Automatic Artefact Removal and CO₂ Prediction from the EEG Signals of Preterm Babies

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Abstract

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This dissertation describes research whose the purpose is to remove artefacts from the EEG signals of preterm neonates, thereby facilitating the prediction of carbon dioxide levels dissolved in the blood; this was achieved using key statistics obtained from the EEG. The EEG signals of neonates were recorded over a 24 – 36 hours period using LabVIEW (National Instruments) software and a XLTEK EMU40EX breakout head box with a 7-electrodes configuration. Raw EEG signals of neonates were processed using discrete wavelet transform multiresolution analysis to remove artefacts. A nonlinear energy operator was used to calculate the energy of the artefact-free neonate’s EEG signals. Threshold detection was used to find the bursts and the interburst intervals. Spectral power analysis was performed on every burst-interburst interval cycle to calculate the relative powers in the delta (0.5-3.5 Hz), theta (4.0-7.5 Hz), alpha (8-12.5 Hz), and beta (13-30 Hz) frequency bands in each burst-interburst interval cycle of the neonate’s EEG signals. A two minute arithmetic average of the interburst intervals, and the burst-interburst interval relative powers were used to develop a linear regression equation for the prediction of the carbon dioxide level. The EEG signals of different gestational age neonates were processed offline. Results were compared with the readings of ABL800 FLEX blood gas analyser (a blood gas machine) with a measuring range of 0.67 – 33.3 kilopascals. For the clean neonate’s EEG signals, the absolute prediction error lay between 0 – 1.0 kilopascals.
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Chapter 1: Introduction

This research is aimed at artefact removal from the electroencephalograph (EEG) of premature neonates and the estimation of carbon dioxide (CO$_2$) blood gas tension from the artefact-free premature neonate’s EEG signals. An infant with a gestational age of less than 36 weeks is categorized as a premature infant. It is the human brain that generates EEG signals. Therefore, the report starts with a brief introduction of the human central nervous system and the elements that generate these signals.

1.1 The Human Central Nervous System (CNS)

The Central Nervous System (CNS) of human being consists of nerve cells called neurons (figure 1-1) and non-nerve also called glial, neuroglia, or simply glia cells.

Neurons or nerve cells are electrically excitable cells that respond to stimuli and transmit information over distance, typically to other cells. Neurons consist of axons, dendrites and cell bodies. The axon is fibre like and transmits electrical impulses. Dendrites are the relaying stations and are connected to either the axons or dendrites of other cells. In the human brain each nerve is connected to approximately 10,000 other nerves, mostly through dendritic connections (S. Sanei, 2007).

![Figure 1-1 Structure of Typical Neuron](Anon., n.d.)

The neuroglia cells maintain the stability of the layered dielectric material called myelin. Neuroglia is essential for the proper functioning of the nervous system around the axon as they support and protects neurons in the brain and the peripheral nervous system.
1.2 Action Potential (AP)

The action potential (AP), as the name suggests is a change in the membrane potential. This potential is thus the information transmitted by the nerve and is caused by ion exchange across the neuron membrane. The AP is usually initiated in the cell body and normally travels in one direction. In figure 1-2, the membrane potential becomes more positive, producing a spike called the depolarization. After the peak of the positive spike the membrane potential starts falling and then under-shoots the resting state before returning to it, called the repolarization. It is reported that these spikes or the membrane potentials (action potentials) of most nerves last for 5 – 10 milliseconds with a conduction velocity of 1 – 100 m/s (S. Sanei, 2007).

APs are initiated by different types of stimuli e.g. chemical, light, electricity, pressure, touch, and stretching. A strong stimulus sets off an AP and a further increase in the stimulus causes the AP to appear and travel down the nerve. A very weak stimulus may produce small local electrical disturbance, but cannot produce a transmitted AP (S. Sanei, 2007).

![Action Potential Diagram](image-url)

Figure 1-2 Action Potential (Anon., n.d.)
1.3 The Electroencephalogram (EEG)

The electroencephalogram (EEG) is a recording of the electrical activity of the human brain. It is often captured at the surface of the scalp.

The basic hardware of EEG systems includes a pair of electrodes and a differential amplifier for each channel. An EEG montage is represented by EEG n, where n indicates the number of electrodes. Montage EEG 25, EEG 33, EEG 35, EEG 37, EEG 41, EEG 43, and EEG 64-256 are used for the electrodes placement to cover the whole head. An EEG with more electrodes with correct placement leads to a better resolution of topographic features (Christoph M. Michela, 2004). Mostly, electrodes are applied to the scalp in accordance with the International 10-20 System (The International Federation of Societies for Electroencephalography and Clinical Neuro – physiology Recommendations), shown in figure 1-3.

