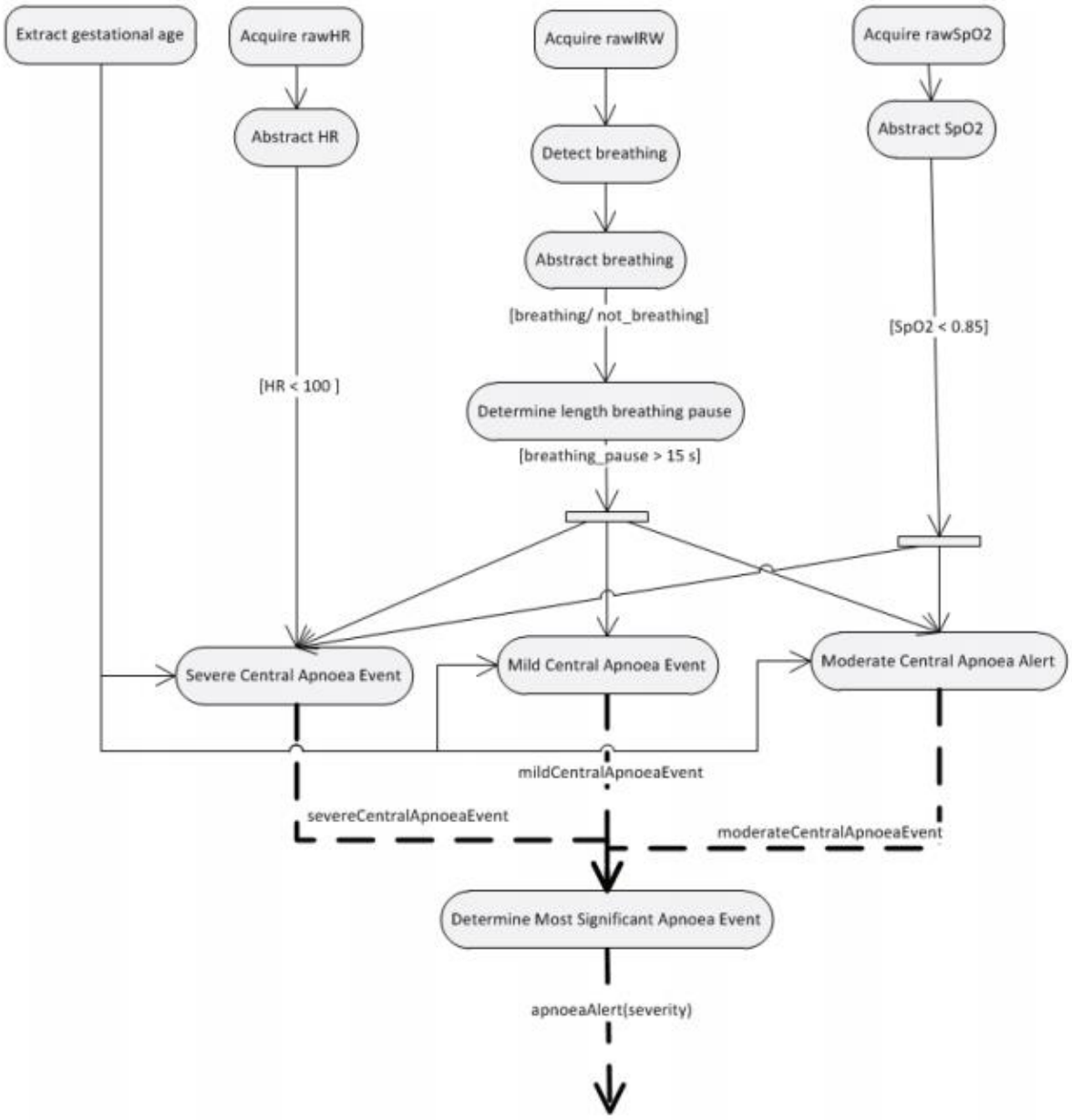


Figure 22. Overall depiction of InfoSphere Streams and the individual alert modules that are currently in place within the frameworks toolkit for research done with Apnoea of Prematurity that can be applied to sleep-wake cycling in neonates (Catley et al., 2011)

Within the Artemis platform raw streams are either numerical periodic data or waveform data. The framework can also support multiple algorithms that are designed to detect different anomalies or features in a specific data stream, in this case the EEG and aEEG signals. Profiles for each event detected are determined creating a correlation between events in multiple streams

and any rule based on logic can be implemented to analyse the episode profile to determine the overall event that would represent a change between sleep/and wake states, a change in impedance levels or the change in background electrical activity.

In the theoretical InfoSphere Streams design from the perspective of a top-down approach, each of the 3 variables would be the starting points. Gestational age can also be received at the start to provide background context for the analysis. The variables include impedance, background classification and sleep-wake cycling. The first acquisition would be that of impedance levels to determine the quality of the data through the classification into the three kilo Ohm ranges. At this point a fork node could be implemented to separate good and marginal data for further analysis and discard poor data. After the abstraction of this data the classification of the overall background activity would be acquired and is classified into the three categories used in clinical practice. These are continuous normal voltage (CNV), discontinuous normal voltage (DNV) and continuous low voltage (CLV) based on the associated microvoltage ranges for the upper and lower margins of the race. This value will also have a timestamp associated with it as the background electrical activity may change throughout a patients trace. Another fork node can be implemented at this stage of the streams framework to discard CLV data and continue analysis on CNV or DNV the data that is acquired for the abstraction of sleep-wake cycling patterns.

The final classification of sleep-wake cycling will also contain a timestamp associated with the data as this is a critical component to determining periods of sleep and wake. Periods must be of a specific time to be considered as such. Analysis of upper and lower margins and their movement is the other critical component to identifying the changes between when the patient is asleep or awake. Depending on the thresholds of the classifications, detection of data can occur at one reading every second (1 Hertz) to get a more accurate representation of the trace as the current window is one data point every 30 seconds.

The use of Streams for detection of sleep-wake cycling requires the identification of desired features from waveform data that can often be contaminated with artefact from the NICU environment. Streams does not employ a zero derivative method because of the potential noise associated with the cerebral function monitor (CFM) signal and the accidental zero-crossings that may occur. Other frameworks minimize false detections through smoothing and the use of a low pass filter application. This is not the case in Streams as peaks are identified by comparing every

new value to the previous maximum or minimum and if a certain threshold is eclipsed, the signal can be classified or identified as artefact (Thommandram, 2013).

A critical component of the InfoSphere Streams framework is its ability to make complex classifications and detect anomalies within the individual streams. After outliers have been disregarded, individual events are processed for correlation downstream in the logic. The existing InfoSphere Streams framework uses a toolkit with individual feature detection and if any different classification algorithms need to be implemented, the existing modules will be used and for generating individual alerts and various types of data with the capability to program new ones (Thommandram, 2013). This is important as the streaming of EEG and aEEG data has not taken place to this date.

In order to find out how much time has elapsed using the Streams platform, live peak location is employed which is designed to output a tuple for every data input along with a timestamp indicating how much time has elapsed (Thommandram, 2013). Once this has occurred synchronization of the streams takes place to correlate the alerts, giving them meaning. Through the synchronization, the order of all relevant signals and validity streams can be determined and can be easily performed for multiple signals (Thommandram, 2013). Another analytical feature of the framework is its capability to analyse hours of retrospective data in minutes that is extremely beneficial in the current scenario with this research as the algorithm has only been applied retrospectively. In addition to this, when transitioning from retrospective analysis to live streaming the algorithm only requires few simplistic changes which is the primary component that sets streams apart from other platforms.

Creating an episode profile for events is the final stage within the framework of Streams. These profiles determine valid and invalid episodes based on the programmed criteria and will either be sent to the episode classifier for analysis or not (Thommandram, 2013). Classification is normally based on the sequence of events within the episode that is sorted by a timestamp. Classifiers analyse sequences of events and match them to a knowledge based event sequence-logic pair to finalise the classification (Thommandram, 2013). The resulting output will consist of a timestamp, a patient identifier and an output to identify the impedance range, a number to identify the background activity of the trace and finally a numeric value to identify the presence or absence of sleep-wake cycling, background classification and impedance.

Through the current framework that is in place, Streams would be a feasible system to detect sleep-wake cycling patterns in neonates both in real-time and retrospectively. This may require small adjustments in the algorithms from those developed in Matlab however the design is very similar. The next stage of this research would be to test the development of these algorithms in what has been outlined above.

Chapter 5 Results

This section of the thesis presents the results for all of the experiments completed utilising the methods presented in the previous chapter. Throughout the results process my role consisted of verification and validation of the algorithm's output against expert annotation, literature and statistical analysis. Dr. Mikael Eklund's role consisted of the continued development of the algorithm after consultation with me, making all of the changes in the coding and providing the results to be analysed. The first section of this chapter includes the results obtained for the impedance algorithm that was designed, followed by the results for the algorithm designed for the overall background classification of the electrical activity. Finally the algorithm performance for the identification of sleep-wake cycling is outlined at the end of the chapter.

5.1 Impedance Results - Training Set

Initially, the algorithm was tested on the first five patients of the 15 that comprise the training set. The patients were selected at random from the training set. These patient sets varied in the length of CFM monitoring from 9 hours to 24 hours. The algorithm's output consists of impedance levels characterized as good, marginal or poor, as well as the presence or absence of sleep-wake cycling as per my design for the algorithm. The last variable was the classification of the overall background trace as either: Continuous Normal Voltage, Discontinuous Normal Voltage, Continuous Low Voltage, Burst Suppression or Flat Trace in accordance with my design of the algorithm.

The use of CFM in the NICU and minimizing impedance levels is an ongoing challenge. This is why the first algorithm designed in this thesis was to detect levels of impedance for each patient. Electrode connectivity and placement are fundamental to strong CFM signals, and if impedance is poor then the subsequent data and quality of the signal will also be poor and not suitable for analysis. Patient data that have poor impedance cannot contain sleep-wake cycling within the three-hour epoch, while if marginal or good, cycling can be seen. The results for the impedance variable were calculated in a straight forward manner, measuring concordance with the expert annotations. A screenshot example of a three-hour epoch of patient data displaying marginal impedance is shown in Figure 23 and an example displaying good impedance is shown in Figure 24.