![Image of International 10-20 System](image.png)

Figure 1-3 International 10-20 System (Anon., n.d.)

Different regions of the brain are identified as Fp (front to polar), F (frontal), C (central), P (parietal), O (occipital) and T (temporal). Odd numbers refer to the left side of the scalp while even to the right side of the scalp, and Z to midline placements. In figure 1-3, A signifies to an ear channel.

For the international 10-20 system, clinicians measure the distance from the nasion to the inion and the head circumference. Then they mark precisely based on 10% - 20% intervals of those distances for electrode locations excluding ear electrodes.
The effective bandwidth of an adult EEG is typically 0 – 100 Hz (S. Sanei, 2007). For the assessment of the EEG signals of premature neonates, a bandwidth of 0.5 – 70 Hz is typically used (Mona C. Toet, 2002), (S. Victor, 2005). Highest maximum amplitude of 300 μV has been reported for a normal EEG of premature neonates (D. Selton, 2000). Typically, an EEG signal will be sampled at 200 Hz with a 16 bit resolution, generating 3200 bits-per-second (bps) of data per channel. The memory requirement for the recording system is considerable but easily accommodated by modern devices.

The EEG signals are generally categorized into alpha (α), beta (β), theta (θ), delta (δ), and gamma (γ) waves based on the frequencies.

Alpha waves (8 – 13 Hz) indicate relaxed awareness without any attention or concentration.

Beta waves (14 – 30 Hz) indicate high activeness e.g. thinking, attention, focus, problem solving. Beta waves are mostly found in normal adults. A high-level beta wave may be indicative of panic (S. Sanei, 2007).

Figure 1-4 Typical dominant Human Being Brain Waves in Adults
Theta waves (4 – 7 Hz) are an indication of consciousness and are related to the level of stimulation.

Delta waves (0.15 – 4 Hz) are associated with deep sleep and consist of bursts. The duration between successive bursts is called the inter-burst. These waves are normally found in babies as shown in figure 1-5.

In figure 1-5, time is indicated in terms of samples; at the given sampling frequency of 200 samples/ sec this corresponds to a 60 seconds data trace.

All waves of frequency above 30 Hz are named gamma waves, also called fast beta waves. The amplitudes of these waves are very low and their occurrence is rare (S. Sanei, 2007). Gamma waves indicate the event-related signals of the brain (Erol Basar, 1999).

1.4 Challenges in Preterm Neonate’s EEG Signal Processing

Figure 1-6 shows typical EEG signals of a premature neonate, featuring bursts of high electrical activity (bordered with a rectangle) interspersed by periods of electrical quiescence called the interburst interval (IBI). This contrasts with the EEG signals of term neonates and adults, which feature constant electrical activity.

The major challenge faced in capturing and processing the EEG signals of preterm infants was artefacts. Artefacts that significantly distort the background EEG can be visually detected. However, artefacts having high energy contents often copy burst patterns and cannot be visually detected (S. Bhattacharyya, 2013). Significant amount
of noise or high energy artefacts in preterm EEG signals always misled the detection of the burst, resulting in incorrect measurement of the interburst interval. This in turn increased the risk of incorrect derivation of clinical data based on the burst and IBI e.g. estimation of CO₂.

The medical dictionary defines artefact as “a structure not normally present, but produced by some external actions; something artificial. The distortion of a substance or signal which interferes with or obscures the interpretation of a study, or a structure that is not representative of a specimen’s in vivo state, or which does not reflect the original sample, but rather is the result of an isolation procedure, its handling or other factors” (Segen, 2012).

From a signal processing perspective, an artefact is a form of noise that is an unwanted energy. An artefact distorts the signal of the interest and severely affects the overall signal to noise ratio (SNR). An artefact is either physiological (internal) generated from the patient’s body e.g. body moment, respiration, cardiac activity, eye(s) blink, muscle contraction, or extra physiological (external) from the outside of the patient’s body e.g. loose electrodes, mains hum and electrical and radio frequency (RF) emissions from equipment located within the hospital (S. Bhattacharyya, 2013). Due to their non-stationary nature and variable time/frequency characteristics, artefacts are difficult to accommodate or remove. In digital signal processing, non-stationary refers to a process that has time varying statistics e.g. mean, variance, kurtosis. Artefact detection and
rejection algorithms are normally employed after signal pre-processing (typically the filtering stage).