Hour 0-3

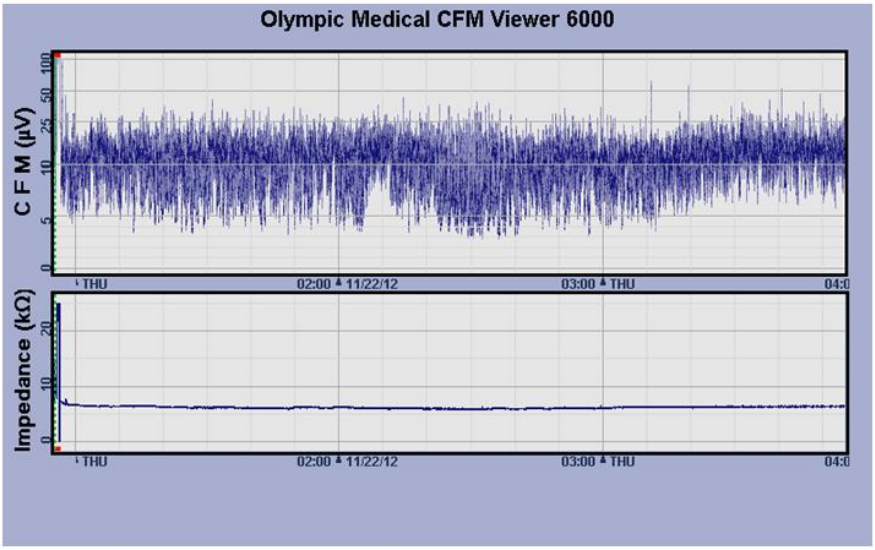


Figure 23. An example screenshot of a patient's first epoch. This particular screenshot displays marginal impedance between 5-10 kOhms

Hour 12-15

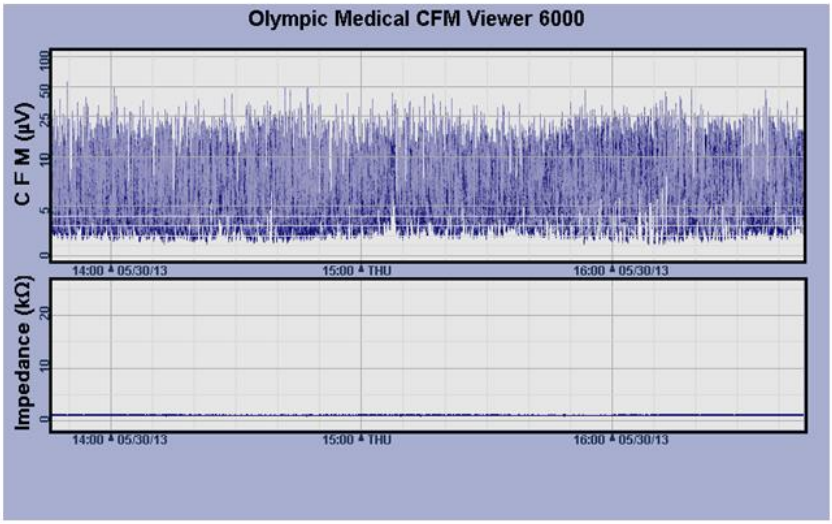
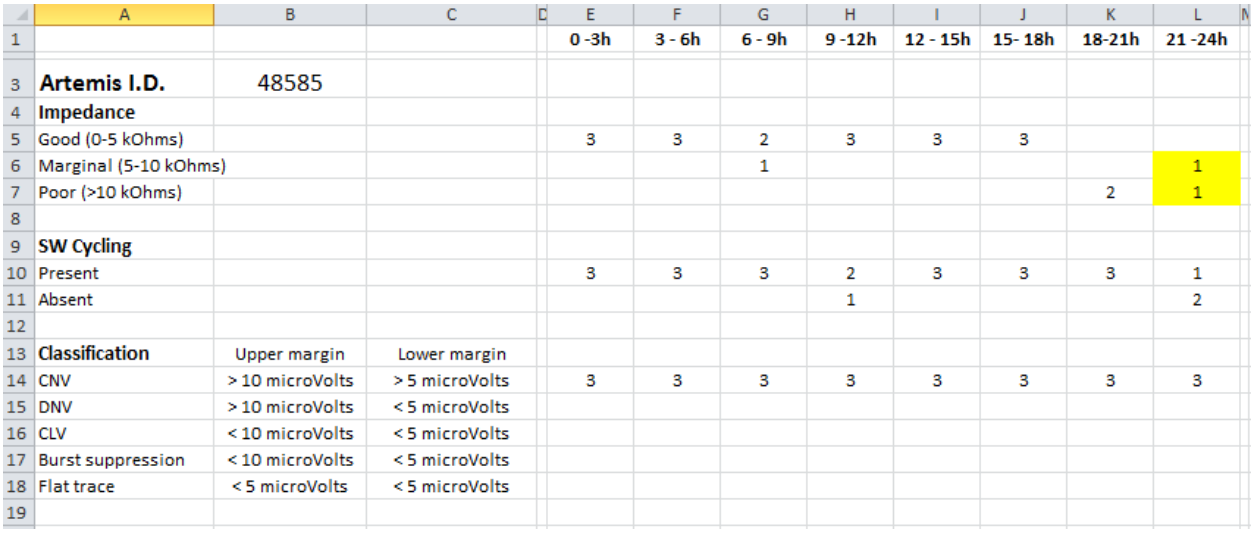


Figure 24. An example of good impedance between 0-5 kOhms

Algorithm performance for each variable was calculated based on the total impedance value for 34 epochs of time with one undetermined response based on conflict between annotators and one incorrect classification of the algorithm which equated to 32 epochs agreeing with the annotations equating to 97% concordance. An example of the process for comparison is shown in Figure 25 for patient 48585. It demonstrates the discrepancy in the last epoch concerning impedance with only two of the annotators providing information. Impedance performance values for the first five patients are displayed in Table 5.



	A	B	C	E	F	G	H	I	J	K	L
1				0 -3h	3 - 6h	6 - 9h	9 -12h	12 - 15h	15- 18h	18-21h	21 -24h
3	**Artemis I.D.**	48585									
4	**Impedance**										
5	Good (0-5 kOhms)			3	3	2	3	3	3		
6	Marginal (5-10 kOhms)					1					1
7	Poor (>10 kOhms)									2	1
8											
9	**SW Cycling**										
10	Present			3	3	3	2	3	3	3	1
11	Absent						1				2
12											
13	**Classification**	Upper margin	Lower margin								
14	CNV	> 10 microVolts	> 5 microVolts	3	3	3	3	3	3	3	3
15	DNV	> 10 microVolts	< 5 microVolts								
16	CLV	< 10 microVolts	< 5 microVolts								
17	Burst suppression	< 10 microVolts	< 5 microVolts								
18	Flat trace	< 5 microVolts	< 5 microVolts								
19											

Figure 25. Patient 48585 displaying the lone discrepancy in the expert annotation for the last epoch's impedance which is highlighted

Table 5. Impedance results for the first 5 patients in the training set

Impedance									**Concordance**
	0-3h	**3-6h**	**6-9h**	**9-12h**	**12-15h**	**15-18h**	**18-21h**	**21-24h**	
Patient									
49087	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
47607B	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	**100%**
47607C	Yes	Yes	No	N/A	N/A	N/A	N/A	N/A	**67%**
48187	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
48585	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	**100%**

'Yes' equates to agreement with the expert annotation for that epoch while 'No' equates to disagreement with the expert annotation. N/A indicates not data available for that specific epoch.

5.2 Algorithm Refinements and Associated Results

Upon completion of the comparison between human annotation and the algorithms developed based on my design using the first five patients in the training set, the clinical experts eliminated the classification of both 'burst suppression' and 'flat trace' as the criteria for these categories overlapped significantly with 'continuous low voltage.' In addition to this, the three categories of background classification versus the five held more clinical relevance to the practice followed in the NICU. Initially during the work with the first five patients of the training set, the annotators provided their expertise separately which resulted in a few instances where a three-hour epoch would contain a different response from each individual in three different categories for the classification of the background trace. This can be seen in Figure 26. These discrepancies were minimized in subsequent annotation by the experts performing the annotations together forming a gold standard in which all three agreed on each epoch for each of the three variables.

	A	B	C	E	F	G	H	I	J	K	L
1				0 -3h	3 - 6h	6 - 9h	9 -12h	12 - 15h	15- 18h	18-21h	21 -24h
3	**Artemis I.D.**	47607B									
4	**Impedance**										
5	Good (0-5 kOhms)										
6	Marginal (5-10 kOhms)			3	3	3	3	3	3	3	
7	Poor (>10 kOhms)										
8											
9	**SW Cycling**										
10	Present							1		2	
11	Absent			3	3	3	3	2	3	1	
12											
13	**Classification**	Upper margin	Lower margin								
14	CNV	> 10 microVolts	> 5 microVolts					2	2	2	
15	DNV	> 10 microVolts	< 5 microVolts	1	1	2	3	1	1	1	
16	CLV	< 10 microVolts	< 5 microVolts	1	1						
17	Burst suppression	< 10 microVolts	< 5 microVolts	1	1	1					
18	Flat trace	< 5 microVolts	< 5 microVolts								
19											

Figure 26. Screenshot of the scorecard for patient 47607B demonstrating the three individual expert annotations prior to creating a consensus decision for each epoch. Note the background classification seen in epochs one and two.

When the remaining 10 patients for the training set were included in the results the impedance concordance equated to 76 of 78 epochs correctly identified or 97.44%. The results for the remaining 10 patient's impedance levels in the training set are displayed in Table 6.

Table 6. Remaining impedance results for patients in training set

Impedance									**Concordance**
	0-3h	**3-6h**	**6-9h**	**9-12h**	**12-15h**	**15-18h**	**18-21h**	**21-24h**	
Patient									
47011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	**100%**
47607A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
48679	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	**100%**
50926	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
51018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
51115	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
51215	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
51238	No	No	Yes	Yes	Yes	Yes	Yes	Yes	**75%**
51583	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
51773	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**

'Yes' equates to agreement with the expert annotation for that epoch while 'No' equates to disagreement with the expert annotation. N/A indicates no data available for that specific epoch

5.3 Impedance Results – Validation Set

The impedance performance remained consistent, throughout the experiments, maintaining concordance above 95%. After clarifying any discrepancies with the expert annotators, the overall concordance of the impedance for the training set consisting of all 15 patients was 96.43%. Upon the selection of the algorithm version with the highest performance for the other variables, the impedance outcome for the validation set for 93 total epochs resulted in four incorrect epochs or 89 correct epochs equating to 95.70% concordance. The impedance results for the validation set can been seen in Table 7.

Table 7. Impedance results for patients in validation set

Impedance									**Concordance**
	0-3h	**3-6h**	**6-9h**	**9-12h**	**12-15h**	**15-18h**	**18-21h**	**21-24h**	
Patient									
46925	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
46687	Yes	Yes	N/A	N/A	N/A	N/A	N/A	N/A	**100%**
46290	Yes	Yes	N/A	N/A	N/A	N/A	N/A	N/A	**100%**
45828	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
45730	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	**100%**
45413	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
45213	Yes	Yes	Yes	Yes	Yes	N/A	N/A	N/A	**100%**
44567	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
44521	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	**100%**
44350	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
42559	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
42553	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
42015	Yes	No	No	No	No	Yes	Yes	Yes	**50%**
41492	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
40771	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**

'Yes' equates to agreement with the expert annotation for that epoch while 'No' equates to disagreement with the expert annotation. N/A indicates no data available for that specific epoch

The only patient the algorithm did not correctly classify the impedance levels for was four epochs for patient 42015. The impedance levels remained consistent between 5-10 kOhms throughout these epochs. This would indicate marginal impedance as the algorithm depicted, however, the expert annotations stated that the impedance levels were good. A diagram of these four epochs is shown in Figure 27. Overall, using an automated algorithm to perform this part of the annotation for the identification of impedance levels as either good marginal or poor was very well executed and had the strongest performance of the algorithms for this research.