1.5 Problem Statement

Carbon dioxide \((\text{CO}_2)\) is produced in the body as a by-product of metabolism, resulting from the chemical breaking down (burning or oxidation) of glucose, fats and amino acids with oxygen \((\text{O}_2)\); this is termed cellular respiration. The oxidation provides heat and energy necessary for the body to function.

Like every human, preterm infants inhale \text{O}_2 and exhale \text{CO}_2. The \text{CO}_2 level in the blood indicates the effectiveness of ventilation, i.e. whether the baby is able to move air in and out of the lungs well enough to obtain the \text{O}_2 it needs. Blood samples may be analysed to determine the level of \text{O}_2 and \text{CO}_2 dissolved in the blood. The blood gas level is measured in partial pressure exerted by oxygen and carbon dioxide gas molecules within blood, measured in kilo Pascals (kPa). “The \text{CO}_2 partial pressure of 5.5 – 8.0 kPa indicates abnormality in the preterm infants while \text{O}_2 partial pressure of 6.0 – 12.0 kPa indicates the normal condition.” (Ward, 2008). Note that a continuous supply of \text{O}_2 creates \text{O}_2 toxicity in the body.

It has been a common practice in hospitals to determine \text{CO}_2 blood gas tension from the blood samples taken from the preterm babies, using a blood gas machine. This has been in practice for many years. However, it is invasive and in many cases it is not desirable to take blood frequently.

Originally, an attempt was made by a research team (S. Victor, 2013) to develop software that non-invasively and continuously predicts blood gas \text{CO}_2 tension in preterm infants from their EEG signals without human intervention. The team observed an inverse relationship between blood gas \text{CO}_2 and relative power in the delta frequency band. A direct relationship between IBI and blood gas \text{CO}_2 was obtained. Thus the software core was based on a linear regression equation of two independent parameters i.e. IBIs and relative power in the delta frequency band of the premature EEG signals. No artefact removal technique was taken into consideration and artefactual data was discarded. Prolonged IBIs (typically because of loose electrodes and typically of more than 30 seconds), moving arithmetic average of 51 IBIs degraded the \text{CO}_2 estimation. Furthermore, for prolonged IBIs moving arithmetic average of 500 points of relative power in the delta frequency band was untimely.
Chapter 2: Artefact Removal Techniques and CO₂ Prediction

In relation to normal EEG activity, a signal with high instantaneous energy and high frequency, normally above 15 Hz, is characterized as artefact (M. van de Velde, 1998). Algorithms to detect whether an artefact is present are much easier to implement than removal. These algorithms require less processing power and are thus attractive in real time applications. First and second order moment are normally used in artefact detection algorithms. From a statistics perspective, a moment is a quantitative measure of the trend or shape of a set of points. The moment order is the power of every point of the set, e.g. the mean is the first order moment with power of one on every set point. The threshold is the core element in artefact detection algorithms. If the output of a particular moment crosses the threshold, that part of data or the time series is marked as artefact and the whole portion of the data crossing the threshold is discarded. Sometimes it is not acceptable to discard the data and thus the utilization of artefact detection algorithms in EEG signal processing is limited.

It is also reported that before crossing the threshold, signals are pre-processed to accentuate spikes and attenuate noise. Otherwise, the algorithm may perform poorly when the signal to noise ratio is much lower (I. Obeid, 2004).

Artefact removal algorithms on the other hand retain the information while removing artefact. Artefact removal algorithms are complex, thus memory and processing power requirements are significant.

1.0 Non-Linear Energy Operator (NLEO)

The energy in the signal is the integration or sum of the square of the signal’s amplitudes and defined in equation 2.1. The energy in the signal is frequency independent. The nonlinear energy operator (NLEO), also called Teager energy operator (TEO), is the energy in the signal that is the square of the instantaneous product of the signal’s amplitudes and frequency as defined in equation 2.2 and 2.3. The nonlinear energy operator depends on both the frequency and the amplitude of the signal (in contrast to just the overall energy). The nonlinear energy operator estimates the energy of a sufficiently sampled signal and is thus considered to be the superior and robust in the presence of noise (I. Obeid, 2004).
In the discrete domain

\[ E[x(n)] = \sum_{n=0}^{n-1} |x(n)|^2 \]  \hspace{1cm} (2.1)

\[ E[x(t)] = \left( \frac{dx(t)}{dt} \right)^2 - x(t) \frac{d^2 x(t)}{dt^2} \]  \hspace{1cm} (2.2)

The detection performance of the NLEO can be improved if it is followed by a window e.g. Bartlett, Hamming. This is known as a smoothing nonlinear energy operator (SNEO) and is defined as

\[ SNEO(k) = NLEO(k) * W_N(k) \]  \hspace{1cm} (2.4)

* represents the convolution operation and \( k \) is the size of window \( W_N \). It has been concluded that size of the window is an important parameter in SNEO. An increase in the window size decreases the number of spikes missed, but it degrades the detection of false spikes. The window size also decreases the gain (S. Mukhopadhyay, 1998). Furthermore, EEG signals are non-stationary in nature and thus very difficult to analyse. Therefore, a window of smaller size is preferable in retaining the stationary characteristics of each EEG segment.