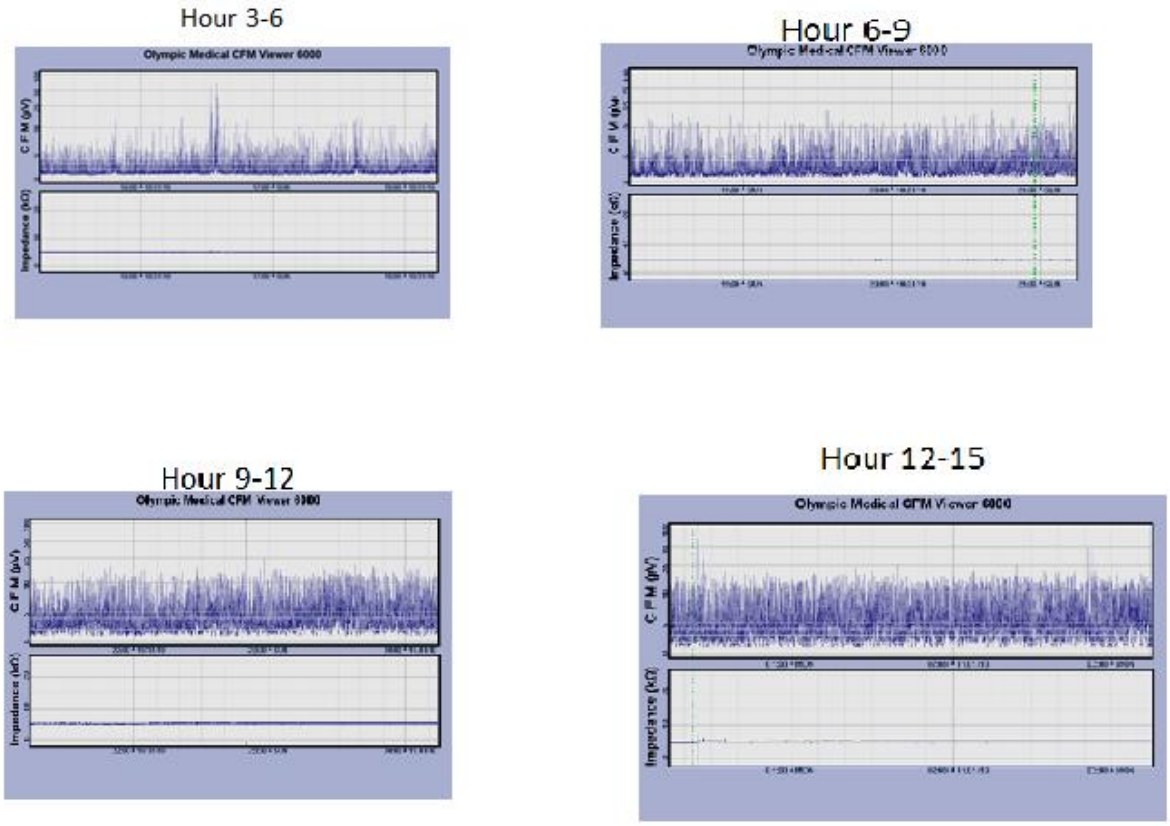


Figure 27. Patient 42015 displaying marginal impedance levels from hours 3-15

5.4 Electrical Activity Background Classification

Once the annotators made the adjustments listed above and were able to provide consensus feedback for each epoch, for all three variables, results for the first five patients consisted of the following: total sleep-wake cycling out of 34 epochs resulted in 29 epochs agreeing with the annotations or 85% concordance. Finally, the total classification for 30 results out of the 24 possible epochs resulted in 28 agreeing with the annotations equating to a 93% concordance. Results were broken down into tables for each patient, an example of which can be seen in Table 8.

Table 8**.** Example of results table for patient 49087

Patient 49087									**Concordance**
	0-3h	**3-6h**	**6-9h**	**9-12h**	**12-15h**	**15-18h**	**18-21h**	**21-24h**	
Impedance	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
SW Cycling	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**88%**
Classification	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	**88%**

'Yes' equates to agreement with the expert annotation for that epoch while 'No' equates to disagreement with the expert annotation. N/A indicates no data available for that specific epoch

Upon meeting with the expert annotators and further discussing discrepancies in the algorithmic output with the annotations, and gaining a better understanding of how the experts annotated the data, additional refinements were made to the algorithm to improve its performance. These adjustments included minor changes to the threshold levels of the algorithm for the detection of the sleep-wake state changes throughout the patient data and the minimum duration of the sleep stage in order for it to be classified as such. In terms of the background classification, adjustments to the algorithm were made to more accurately mimic the expert annotation and how it is performed rather than using each peak and trough of the upper and lower margin, the overall trend of the trace is considered.

The next stage of the results included the remaining 10 patients of the training set. An example of the output for both the algorithm and the expert annotations is shown in Figure 28. These tables provide the data for each variable, the consensus expert annotation indicated by the '1' for each epoch and an 'X' indicating the algorithm output. In the sleep-wake cycling category, the algorithm provides greater detail than just 'present' as it includes the percentage of trace that is sleep-wake cycling within each three-hour epoch.

	A	B	C	E	F	G	H	I	J	K	L
1				**0 -3h**	**3 - 6h**	**6 - 9h**	**9 -12h**	**12 - 15h**	**15- 18h**	**18-21h**	**21 -24h**
3	**Artemis I.D.**	51115									
4	**Impedance**										
5	Good (0-5 kOhms)			1	1	1	1	1	1	1	1
6	Marginal (5-10 kOhms)										
7	Poor (>10 kOhms)										
8											
9	**SW Cycling**										
10	Present			1	1	1	1	1	1	1	1
11	Absent										
12											
13	**Classification**	Upper margin	Lower margin								
14	CNV	> 10 microVolts	> 5 microVolts	1	1	1	1	1	1	1	1
15	DNV	> 10 microVolts	< 5 microVolts								
16	CLV	< 10 microVolts	< 5 microVolts								
17	Burst suppression	< 10 microVolts	< 5 microVolts								
18	Flat trace	< 5 microVolts	< 5 microVolts								
19											
20											
21	**Automated Classification V1-1**			0 - 3h	3 - 6h	6 - 9h	9 - 12h	12 - 15h	15 - 18h	18 - 21h	21 - 24h
22											
23	Artemis I.D.	51115									
24	Impedance										
25	Good (0-5 kOhms)			X	X	X	X	X	X	X	X
26	Marginal (5-10 kOhms)										
27	**Poor (>10 kOhms)**										
28											
29	SW Cycling										
30	Present			36.00%	30.20%	8.60%	16.70%	35.60%	11.20%	22.00%	13.10%
31	**Absent**										
32											
33	Classification	Upper margin	Lower margin								
34	CNV	> 10 microVolts	> 5 microVolts	X	X	X	X	X	X	X	X
35	DNV	> 10 microVolts	< 5 microVolts								
36	CLV	< 10 microVolts	> 5 microVolts								

Figure 28. Example of the output from the expert annotators in comparison to the algorithms output for the same patient below

After supplementary refinements to the algorithms which are outlined below in the sleep-wake cycling results section, the final concordance with the expert annotations and algorithm output for the training set was 83.04 %. Another example of the comparison between the annotations and automated output displaying perfect concordance is shown in Figure 29.

			0 -3h	3 - 6h	6 - 9h	9 -12h	12 - 15h	15- 18h	18-21h	21 -24h
Artemis I.D.	48187									
Impedance										
Good (0-5 kOhms)			1	1	1	1	1	1	1	1
Marginal (5-10 kOhms)										
Poor (>10 kOhms)										
SW Cycling										
Present							1	1	1	1
Absent			1	1	1	1				
Classification	Upper margin	Lower margin								
CNV	> 10 microVolts	> 5 microVolts	1	1	1	1	1	1	1	1
DNV	> 10 microVolts	< 5 microVolts								
CLV	< 10 microVolts	< 5 microVolts								
Burst suppression	< 10 microVolts	< 5 microVolts								
Flat trace	< 5 microVolts	< 5 microVolts								
Automated Classification v1-2			0 - 3h	3 - 6h	6 - 9h	9 - 12h	12 - 15h	15 - 18h	18 - 21h	21 - 24h
Artemis I.D.	48187									
Impedance										
Good (0-5 ohms)			X	X	X	X	X	X	X	X
Marginal (5-10 ohms)										
Poor (>10 ohms)										
SW Cycling										
Present							79.30%	55.40%	56.80%	97.80%
Absent			X	X	X	X				
Classification	Upper margin	Lower margin								
CNV	> 10 microVolts	> 5 microVolts	X	X	X	X	X	X	X	X
DNV	> 10 microVolts	< 5 microVolts								
CLV	< 10 microVolts	> 5 microVolts								

Figure 29. Comparison of the outputs for patient 48187. Noted is the 100% concordance for the background classification

When version 2A 1-2 of the algorithm was subsequently applied to the validation set, the final concordance percentage for the background classification was 76.34%, which is a slight decrease from the training set. The results for the validation set are summarized in Table 9.

Table 9. Background classification results for the validation set after all refinements to the algorithm have been made

Background Classification									**Concordance**
	0-3h	**3-6h**	**6-9h**	**9-12h**	**12-15h**	**15-18h**	**18-21h**	**21-24h**	
Patient									
46925	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
46687	No	No	N/A	N/A	N/A	N/A	N/A	N/A	**0%**
46290	Yes	Yes	N/A	N/A	N/A	N/A	N/A	N/A	**100%**
45828	Yes	Yes	Yes	No	No	Yes	Yes	Yes	**75%**
45730	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	**100%**
45413	Yes	No	No	Yes	Yes	No	No	No	**37.5%**
45213	Yes	Yes	Yes	Yes	Yes	N/A	N/A	N/A	**100%**
44567	N/A	N/A	N/A	No	No	No	No	No	**0%**
44521	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	**100%**
44350	No	No	No	No	No	No	No	No	**0%**
42559	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
42553	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
42015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
41492	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
40771	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**

'Yes' equates to agreement with the expert annotation for that epoch while 'No' equates to disagreement with the expert annotation. N/A indicates no data available for that specific epoch.

5.5 Sleep-Wake Cycling Results

Expert annotations from the health care professionals at The Hospital for Sick Children have been documented in both excel files as depicted as well as in PowerPoint screenshots as previously outlined in the study design chapter. An example annotation is shown for patient 51115 for the first three hours of the signal trace (Figure 30).

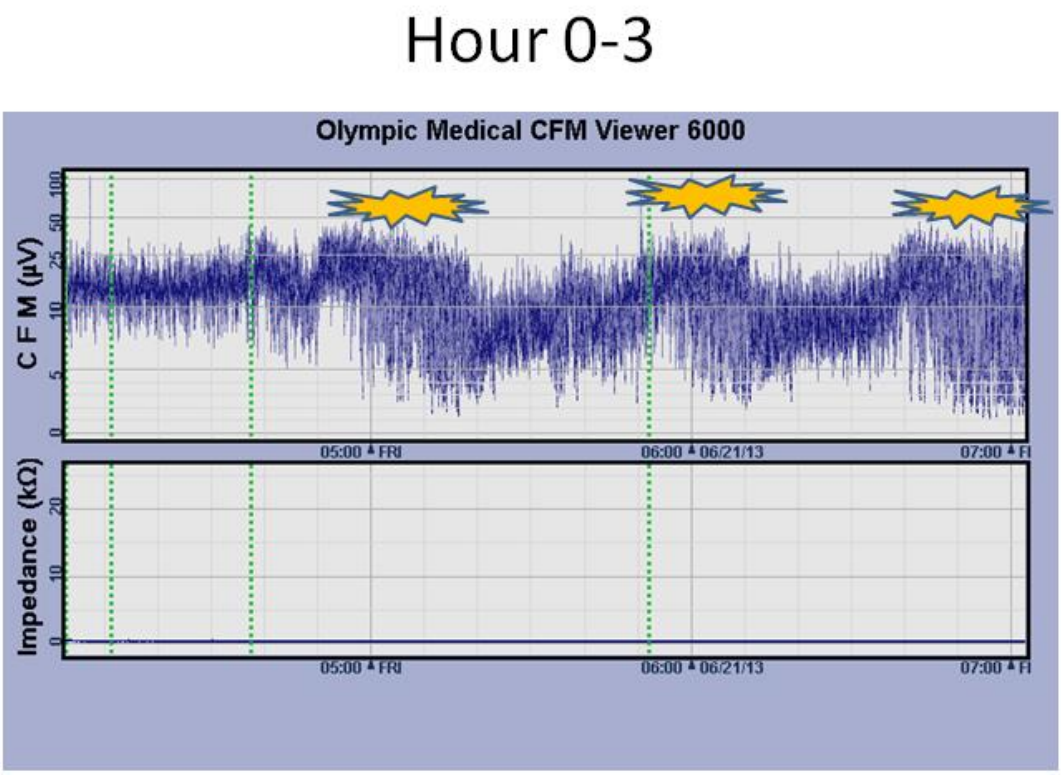


Figure 30. Example screenshot of patient with sleep stages indicated by expert annotation via starburst icon

Thirty of the outputs can be seen in Tables 10 and 11 below displaying the percentage concordance values with the expert annotations for impedance, sleep-wake cycling and background classification respectively. From the concordance percentages from the 45 different variations of the algorithm one version was selected (1-1B) to run on the validation set based on concordance values of 95.28% for impedance, 78.21% for sleep-wake cycling and 77.56% for background classification. This version was tested on the validation set, however, based on the output, the algorithm appeared to be under-classifying and identifying the sleep stages within the patient data. Consequently sensitivity and specificity calculations were performed which confirmed the rather poor performance of this version. Sensitivity equated to 18.75%, specificity was 87.01%, accuracy was 75.27% and precision was 23.08%.

Table 10. Algorithm 2A versions and their concordance values for each of the three variables being measured in this study

2A Summary			
Version	Impedance % Concordance	Sleep-Wake % Concordance	Background Classification % Concordance
V1-0	94.4444	61.0317	74.9206
V1-1	94.4444	70.3571	77.5794
V1-2	94.4444	48.4524	80.1984
V1-3	94.4444	32.619	68.6508
V1-4	94.4444	25.119	51.627
V2-0	94.4444	57.5238	77.5794
V2-1	94.4444	51.1349	78.4127
V2-2	94.4444	47.619	79.3651
V2-3	94.4444	45.9524	80.1984
V2-4	94.4444	44.9444	80.9127
V3-0	94.4444	50.119	78.4127
V3-1	94.4444	49.1667	79.246
V3-2	94.4444	46.5476	80.1984
V3-3	94.4444	49.0476	81.0317
V3-4	94.4444	39.7619	81.746

Table 11. Algorithm 2B versions and their concordance values for each of the three variables being measured in this study

2B Summary			
Version	Impedance % Concordance	Sleep-Wake % Concordance	Background Classification % Concordance
V1-0	94.4444	61.0317	74.9206
V1-1	94.4444	67.5238	77.5794
V1-2	94.4444	40.119	80.1984
V1-3	94.4444	26.2302	68.6508
V1-4	94.4444	25.119	51.627
V2-0	94.4444	53.6905	77.5794
V2-1	94.4444	42.8175	78.4127
V2-2	94.4444	41.5476	79.3651
V2-3	94.4444	41.9841	80.1984
V2-4	94.4444	35.7143	80.9127
V3-0	94.4444	50.119	78.4127
V3-1	94.4444	50.9524	79.246
V3-2	94.4444	49.2857	80.1984
V3-3	94.4444	46.7857	81.0317
V3-4	94.4444	43.0952	81.746

Due to such low detection of sleep in the previous versions of the algorithm, which is the primary goal of this thesis research, sensitivity and specificity calculations were performed for all 45 experimental versions of the algorithm. The formulas used for sensitivity and specificity were:

$$\textit{Sensitivity} = \frac{\textit{\# of True Positives}}{\textit{\# of True Positives + False Negatives}}$$

$$\textit{Specificity} = \frac{\textit{\# of True Negatives}}{\textit{\# of True Negatives + False Positives}}$$

A chart depicting the logic behind the true positives and negatives and false positives and negatives and is shown in Table 12.

Table 12. Sensitivity and specificity calculation logic for true positives and negatives and false positives and negatives

		Expert Annotation	
		Sleep	**Wake**
Algorithm Output	**Present**	True Positive	False Positive
	Absent	False Negative	True Negative

After these calculations were performed, revision of the percentages revealed four variations that produced the best results in each category. Tables 13-16 exhibit the calculations for these best four versions of the algorithm.

Table 13. Sensitivity and Specificity for version 1-2 from 2A

Patient ID	True Positive	True Negative	False Positive	False Negative
47011			7	
47607A			7	1
47607B	1		6	
47607C			3	
48187	3	4		1
48585	6	1		1
48679		7		
49087	1	5	1	1
50926		1	7	
51018		8		
51115	8			
51215		8		
51238		8		
51583	3		5	
51773		7		1
Totals	22	49	36	5

Sensitivity = 81.48% (22/27), Specificity = 57.65% (49/85)

Table 14. Sensitivity and Specificity for version 3-0 from 2B

Patient ID	True Positive	True Negative	False Positive	False Negative
47011			7	
47607A			7	1
47607B	1		6	
47607C			3	
48187	3	4		1
48585	6	2		
48679		7		
49087	1	5	1	1
50926		3	5	
51018		8		
51115	2			6
51215		8		
51238		8		
51583	3	1	4	
51773		7		1
Totals	16	53	33	10

Sensitivity = 61.54% (16/26), Specificity = 61.63% (53/86)

Table 15. Sensitivity and Specificity for version 3-1 from 2B

Patient ID	True Positive	True Negative	False Positive	False Negative
47011			7	
47607A			7	1
47607B	1		6	
47607C			3	
48187	3	4		1
48585	6	2		
48679		7		
49087	1	5	1	1
50926		3	5	
51018		8		
51115	3			5
51215		8		
51238		8		
51583	3	1	4	
51773		7		1
Totals	17	53	33	9

Sensitivity = 65.38% (17/26), Specificity = 61.63% (53/83)

Table 16. Sensitivity and Specificity for version 3-2 from 2B

Patient ID	True Positive	True Negative	False Positive	False Negative
47011			7	
47607A			7	1
47607B	1		6	
47607C			3	
48187	3	4		1
48585	6	2		
48679		7		
49087	2	3	3	
50926		3	5	
51018		8		
51115	3			5
51215		8		
51238		8		
51583	3		5	1
51773		7		
Totals	18	50	36	8

Sensitivity = 69.23% (18/26), Specificity = 58.14% (50/86)

These four variations of the algorithm were selected to run on the validation set of an additional 15 patients. The results of the sensitivity and specificity calculations for the four versions selected to run on the validation set were not as strong as originally expected, therefore further refinements were made to the algorithm. The basic algorithm follows the physicians' guidelines of looking for changes in the width of the CFM band, which indicate either sleep (wider band) or wakefulness (narrower band) while still within the normal upper and lower bands. This method uses fixed thresholds for the width of the band, regardless of the individual. Improvements to the algorithm at this stage of the study uses the mean of the difference between the upper and lower band on an individual, patient-by-patient basis; note this is possibly how the physician interprets the CFM as well, but this is not clear. Depending on the other parameters of the algorithm, the threshold used is between 110% and 125% of this mean of the difference.

From these changes version 2A 1-2 produced the best sensitivity and specificity results for sleep-wake cycling detection, which equated to 73.08% and 77.91% respectively. The breakdown of these calculations can be seen in Table 17.

Table 17. Summarization of training set sensitivity and specificity variables for sleep-wake cycling algorithm

Patient ID	True Positive	True Negative	False Positive	False Negative
47011		7		
47607A		7		1
47607B		6		1
47607C		3		
48187	4	4		
48585	6	1	1	
48679		7		
49087	1	3	3	1
50926		8		
51018		3	5	
51115	7			1
51215		5	3	
51238		5	3	
51583		5		3
51773	1	3	4	
Totals	19	67	19	7

Sensitivity = 73.08% (19/26), Specificity = 77.91% (67/86)

The concordance for sleep-wake cycling in the training set equated to 76.79% after all of the refinements had been made (Table 18). Due to the large improvement from the other versions tested, this version of the algorithm was applied to the validation set. As a result, sensitivity was 81.25% and specificity was 75.32%, both improving from the training set. These calculations are depicted in Table 19 below. The concordance for sleep-wake cycling for the validation set rose slightly to 78.49%, which is a stronger result than percentages obtained in previous versions of the algorithm.