Much research is reported and documented on NLEO and SNEO based artefact detection from EEG signals (N. Koolen, 2013), (K. Palmu, 2010), (H.J Park, 2002).

### 2.2 Correlation

Template matching based artefact detection is also used in some applications where the template called a reference signal, or some mathematical model of the signal to be analysed, is available in advance e.g. an electrocardiogram (ECG) template. Sometimes, before applying the template matching algorithm, a library of templates is developed. Much research is reported and documented that the Ballistocardiogram
(BCG) artefact does not resemble the ECG pattern, therefore, a template is proposed for the BCG artefact as a reference signal. BCG is a graphical representation of repetitive motions of the human body. Similarly, a well-defined template of eye movement to remove ocular artefacts is reported (A.Arabi, 2007). The paper describes how amplitudes between 0.9 to 1.10 of the maximum amplitude of the template on two bipolar channels Fp1-C3 and Fp2-C4 were marked as an ocular artefact. Finally, correlation was performed between all the bipolar channels to find simultaneous artefacts. All patterns with correlation coefficient greater than a predefined threshold were marked artefact. Similarly, a QRS complex template was correlated with all the bipolar EEG channels and then passed through a predefined threshold to remove ECG artefact.

The fundamental operation in template based artefact detection is the correlation coefficient and is expressed as

\[
y[n] = \sum_{k=0}^{M-1} x_1[k]x_2[n + k]
\] (2.5)

The output \(y[n]\) is passed through a threshold detector and hence categorized as threshold detection. This algorithm also performs poorly in low SNR environment.

### 2.3 Adaptive Filters

In the case when artefact and the signal of interest occupy the same bandwidth, the use of conventional filters is normally dismissed. In the presence of a reference signal, a template function, or a mathematical model, adaptive filters have been widely used. Much research is reported and documented in removing power line noise, ocular artefacts, and BCG artefacts from EEG signals (X.Navarro, 2012), (D.Olguin, 2005), (P. Celka, 2001). In removing ocular artefacts, electrode pairs Fp1 and Fp2 serves as the reference signal while in removing ECG artefacts, BCG template serves as the reference signal. It is claimed that the combination of adaptive filters with empirical mode decomposition effectively remove ECG artefact from the EEG of preterm infants (X.Navarro, 2012). Here, the recursive least square (RLS) algorithm was used. In real time applications where transients or artefacts are stationary, adaptive filters are the ideal choice.
In contrast to conventional filters, adaptive filters are time varying and non-linear systems (filters) that adjust their parameters (coefficients) in accordance with the input signal(s), based on some algorithm(s) e.g. mean square error between the desired signal and the actual output (Gaydecki, 2004).

An adaptive filter outperforms in the scenarios when the signal and the interference (noise) occupy the same bandwidth. This is the case when a broadband information signal is degraded by narrowband interference e.g. artefact in EEG signals, a speech signal degraded by generator noise, or the interference is spread across the spectrum of the signal i.e. the frequency of the interfering signal is continuously changing (Gaydecki, 2004). Figure 2-1 shows the spectrum of a narrow band signal (red), i.e. a sine wave of 50 Hz and broadband noise (blue), i.e. generated electronically using a transistor in an open collector configuration.

![Figure 2-1 Spectrum of Narrow Band Signal with Wideband Noise](image)

In summary the adaptive filter comprises a filter finite impulse response (FIR) or infinite impulse response (IIR), a feedback system to update the coefficients, and the input(s). The basic block diagram of an adaptive filter is shown in figure 2-2.
In figure 2-2, \(x(n)\) is the reference signal vector defined, \(d(n)\) is the desired signal, i.e. the combination of the reference signal and the information signal, \(w(n)\) represents the filter coefficient vector.