Table 18. Sleep-wake cycling results for training set data

Impedance									**Concordance**
	0-3h	**3-6h**	**6-9h**	**9-12h**	**12-15h**	**15-18h**	**18-21h**	**21-24h**	
Patient									
47011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	**100%**
47607A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	**87.5%**
47607B	Yes	Yes	Yes	Yes	Yes	Yes	No	N/A	**85.71%**
47607C	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	**100%**
48187	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
48585	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	**87.5%**
48679	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	**100%**
49087	No	No	Yes	Yes	Yes	No	Yes	No	**50%**
50926	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**100%**
51018	Yes	Yes	Yes	No	No	No	No	No	**37.5%**
51115	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	**87.5%**
51215	Yes	Yes	Yes	Yes	Yes	No	No	No	**62.5%**
51238	No	No	Yes	Yes	Yes	Yes	Yes	No	**62.5%**
51583	No	No	No	Yes	Yes	Yes	Yes	Yes	**62.5%**
51773	Yes	Yes	Yes	Yes	No	No	No	No	**100%**

'Yes' equates to agreement with the expert annotation for that epoch while 'No' equates to the disagreement with the expert annotation. N/A indicates no data available for that specific epoch.

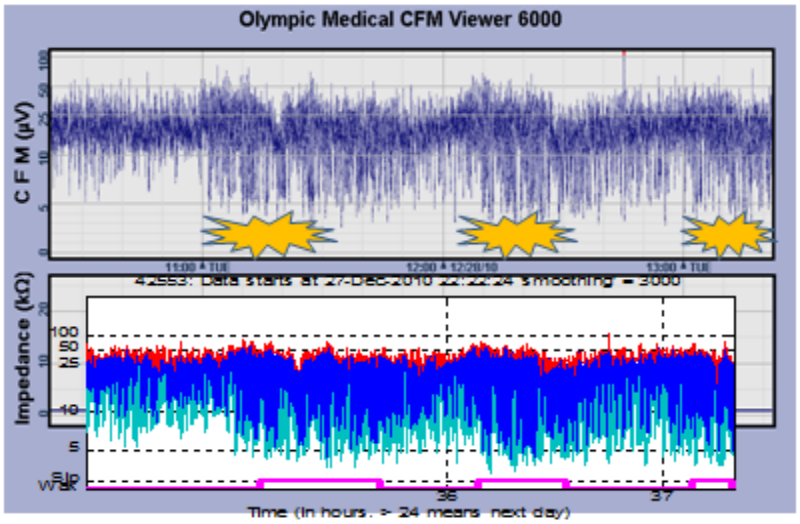
Table 19. Summarization of validation set sensitivity and specificity variables for sleep-wake cycling algorithm

Patient ID	True Positive	True Negative	False Positive	False Negative
40771		8		
41492		8		
42015		6	2	
42553	4	3	1	
42559		8		
44350		4	4	
44521	1	1	1	
44567		3	2	
45213	4			1
45413		4	4	
45730		4		
45828		6	2	
46290			2	
46687		2		
46925	4	1	1	2
Totals	13	58	19	3

Sensitivity = 81.25% (13/16), Specificity = 75.32% (58/77)

Two examples of the algorithm output for patient 42553 are depicted in Figures 31 and 32 below. Figure 31 shows the correct identification of sleep-wake cycling that matched the expert annotations in both cases. The upper margin is outlined in red while the lower margin is outlined in turquoise. Between these two bands, the central portion of the trace is the region that is often considered by the experts while performing their annotations, disregarding any extreme anomalies in the trace. The magenta line at the bottom of the trace represents the binary function of whether sleep is present = 1 or not = 0. This computer generated output of the algorithms result is on the same scale as cerebral function monitors with the microvoltage value on the y-axis and the time along the x-axis.

Hour 12-15



Hour 21-24

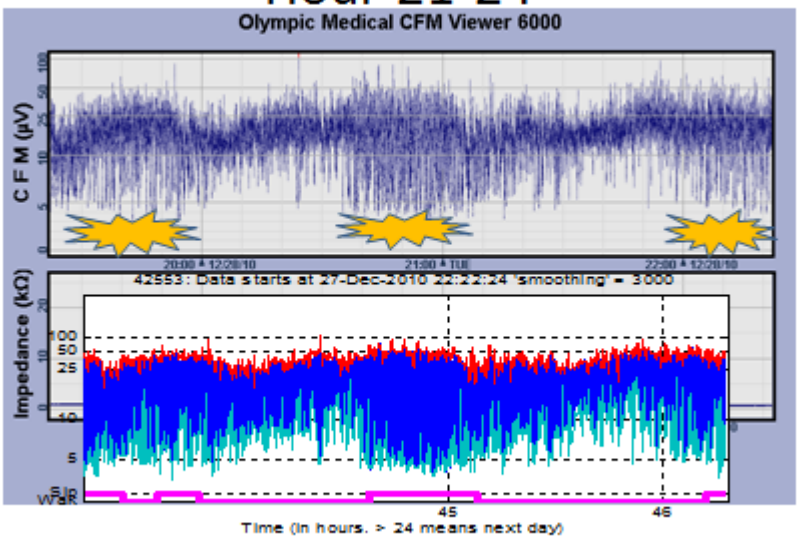


Figure 31. Two examples of the algorithm output below the expert annotations for the same epoch of patient 42553 correctly identifying sleep-wake cycling as indicated by the magenta line

Two examples from patient 45413 are displayed in Figure 32 below which demonstrates the incorrect identification of sleep-wake cycling as there were discrepancies between the algorithm's identification of the sleep and the expert annotators indicting the lack of cycling.

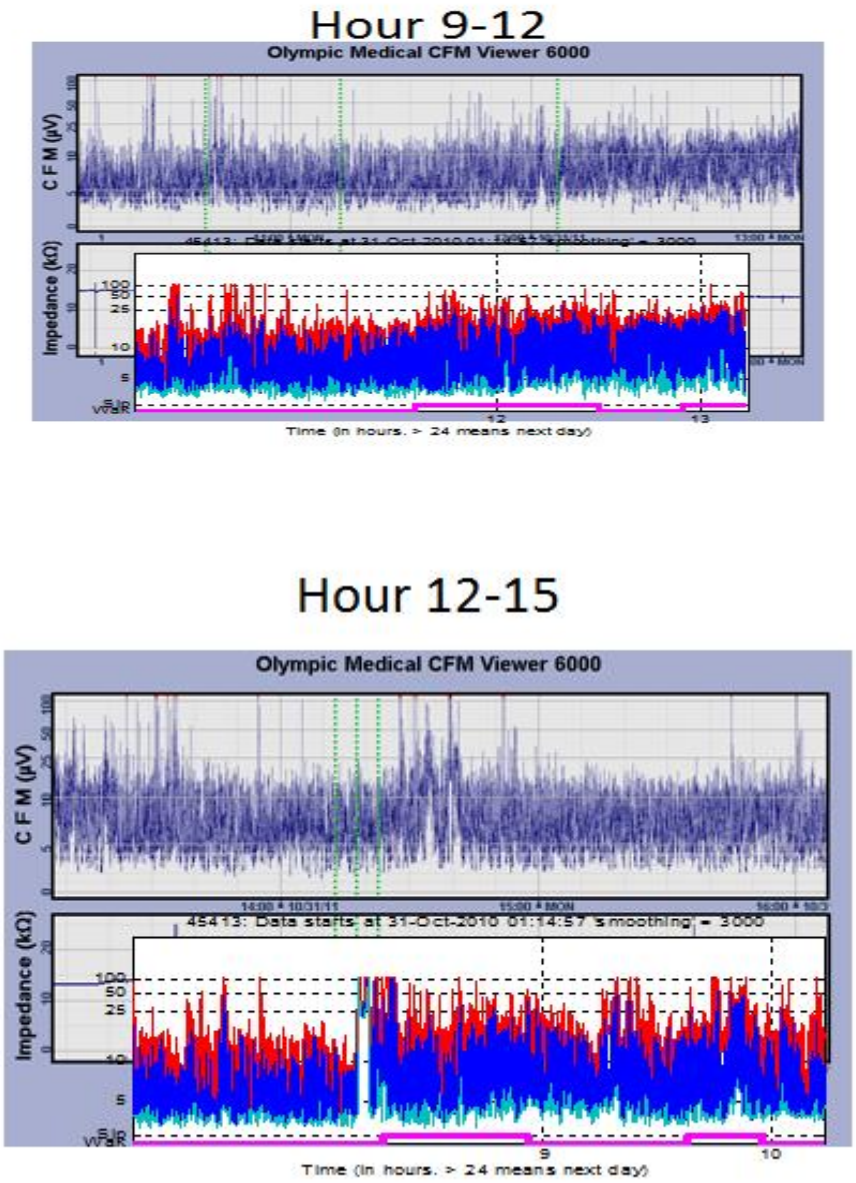


Figure 32. Two examples of the algorithm output below the expert annotations for the same epoch of patient 42553 incorrectly identifying sleep-wake cycling as indicated by the magenta line and lack of annotation on the top trace from the experts

Table 20. Summary of training and validation set algorithm performance

	Training Set Algorithm Performance	Validation Set Algorithm Performance
Impedance	96.43%	95.70%
Background Classification	83.04%	76.34%
Sleep-Wake Cycling	76.79%	78.49%
SWC Sensitivity	73.08%	81.25%
SWC Specificity	77.91%	75.32%

This chapter has presented three algorithms that contribute to the automated detection of three clinically relevant variables from neonatal aEEG signals. Impedance measured in kOhms was detected at 95.70% concordance with expert clinical annotations. Overall background electrical activity for patients measured in microvolts had a final concordance value of 76.34% with the expert clinical annotations. The third algorithm was designed to detect the sleep-wake cycling in patient CFM traces which was achieved to a concordance of 78.49%, a sensitivity of 81.25% and a specificity of 75.32% in comparison to expert clinical annotations. These results demonstrate that the process of manual annotation is an appropriate problem for consideration for automation using real-time streams computing techniques to automate the classification. The subsequent chapter will discuss these results and provide explanations as to why there were discrepancies in the algorithmic output as well as highlights of good quality automated performance. Overall the performance of the algorithm was much higher than original results through the adjustments that were made and indicate that this type of automation is possible to a significant degree of success.

Chapter 6 Discussion

In this chapter a discussion of relevant literature is highlighted in relation to the results presented in the thesis. Due to the fact that the automation of sleep-wake cycling via CFM signals is a unique and novel concept there are very few research articles that describe work relating exactly to the research presented in this thesis. As a result, similar concepts relating to neonatal sleep and cycling patterns often involving EEG signals and any relative sequences of data extracted from literature involving automated sleep-wake detection from cerebral function monitors are discussed in comparison to what was obtained in this study.

Original automation strategies to identify neonatal sleep via EEG used spectral energy and made the assumption that the EEG signals were stationary (Scher, 2004). Since this presumption it has been revealed that in order to accurately and automatically identify sleep in neonates, the time-dependent element of the signal must be considered. One of the main elements that was incorporated into the design of the algorithms incorporated in this thesis to detect periods of sleep via CFM signal was the time-dependent factor to determine whether or not sleep was in fact occurring based on the duration of discontinuous data (Scher, 2004).