### 2.3.1 Least Mean Square Algorithm (LMS)

To obtain the optimal filter coefficients to minimize the mean square error, the LMS algorithm, a successive-approximation technique, is widely used. It is defined as:

\[
\begin{align*}
    w(n + 1) &= w(n) + 2\mu e(n)x(n) \\
    0 < \mu < \frac{1}{10MP_x}
\end{align*}
\]  

(2.6)

Where, \(\mu\) is the convergence rate. Large values of \(\mu\) make the algorithm unstable while lower values slow the convergence rate. An optimal range of values that ensures stability and provides a suitable convergence rate must satisfy the following condition.

In equation 2.7, \(M\) represents the filter order and \(P_x\) is the average power of the input signal.

### 2.3.2 Normalized Least Mean Square Algorithm (NLMS)

The NLMS is a modified form of the LMS algorithm. In the LMS algorithm, the performance measures i.e. stability and convergence speed depend on the step size \(\mu\) and the power of the reference signal. The NLMS is an important modification in the
LMS algorithm that optimizes the convergence speed while maintaining the desired performance (Kuo, 2001). The NLMS algorithm is expressed as

\[ w(n + 1) = w(n) + \mu(n)e(n)x(n) \]  \hspace{1cm} (2.8)

Where, \( \mu(n) \) is the adaptive step size and is computed as

\[ \mu(n) = \frac{\alpha}{MP_x + C} \]  \hspace{1cm} (2.9)

\( M \) represents the filter order and \( P_x \) is the average power of the signal segment of length equals to the filter order (in contrast to the average power of the overall signal). This updates \( \mu(n) \) after every iteration and thus it becomes adaptive. \( C \) is a small constant to avoid invalid division, while \( \alpha \) is a normalized step size that satisfies the criterion

\[ 0 < \alpha < 2 \]  \hspace{1cm} (2.10)

2.3.3 Adaptive filter evaluation

An experiment was designed to validate the performance of LMS and NLMS algorithms for real signals.

A BC184L transistor in an open collector configuration was used to generate thermal electrical noise. An LF351 op-amp in inverting configuration with a gain of 10 was used to amplify the noise signal from the amplifying transistor.

Due to the frequency and voltage limitation of the sound card used to record the data, a 5th order Sallen Key low-pass filter was also used. The filter’s output was combined with a pure sine wave using an LF35- based adder circuit. To verify the effectiveness of an adaptive filter the final SNR of the desired signal was set to be 0.33 by adjusting the gain of the signal and noise amplifiers.

This corrupted sine wave called the *desired signal* and the noise called the *reference signal* was recorded for 15.0 seconds through a stereo jack, using both MATLAB and Cool Edit, the latter being an audio file editing software suite. The sample frequency was 48 kilo samples per second (ksps) and the resolution was 16 bits.
As the two signals i.e. the reference signal and the desired signal are correlated, a dual input and a single output adaptive filter configuration with the NLMS and LMS algorithms was used.

Figure 2-3 Results of LMS and NLMS Algorithm

Figure 2-3 shows the corrupted signal (blue), the LMS output (top red) and NLMS output (bottom red). By comparing both the plots, it is clear that for the same filter order and with shorter step size, NLMS converged faster than the LMS algorithm with longer step size.

2.3.4 Limitations of Adaptive Filters

Regardless of the algorithm and structure used, there are some limitations associated with adaptive filters in EEG signal processing.
In a stationary environment, the adaptive filter normally converges to the optimum point due to constant shape and orientation of the error performance surface, i.e. the mean square error. But for non-stationary signals e.g. EEG signals, the shape and orientation of the cost function fluctuates, hence the adaptive filter not only seeks for the minimum point of the surface but also tracks the changing position of the minimum point. Eventually, this leads to a significant lessening of the performance; further fluctuations in the cost function worsen the performance and the adaptive filter may not track the signal variations completely. There are some algorithms that overcome this issue but at the cost of additional complexity and thereby an increase in processing power and memory requirements, beside the processing speed (Ifeachor, 2001).

The performance of the adaptive filter relies on the correlation between the reference signal and the desired signal. Furthermore, very weak or theoretically zero correlation between the reference and the information signal is not always practically possible but it positively affects the adaptive filter performance. In some applications, the reference signal may be contaminated by sporadic noise or interference, therefore leading to the cancellation of the desired output (Ifeachor, 2001).

In some applications, the reference signal is not readily available and hence the use of adaptive filter is limited. In EEG signal processing, there is no reference signal reported to remove moment artefact.

### 2.4 Wavelet Transform

Wavelet transform (continuous and discrete) is also a widely used technique in signal segmentation, artefact detection and rejection and feature extraction from a variety of biomedical signals (H.J. Niemarkt, 2008), (J.P Turnbull, 2001), (G. Calvagno, 2000). The discrete wavelet may be applied to effectively reject artefacts that are well localized in time and frequency. It is claimed that the combination of DWT and independent component analysis (ICA) effectively removes ECG artefacts from EEG signals. (S. Calcagno, 2014).