6.1 Analysis and Explanations of Results

Using neonates as a study population often poses many complications and challenges when acquiring and analysing data because of the nature of their environment and physiological conditions. Despite almost a decade of research, at present there is still no commercially available multi-channel based EEG neonatal seizure detection algorithm that is widely acceptable in clinical practice (Cherian et al, 2011). When considering bedside monitoring involving cerebral activity, data can be contaminated with various artefact and abnormal impedance levels. In this research, the challenge of impedance was minimized through the initial quantification of acceptable and non-acceptable values. This however does not separate all of the patient data possessing noise within their traces that may cause the algorithm to identify periods of sleep when they are not present or the reverse of this. The same can be said for the background classification of the electrical activity.

While performing algorithm testing on the 15 patients of the training set, patient 47011 consistently resulted in inaccurate output. This included both the over-classification of sleep periods and the improper classification of the background tracing. Upon consultation with the expert annotators they concluded that this particular patient was difficult to annotate because of the large presence of bursts throughout each epoch. Due to the nature and frequency of these bursts, the trace could be easily mistaken for an overall background classification of discontinuous normal voltage. The last version of the training set algorithm was able to correctly detect the absence of sleep however the background classification was incorrectly identified as discontinuous normal voltage when in fact it should have been continuous low voltage. An example epoch from this trace is shown in Figure 33.

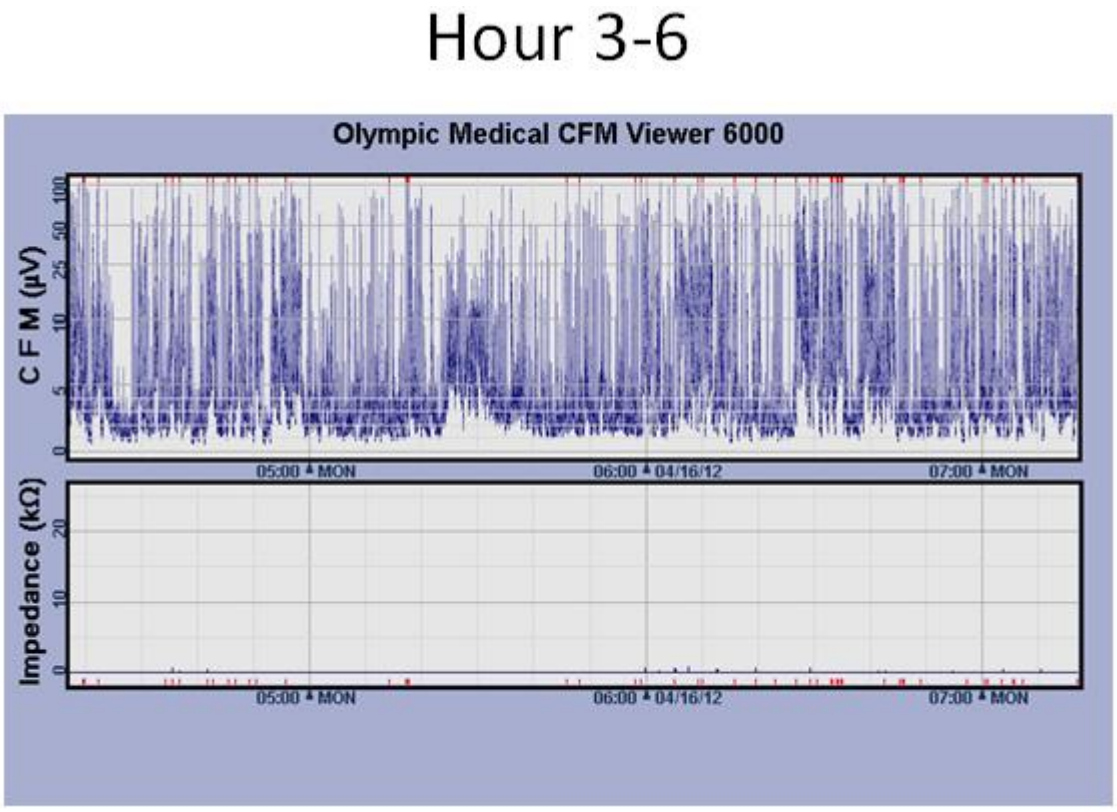


Figure 33. Patient 47011 example epoch of the busts displayed throughout the trace

Upon the analysis and calculation of concordance values for the training and validation set, a slight decrease in both the percentage concordance for background classification and impedance

levels was observed. A very slight increase in the concordance for the detection of sleep-wake cycling between the data sets was achieved. These results can partially be attributed to the nature of the patient data in the validation set. The data in several patients was unclear and challenging to distinctly classify whether it be the background activity or sleep wake cycling, including one patient displaying seizure activity throughout several epochs. For example, for patient 42553 the annotators indicated that there were debates over whether or not sleep-wake cycling was present or not for some of the three-hour epochs, and the algorithm identified sleep where the experts did not. The same scenario occurred for patient 44350 where there was debate over sleep-wake cycling between the annotators stating that it was not very well defined where the algorithm output identified sleep in these epochs where the experts were unsure. Due to the fact that the cycling was not as defined as it could be, the consensus decision was to mark the cycling absent. This presents a strong demonstration of the subjectivity involved in the classification of CFM signals in the NICU and the challenges that automated detection faces when considering sleep-wake cycling.

In the instances for patients 44350 and 45413, there were significant discrepancies between the expert annotations and the algorithm output for the background classification. This again can be attributed in part to the nature of the CFM traces and the patient data. In Figure 34, which displays a screenshot of hours 9-12 for patient 44350, the lower margin contains many anomalies, which the algorithm identified as part of the trace, which would have altered its output from continuous normal voltage to discontinuous normal voltage because these valleys were considered by the algorithm. The expert annotators made the consensus decision to define the trace as CNV, which again attributes to the subjectivity of the classification process.

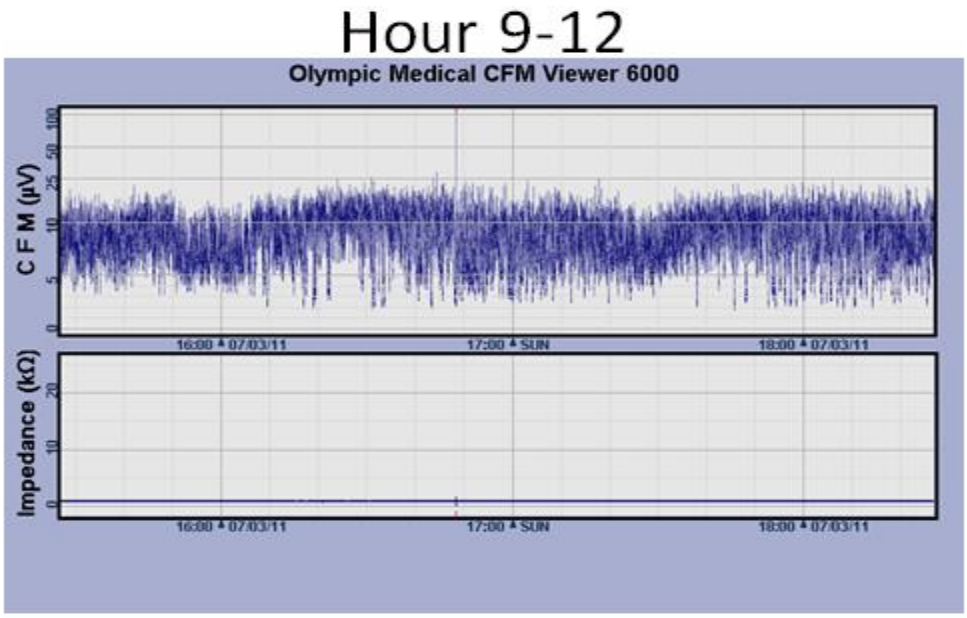


Figure 34. Patient 44350 epoch 9-12 displaying lower margin outliers that the algorithm considered in its output while the expert annotators did not. The result was a discrepancy between the two background classifications

A similar scenario occurred for patient 45413, where the patient trace displayed many outliers in the upper bound resulting in the expert classification of CNV as they disregarded these outliers while the algorithm factored in a percentage of these peaks resulting in a discontinuous normal voltage output. An example epoch from patient 45413 is shown in Figure 35. Both these cases have illustrated where improvements can be made to the algorithm in future work. More consultation with the experts is needed to include the trends and tendencies that are involved in the annotation decision making process.

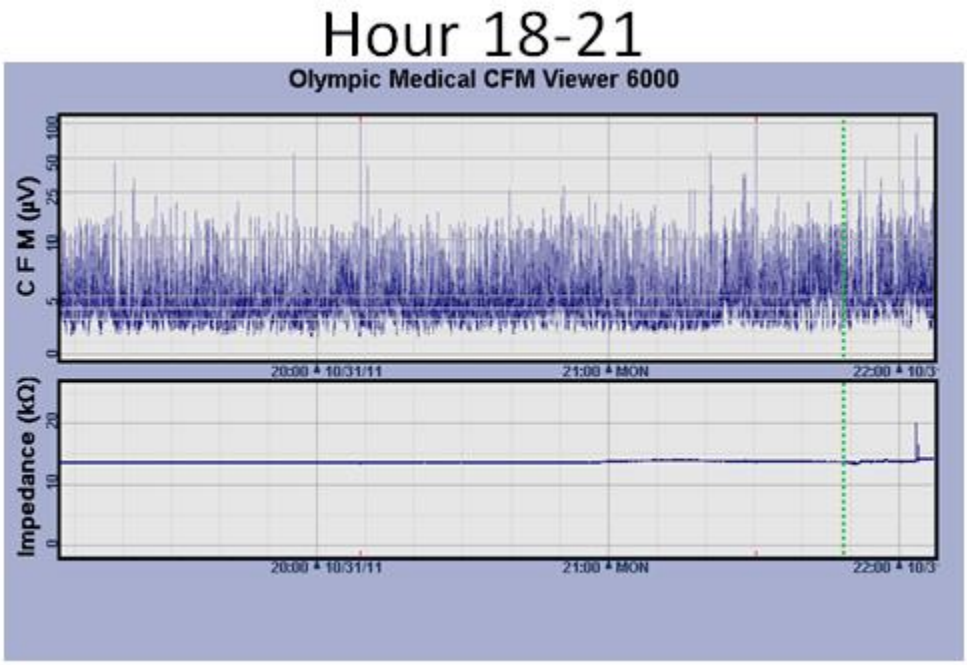


Figure 35. Patient 45413 epoch 8-21 displaying upper margin outliers that the algorithm considered in its output while the expert annotators did not. The result was a discrepancy between the two background classifications

This to a certain extent is a limitation to the data used in this study as the algorithm only considers each three-hour epoch, whereas the experts may have considered the entire data trace to gain an understanding of the infant's condition and made their epoch to epoch annotations based on these facts. The expert annotators had each patient's data and were not blinded, this being said the annotators were asked to make their decisions solely based on what was visualized in the screen shots of the three-hour epochs; not based on the clinical context of what complications the patient may have been experiencing and the resulting medical intervention. In the future data could be made completely anonymous so that the experts are blinded to which patient they are annotating and the associated medical complications, as well as observation of the experts to ensure annotations are being made on an epoch-to-epoch basis. On this note, if the algorithm were to be developed so that it could analyse CFM data in real-time this complication would no longer become a factor and the process would become more consistent with actual clinical practice.

6.2 Related Findings in Literature

Palmu et al., (2013) have worked with automating the detection of spontaneous activity transients or bursts within sleep-wake cycling traces of premature infants, however they attempted this using continuous EEG (cEEG) and not amplitude-integrated EEG (aEEG). They have validated their algorithm based on polysomnography gold standards in comparison with their novel EEG-based index. This research attempted to automatically identify the stages of sleep that were present within EEG traces, however had to rely on other monitors within the NICU such as electromyography (EMG) and electrooculography (EOG) signals (Palmu et al., 2013). Automation of patterns within the trace was based on calculating root-mean square values. Depending on the deviance from these values based on the median and times series classification, the resulting output was binary as either a burst or not. The authors were able to achieve moderate success using this method.

In the work by Cherian et al., (2011) an automated seizure detection algorithm was designed and developed using cEEG monitoring. The algorithm that the authors developed used two detectors that run in parallel consisting of a spike detector identifying high-energy segments and analysing the correlation between them. The second component included an oscillating seizure detection system that identifies increases in low frequency activity. For this thesis, the frequency of the traces was not considered due to the fact that aEEG was used and not cEEG which only uses a limited frequency range of 2-15 Hz. Parameters and criteria were set for classification within this range for the algorithms developed in the thesis. Cherian et al., (2011) found that the most significant artefact affecting seizure detection originated from spikes, blood vessel pulsation and respiration. Results revealed performance of the algorithm with approximate sensitivity of 86% and a positive predictive value of 89%; however the results were not compared to visual detection using aEEG which is often used in the NICU as an initial and reliable predictive tool.

There has been hesitation amongst the medical, informatics and biomedical engineering communities in regards to the automation of sleep state detection based on thresholds of detection for specific physiologic measures due to the believed decline in performance of algorithms that are implemented into the software because of the technical and medical conditions varying so much for each patient (Scher, 2004). To combat this belief there have been attempts to maintain the highest performance possible for automation of sleep particularly in

adults based on EEG in the work done by Agarwal et al., (2001). The stages included the automation of the naturally occurring patterns within the sleep trace that were first visually identified which were followed by the revalidation by visual analysis automated output. These authors avoided the use of using hard thresholds for their automated system so that their system could adjust and adapt to changes seen in different cases as well as support user preferences. The research conducted for this thesis involved similar practices for the design of an algorithm that attempted to mimic the pattern recognition of human annotators by using a multi-stage algorithm to increase performance. The output of the algorithm was also validated through expert visual inspection in addition to the gold standard of comparison.

Other methods for identification of patterns within EEG have used spectral analysis, which involves the four main frequency wavelengths seen during sleep that include: Alpha, Beta, Delta and Theta. More recently in work that has attempted to determine the specific stages of neonatal sleep using EEG signals, a combination of spectral and non-linear dynamic characteristics produce the best overall discrimination between stages due to the high non-linearity of the neurophysiological mechanisms that generate the EEG signals (Piryantinska et al., 2009). The spectral analysis of the signals often involves discrete fast Fourier transforms and the estimations of power spectral density (Piryantinska et al., 2009). The authors were able to achieve 80% agreement with expert annotation via polysomnography.

Other methods for the detection of seizures and brain tumours have utilised multi-wavelet transform decomposition as well as through the use of approximate entropy which is used to quantify the amount of regularity and unpredictability of fluctuations over time. Implementation of artificial neural networks completed the aggregation of methods to complete the automated identification tasks to upwards of 70% sensitivity and 78% specificity for brain tumour identification. (Sharanreddy and Kulkarni, 2013). Frequency domain representations were chosen and designed to detect different forms of periodic fluctuations based on Fourier transform for detection in white Gaussian noise. Discrete wavelet transform can detect periods of fluctuation when the underlying wave shape is not sinusoidal (Stevenson et al., 2014; Turnbull et al., 2001). These more complex methods than the ones utilized in this thesis could be applied in future work and would be an interesting comparison between the output and results obtained in this work and the more complex measures of automated detection and classification of traces.

As previously stated, the relationship between the early appearance of sleep-wake cycling patterns and later neurological developmental outcomes has been considered valuable during NICU care. Temporal patterns of sleep EEG in neonates have been shown to be useful in the assessment of functional brain maturation of infants who are at risk of developmental disabilities. (Piryantinska, 2009). Unfortunately the development and lack of progress related to the continued evolution of this practice and measure is directly related to the lack of objective measures for the quantification. The algorithm designed for this research is primarily based on qualitative and subjective annotations made by professionals at one particular institution, making this a challenging aspect to standardize amongst different centres.

Very recent research has looked at the use of long-term polysomnographic recordings of preterm infants that display spontaneous activity transients or bursts that potentially can aid in the measurement of sleep-wake cycling patterns (Stevenson et al., 2014). Two technical problems that are associated with the automation and real-time measurement of sleep-wake cycling from long-term EEG recordings which are the time variant nature rather than strictly periodic nature of the cycling and the noise in the signal is still unknown. This is associated with the mean period of cycling being affected by factors that relate to the infant and the care it is receiving. The second issue revolves around the nature of the signal and the technical artefacts generated from less than ideal recording conditions meaning that measures of sleep-wake cycling need to be robust enough against missing data segments as well as brief artefact segments lasting upwards of 10 minutes (Stevenson et al., 2014).

Stevenson et al., (2014) also found that interpolating across missing data introduces an error into the estimation of sleep-wake cycling. Biological time-series are characteristically non-stationary and as the time scale of analysis increases the non-stationary nature of the signal becomes more obvious. This is one of the challenges in working with aEEG signals and different patients despite the varying length of time windows developed in the algorithms. One fixed length of time is selected for the window and applied to all of the patients when in fact each patient is different. Slow variations in the signal can be dealt with by using short overlapping analysis epochs and by summarizing activity with respect to frequency bands rather than discrete frequencies. Stevenson et al., (2014) established measures of the cycling without directly claiming its equivalence with genuine sleep states.

A quantitative scoring system was developed in recent research which used four-hour epochs of aEEG data and categorized traces into four grades from zero being no cycling with no fluctuations in aEEG trend, one: containing imminent cycling with at least two fluctuations during the epoch, two: immature cycling with visually apparent cycling but irregular throughout the four hours and finally three: developed and stable cycling with stable and relatively periodic fluctuations (Wilkstrom et al., 2012). Research has begun to attempt the quantification of sleep-wake cycling to make automation easier however the success has been limited and a widely acceptable scoring system is still not in place throughout the medical community.

Another factor that is considered when analysing patient data of this nature is the understanding that each patient is different and may display different traces or background activity that correspond to the same thing, most importantly the cycling between sleep and wake. Establishing a baseline of electrical activity for each patient is ideal, to aid in the determination of when the background trace becomes more discontinuous or continuous during sleep-wake cycling. Westover et al, (2013) demonstrated that when patient specific optimization of classification thresholds are applied, the algorithms automated detection of burst suppression from a raw EEG signal resulted in improved performance from the standardized application of thresholds in comparison to standard expert interpretation. This was found to occur across the entire patient population for the study.

Another key point raised by Scher, (2004) was the user preference settings that can be adjusted in an automated system which may skew results depending on the individuals practice. The settings of the algorithm were based on standard practice in the NICU at The Hospital for Sick Children, Toronto which may slightly vary between NICUs in different Hospitals despite generalized patterns and values that are accepted amongst health care professionals in this field. The algorithm went through a series of refinements and adjustments to attempt to enhance its performance in identifying when sleep is occurring and what the overall background classification of the signal trace is based on the expert annotators opinion in which a small degree of error must be considered.

In conclusion, computerization or automation of neonatal aEEG traces can provide novel and time efficient strategies to acquire diagnostic and prognostic data enhancing the usefulness and optimizing CFM as a clinical decision making tool. This is particularly true in enhancing care for

neonates through earlier intervention to potentially lessen neurological morbidities. Researchers have found that for sleep identification, scoring pattern recognition and wave detection have proven to generate the highest performance between the range of 75-85% (Scher, 2004).

After performing the testing on the algorithm numerous times on the training set utilizing the three different versions two main problems arose. The first being the classification of signal and the overall background activity, using each three-hour epoch and secondly the positive identification of sleep-wake cycling. These issues all relate to those discussed above including a standard baseline estimation for each patient in the trace versus individual baselines on a patient to patient basis, the judgement with outliers and whether or not they are statistically significant or not. When do these get ignored and at which point should outliers be included and whether or not clinicians have a full understanding of this needs resolution for automated tools to maximize their effectiveness.

Chapter 7 Conclusion

This thesis has presented a reasonably accurate, reliable, and valid automated algorithm designed to detect normal and abnormal traces and sleep-wake cycling from an amplitude-integrated EEG (aEEG) signal in neonates greater than 29 weeks gestational age. There is a need for the improvement of the time and resource consuming process of manual cerebral function monitor annotation by clinicians. This was shown through the novel and unique algorithms designed for this thesis and the successful automated classification results. Consequently, through the development and application of these robust algorithms for analysis of aEEG data streams captured at the bedside, this is the first step to providing aid in the diagnosis and determination of variations in the normal sleep-wake cycling patterns.

The research outlines the link between this clinical need and the informatics and technology designed to automate the clinical rules. Through the extensive search of medical literature, algorithms have been designed, evaluated and validated to perform a task that is manually completed frequently in the neonatal intensive care unit (NICU). The retrospective analysis of de-identified patient data will determine whether or not it is applicable to a real-time computer software environment enabled by stream computing. The scope of this thesis includes the design, verification and validation of the algorithms that were developed in order to automate the detection of normal and abnormal aEEG traces and sleep-wake cycling patterns produced by CFM in neonates. Determining how these algorithms could be designed based on the principles of stream based computing as the paradigm within which they were coded fits within the scope of this thesis as well.

The intensive care of neonates has continued to develop throughout its existence. The next stages of this continued improvement in the delivery of care involves the automation of medical practices that utilize bedside devices that continuously monitor a patient's physiological state and increase the functionality as a clinical decision tool. This thesis presented the design of an algorithm for the automated detection of normal and abnormal aEEG traces and sleep-wake cycling in term infants. The research outlines the link between this innovative potential clinical solution and the informatics and technology designed to automate the current manual practice. The current manual practice of annotating CFM traces for abnormalities in background electrical activity at the bedside by health care professionals is a tedious and time consuming process.