A transform is an alternative way of representing a signal and extracting the information embedded within one domain e.g. frequency or space, that is not readily available in the original domain e.g. time. Mathematically, this form of signal representation requires a summation or an integration of the inner product of the kernel and the signal under investigation. The kernel is also called the basis function or
template function. The transform yields a number of coefficients or a sequence that shows the closeness of the kernel with the signal of the interest. The higher the values of the coefficients, the greater the similarity between the signal and the kernel. This means that a transformation converts the original data in the form of kernel. The mathematical benefit of a transform is the simplicity in finding the solutions of the system or the set of equations. This is because some complex mathematical operations such as convolution in one domain become simple in another domain.

Mathematically, any transform can be represented as:

$$c_n = \int_{-\infty}^{\infty} x(t)\psi_n^*(t) \, dt \quad (2.11)$$

Where, * shows the complex conjugate of the kernel \(\psi(t)\).

Table 2-1 shows some of the popular transforms with their kernels.

<table>
<thead>
<tr>
<th>Transform</th>
<th>Conjugated Kernel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fourier Series</td>
<td>(e^{-jk\omega_0 t} = e^{-jk\frac{2\pi}{T_0}})</td>
</tr>
<tr>
<td>Fourier</td>
<td>(e^{-j\omega t}) or (e^{-j\omega m})</td>
</tr>
<tr>
<td>Laplace</td>
<td>(e^{-st}), (\text{Where } s = \delta + j\omega)</td>
</tr>
<tr>
<td>DFT</td>
<td>(W_N^{kn}), (\text{Where } W_N = e^{-j\frac{2\pi}{N}})</td>
</tr>
<tr>
<td>STFT</td>
<td>Windowed (e^{-j\omega t})</td>
</tr>
<tr>
<td>Z</td>
<td>(z^{-1}), (\text{Where } z = re^{j\omega})</td>
</tr>
</tbody>
</table>

Table 2-1 List of Transforms with kernels
2.4.1 Basic Wavelet Transform Theory

The basic theory and mathematics of the wavelet transform are as described in section 2.4, except for the kernel. In the wavelet transform the kernel is a wave of a small duration, called a mother wavelet or prototype wavelet that satisfies the conditions of being absolutely integrable and square integrable. Furthermore, the mother wavelet must have zero mean and square norm one. Mathematically,

\[ \int_{-\infty}^{\infty} \psi(t) \, dt < \infty \]  
(2.12)

\[ \int_{-\infty}^{\infty} |\psi(t)|^2 \, dt < \infty \]  
(2.13)

\[ \int_{-\infty}^{\infty} \psi(t) \, dt = 0 \]  
(2.14)

\[ \int_{-\infty}^{\infty} |\psi(t)|^2 \, dt = 1 \]  
(2.15)

The scaling (dilation) by a factor ‘\(a\)’ and shifting (translation) by a factor ‘\(b\)’ generate a family of wavelets called wave table under Morlet’s formula described in equation 2.16.

\[ \psi_{a,b}(t) = \frac{1}{\sqrt{a}} \psi \left( \frac{t - b}{a} \right) \quad \exists \ a, b \in \mathbb{R} \ \forall \ a \neq 0 \]  
(2.16)

Therefore, the wavelet transform of an arbitrary signal \(x(t)\) can be expressed as:

\[ Wt(a, b) = \langle x, \psi_{a,b} \rangle = \frac{1}{\sqrt{a}} \int_{-\infty}^{\infty} x(t) \psi^* \left( \frac{t - b}{a} \right) \, dt \]  
(2.17)

2.4.2 The Necessity of the Wavelet Transform

A careful look at the kernels shown in Table 2-1 reveals that these transforms have exponential kernels extending over infinite period of time and with some restrictions,
conform to the Fourier Transform. Therefore, these transforms provide global localization of the signal in the frequency domain rather than local. This means that any local information in time is spread out over the whole frequency range. Therefore the Fourier transform cannot characterize signals that manifest non-stationary transients of short duration or continuous changes in the signal frequency.

Due to this fact, signals are captured at discrete time intervals within a total duration of measurement and processed in a discrete fashion. Therefore, the discrete Fourier transform (DFT) is the most viable transform that produces a discrete spectrum of discrete time signals as opposed to the analytic Fourier transform and its extensions e.g. Laplace, Z- transform. The number of arithmetic operations required to obtain a DFT is proportional to $N^2$ where $N$ is the length of the input signal. Hence, computational time increases as the square of the number of samples. The Fast Fourier transform (FFT) solves the problem of increased processing time by recursively breaking down the large DFT into many smaller DFTs. This is achieved by dividing the $N$-point data into two $N/2$ (radix-2) or $N/4$ data (radix-4) points at each step. The FFT requires $N \log(N)$ arithmetic operations as compared to the DFT’s $N^2$ arithmetic operations. The computational frequency resolution of an $N$ point DFT is $F_s/N$ where $F_s$ is the sampling frequency. Therefore, an FFT characterizes the signal for a limited time and only calculates the result for certain discrete frequency values called frequency bins.

There are two practical problems associated in calculating the DFT/ FFT: spectral leakage and aliasing.

Spectral leakage will always occur in a DFT since it is essentially generating a set of discrete harmonics from a continuous signal; since there is no information regarding the frequencies between frequency bins, the energy is smeared across adjacent bins. Spectral leakage can of course be avoided by an infinite time record, yielding a continuous spectrum, but this is not practically possible. However, it can be minimised by spectrum sufficiently long record and the use of a window function. Windowing the signal i.e. multiplying the signal with a window function can lessen the effects of the spectral leakage while avoiding the constraint associated with the above solutions but at the cost of contributing its own frequency information to the signal.

The size of the window auspiciously affects the windowed signal and thus the main lobe’s height increases while its width becomes narrower and thereby the DFT/ FFT’s
spectrum becomes closer to the true spectrum. On other the hand, an increase in the
window size also increases the peak of the side lobes as a ratio of the main lobe to the
first side lobe of 13 dB (Kuo, 2001).

Aliasing is due to the violation of Shannon’s sampling theorem i.e. the sampling
frequency must be at least twice of the maximum frequency component contained in
the signal or the bandwidth (in terms of a broadband signal).

The Short time Fourier transform (STFT) is an FFT with the analysis window of a
certain fixed length that slides through the signal with the assumption that the signal
segments within the window function are stationary. In this way, this transform not
only reduces the effects of spectral leakage but also provides time-localized frequency
information with uniform time-frequency resolution. Adjustment of the window size
effectively controls the time-frequency resolution.

According to the uncertainty principle, time and frequency cannot be determined with
complete accuracy at the same time. Specifically, the product of the time and frequency
resolutions is lower bounded by:

$$\Delta \tau \ast \Delta f \geq \frac{1}{4\pi}$$

(2.18)

Where, $\Delta \tau$ is the root mean square time-width of the windowing function, i.e. the time
resolution and $\Delta f$ is the root mean square of the bandwidth of the windowing function
known as the frequency resolution (X.Gao, 2011).
Equation 2.16 suggests that a set of different wavelet functions/templates functions can be obtained with different combinations of scaling factor ‘a’ and the translation factor ‘b’ from the mother wavelet. This set of template functions provides a window of variable size as oppose to the fixed window size of the STFT. Because of the set of template functions, the wavelet transform elegantly solves the issue of time-frequency resolution as shown in figure 2-4.

2.4.3 **Discrete Wavelet Transform (DWT)**

The majority of real world signals are available in discrete form and therefore the analytical form of signal \( x(t) \) is generally not accessible. Furthermore, a continuous wavelet transform leads to redundant information (coefficients) if the scaling factor ‘a’ and the translation factor ‘b’ are varied continuously. This would increase the computational time and memory requirement of any system based on this transform. This redundancy can be controlled while preserving the information content in the original signal by the discretization of the scaling and the translation factor. A natural way of discretization is the logarithmic discretization and is expressed as:

\[
\begin{align*}
  a &= a_0^j \\
  b &= kb_0a_0^j \\
  a_0 < 1, j \in Z, k \in Z, b_0 \neq 0
\end{align*}
\]  

(2.19)

\( Z \) in equation 2.19 is an integer. By replacing “a” and “b” of equation 2.16 with equation 2.19, we get
\[ \psi_{j,k}(t) = \frac{1}{\sqrt{a_0^j}} \psi \left( \frac{t - kb_0a_0^j}{a_0^j} \right) \quad (2.20) \]

The dyadic discretization i.e. \( a_0 = 2, b_0 = 1 \) constitutes an orthogonal basis wavelet. For the dyadic discretization, equation 2.20 becomes

\[ \psi_{j,k}(t) = \frac{1}{\sqrt{2^j}} \psi \left( \frac{t - 2^j k}{2^j} \right) \quad (2.21) \]