Automating this practice has the potential to provide multiple benefits to both the care of the patients and the health care professionals providing care in the intensive care environment. The design of multiple algorithms working in unison to mimic the work of humans is described in the thesis. A combination of relevant literature and first-hand expert knowledge were the basis of the algorithms characteristic's and features. The methodology of the experiments as detailed in chapter 4 were implemented to design, develop and validate the algorithms in their ability to detect impedance levels, presence of sleep-wake cycling and the overall background electrical activity of patient data via CFM. The performance of these algorithms was measured based on the gold standard of three experts in the field who provided amalgamated annotations for each patient included in the study. The results of this were reported in chapter 5. As a novel concept the benefits of automating this process are outlined in chapter 6 and the potential for continued work and further research on this topic are defined. Further details on the research and results are presented below.

7.1 Research and Findings

A literature review was completed and reported in chapter 2 to assess the current status of cerebral function monitors in the NICU or other health care environments and the associated automation of their output through software programs. There have been many attempts using cerebral function monitors to automate the detection of seizures which is one of the key outputs from this device however many have had limited success. Upon completion of the review it was revealed that there is a complete lack of automated output with regards to sleep-wake cycling, and overall background classification of the trace, which is outlined in chapter 2. Details of the Artemis Platform an extensive and sophisticated Big Data informatics platform within which compatible algorithms such as the one designed in this thesis for sleep-wake cycling modelling can be functionally deployed is outlined in Chapter 3. A detailed review of the study schema from the population, data collection, design and application of the algorithm inclusive of its various characteristics, classification and application in the automation of the CFM signal is delineated in Chapter 4. Another alternative to the methodology proposed using MatLab for the development of the algorithms for the identification of impedance levels, detection of sleep-wake cycling and classification of the background trace is the use of the data stream processing environment InfoSphere Streams.

The retrospective analysis of de-identified patient data from 15 patients representing a training set and a further 15 patients representing a validation set helped determine whether or not it is applicable to a real-time computer software environment enabled by stream computing. Upon the completion of the study it has been confirmed that despite utilizing a different coding platform, the algorithm logic and code can be converted to Streams Processing Language and can be applied to the Artemis platform. Currently the only drawback, of significant nature is the lack of compatibility with the CFM monitors in the NICU and the Artemis platform. Once this complication is resolved streaming of the CFM data in real-time is a possibility from the bedside. After establishing this, alert systems will have to be implemented to identify when the patient's cerebral activity becomes abnormal and when sleep is occurring.

The research question posed at the onset of this thesis was whether the design of a valid automated algorithm can be developed to detect the presence or absence of sleep-wake cycling from an aEEG signal in neonates aged 29-44 weeks gestational age. This algorithm was designed in manner to mimic the manual interpretation completed by health care professionals in the NICU. Through the verification of the algorithms output based on previous literature of standard tracings and the validation compared to expert annotation, normal and abnormal as well as sleep wake-cycling in patient traces was identified. Thus this research question has been proven.

Chapter 5 outlines the results of the study, comparing the fifteen patients in the training set to the 15 patients of the validation set. This chapter delves into a detailed summarization of the algorithm's output and the associated statistical analysis and concordance values in comparison to the expert annotation. These measures of performance revealed that algorithms can be developed to automate detection and classification of a CFM signal. Multiple tests of the algorithm's output were run on one patient's test file, the first 5 patient traces, followed by the next 10 patient traces that comprised the training set for the study. Through the adjustments and refinements made to the algorithm after each run, concordance values were 96.43% for impedance, 76.79% for sleep-wake cycling, 73.08% sensitivity and 77.91% specificity for sleep-wake detection and finally 83.04% for background classification. After finalizing the algorithm for the purposes of this thesis, the next 15 patients of the validation set were then tested against the algorithm and its performance was again measured in comparison to the expert clinical annotations. These results produced concordance values of 95.70% for impedance, 78.49%,

81.25% sensitivity and 75.32% specificity for sleep-wake cycling and finally 76.34% for background classification. Chapter 6 then discusses these results that were obtained and compares this information to relevant published literature relating to the automation of CFM signals.

This novel research has the potential to make a significant contribution to the medical and informatics field through further studies and applications. This thesis has taken an initial step in automating the detection of periods of sleep cycling in critically ill neonates based on CFM signals. The algorithms developed also have the ability to detect impedance levels in the patient's data as well as the classification of the overall background activity for patient traces. The automated detection has the potential to have an impact on the increased availability of health care professionals who dedicate time to performing the CFM annotations, the timing of medical intervention on patients, and potential for more detailed analysis in conjunction with other physiological data streams. Automation through the development within the Artemis platform could potentially reduce the time and effort for a health care professional to assess health data from numerous sources, it could also allow for health care professionals to control the rules implemented in Artemis to enrich clinical care within their unique environments. Automation may also provide the ability to apply clinical alerts to both synchronous and asynchronous data as well as the continuous processing of data in real-time

This research also explores an avenue that has not been addressed in regards to the Artemis project. No study has been undertaken that has attempted what has been accomplished in this thesis. As a result, the work in this thesis has been the first step in broadening the realm of the overall Artemis project into the field of brain monitoring. The study has demonstrated that an algorithm can be developed to identify sleep, classify background tracing and impedance levels which was one of the main goals of the study and is the primary contribution of this study.

7.2 Limitations and Suggestions for Future Work

Potential weaknesses in this research include: a lack of a known baseline or normal pattern that can be applied to every patient in the NICU, in addition to the fragility and possible

underdevelopment of these subjects. In relation to a standardized normal pattern, every patient who enters the NICU is different and their varying conditions results in different aEEG tracings. Despite standardized voltage values, interpretation is based on subjective expert analysis in which a small percentage of error must be considered when making this the gold standard comparison to the algorithms performance. The patients have often been born prematurely and as a result have been in intensive care for potentially long durations and this must be considered when analysing the data as the prematurity does not correlate to strong sleep-wake cycling patterns. These patients are often unhealthy which is why they are undergoing treatment in the NICU and as it was discovered through the study, not many display distinct cycling between sleep and wake stages. An ideal subject group for this type of study would be healthy term infants however this does not correlate to clinical practice and treatment and monitoring of patients under critical care. This is one of the primary challenges with the subject group and population of the study.

Another limitation is the algorithms' coding has been completed in MATLAB and not in SPL which the Artemis Platform uses as its primary coding language and due to technical complications in conversion of EEG signals. As outlined in Chapter 4, a theoretical design of the algorithms utilized in this thesis has been completed using Streams and SPL. Future work would attempt to implement this theoretical design in streams and test the implementation on this platform. This avenue of research presents future opportunities a few of which could include the use of full 24 hour data sets for all patients as well as the continuous analysis of the data in real-time.

The output of the algorithm was tested against the gold standard expert annotations however the algorithm's output was not compared to polysomnography data which is the true gold standard for determining sleep and wake states in neonates. Unfortunately due to the time constraints of the thesis, data from sleep studies utilizing polysomnography was not available. This would have been useful to potentially establish baselines for the algorithms and allowed for more accurate results in the detection of sleep-wake cycling in the population study in this thesis.

Relating to the lack of comparison to the gold standard polysomnography sleep data, the conversion of the 12-lead EEG data acquired from the sample sleep study that was to be used for this thesis could not be manually converted to aEEG for analysis. There is a complete absence of any form of description detailing how the software systems are programmed within the CFM devices used in the NICU for the output of converted aEEG from the raw EEG signal. Work was attempted to complete this task and achieved moderate success, however was not accurate enough to apply and use as a gold standard for sleep-wake cycling patterns for this thesis.

The algorithm that detects both sleep and the background classification can be improved but due to the time constraints for the completion of this Master's thesis, further refinements could not be made. Areas of improvement for future work with the algorithm include enhancing the sensitivity and specificity to increase its accuracy through the enhancement of the baseline generated for each patient so that the variance from this can allow for easier detection of state changes represented by the phenomenon of continuous and discontinuous cerebral voltage. Gaining additional knowledge from the health care professional's perspective to help minimize the subjectivity of the classifications would also be helpful in the future.

The data in this thesis was secondary use which is often associated with the criticism that the population was not specifically selected for the purposes of the study and that the data acquired may not be optimal. The data used in this research had to come from the NICU at The Hospital for Sick Children, Toronto, and from Artemis bed spaces in order to further the development of the overall Artemis Project. Many cases encountered throughout this research were unique making it almost impossible to standardize for testing purposes as all patients enrolled in the study met the standards for the inclusion criteria. Although an important and useful tool in the NICU for its predicative results, CFM still requires common definitions, parameters and a standardized reporting strategy (Griesmaier et al., 2013). Consequently, comprehensive interpretation of CFM is often limited by the lack of simple methods for reliably summarizing and quantifying the data.

7.3 Concluding Remarks

The research in automated detection of sleep-wake cycling and classification of the background tracing in neonatal aEEG has not been attempted before. Most work has involved EEG and the detection of seizures as well as the identification of sleep stages in infants. Cerebral function monitors have been developed with algorithms that alert when impedance levels eclipse a standard threshold but aside from this no other algorithms have been developed commercially or in research that have accomplished what this thesis has shown. Work has been attempted on the automation of seizure detection from CFM with limited success as pattern recognition is a difficult task to computerize, which was discovered in the work for this thesis.

This research has outlined a design for the automated detection of impedance levels, the primary determinant in whether the patient data is good or poor quality. This has a significant effect on the interpretation of the data as well as its relevance and meaningfulness to the health care professional monitoring the cerebral activity of the patient. In addition to this, a design was implemented for the automated detection of when a patient is in a period of sleep or not which was accomplished with expert annotations. Finally, criteria was defined for classifying the overall background activity of patient traces which is an extremely difficult task to automate considering the many variations of trace that can be seen based on the countless conditions a patient may present. The algorithm was able to produce results based on three categories of background classification which were those commonly used in the NICU by health care professionals in their neurological assessment of patients under cerebral function monitoring. These included continuous normal voltage, discontinuous normal voltage and continuous low voltage.

In conclusion, the primary goal of this thesis was to design an algorithm for the automation of sleep-wake cycling detection and the classification of term infant's overall background classification of the signal trace. In parallel with this goal, another objective was to determine whether or not it is an applicable problem to apply real-time computer software environment enabled by stream computing through this retrospective analysis of de-identified patient data. Research has shown that this is possible from the software development and computing end. Compatibility with the medical devices in the NICU is currently a concern, however new monitors are being developed and introduced into commercial practice which gives confidence

that the applicability and future work with what has been accomplished in this thesis will lead to innovative automated systems integrated into clinical practice.

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