Hence equation 2.17 becomes

\[ Wt(j,k) = \langle x, \psi_{j,k} \rangle = \frac{1}{\sqrt{2^j}} \int_{-\infty}^{\infty} x(t) \psi^* \left( \frac{t - 2^j k}{2^j} \right) dt \quad (2.22) \]

Signal reconstruction is only possible when some dual function of the template wavelet exists. Signal reconstruction is expressed as:

\[ x(t) = \sum_{j,k} Wt(j,k) \psi_{j,k}(t), \quad \forall \psi_{j,k}(t) \ni \bar{\psi}_{j,k}(t) \quad (2.23) \]

### 2.4.4 Multiresolution Analysis (MRA)

DWT based multiresolution processing helps in feature extraction, e.g. peak detection. The DWT decomposes the signal into approximation and detailed coefficients. A multiresolution of the space \( L^2(\mathbb{R}) \) consists of a sequence of successive approximations subspaces \( \{V_j, j \in \mathbb{Z} \} \) that satisfies the following properties.

- **Monotonicity**, i.e. \( \cdots \subset V_2 \subset V_1 \subset V_0 \)

- **Completeness**, i.e. \( \cap V_j = \{0\}; \cup V_j = L^2(\mathbb{R}), \forall j \in \mathbb{Z} \)

- **Dilation Regularity**, i.e. \( x(t) \in V_j \iff x(2^j t) \in V_0 \)

- **Translation Invariance**, i.e. \( x(t) \in V_0 \Rightarrow x(t - n) \in V_0, \forall n \in \mathbb{Z} \)
Existence of orthogonal basis, i.e. \( \exists \Phi(t) \in V_0, \int \Phi(t - n)\Phi(t - m)dt = \delta_{m,n} \)

![Illustration of (a) Inclusion Relationship (b) Wavelet Subspaces](image)

Figure 2-5 Illustration of (a) Inclusion Relationship (b) Wavelet Subspaces

From the above properties, it is clear that all closed subspaces \( \{V_j, j \in Z\} \) are formed from the same scale function \( \Phi(t) \) with different translation values as shown in figure 2-5 (a).

It is also true that the closed subspaces \( \{V_j, j \in Z\} \) holding the inclusion relationship are not orthogonal, and thus the basis cannot be used as the orthogonal basis in \( L^2(\mathbb{R}) \) space. To find the orthogonal basis in \( L^2(\mathbb{R}) \) space, we define \( W_j \) as an orthogonal complement of \( V_j \) in \( V_{j-1} \), mathematically,

\[
V_{j-1} = V_j \oplus W_j
\]  

(2.24)

For \( j < J \),

\[
V_j = V_j \oplus \sum_{k=0}^{j-1} W_{j-k}
\]  

(2.25)
Where, the $W_j$ are orthogonal, and form the $L^2(R)$ space as:

$$L^2(R) = \bigoplus W_j, \forall j \in Z$$  \hspace{1cm} (2.26)

The $W_j$ spaces inherit the scaling property from the $V_j$, i.e.

$$x(t) \in W_0 \iff x(2^{-j}t) \in W_j$$  \hspace{1cm} (2.27)

The basis for $V_j$

$$\Phi_{-1,k}(t) = 2^\frac{j}{2}\Phi(2t - k) = \sqrt{2}\Phi(2t - k), k \in Z$$  \hspace{1cm} (2.28)

Therefore,

$$\Phi(t) = \sum_k \sqrt{2}\Phi(2t - k) = \sum_k h[k]\Phi(2t - k), \forall k \in Z$$  \hspace{1cm} (2.29)

$\Phi(t)$ is the scale function, also called father wavelet, because it derives an approximation in $V_0$. Similarly the basis for $W_{-1}$

$$\psi(t) = \sum_k (-1)^k h[-k + 1]\Phi(2t - k) = \sum_k g[k]\Phi(2t - k)$$  \hspace{1cm} (2.30)

$\psi(t)$ is the wavelet function also called mother wavelet because it derives detail in $W_0$.

$h[k]$ and $g[k]$ in equation 2.29 and 2.30 are symmetric, where

$$\begin{cases} h[k] = \langle \Phi, \Phi_{-1,k} \rangle \\ g[k] = \langle \psi, \Phi_{-1,k} \rangle \end{cases}$$  \hspace{1cm} (2.31)

The dual scale relationship between the scale function and the wavelet function only exists between the two successive $j$, e.g., $j$ and $j-1$. 

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2.5 Independent Component Analysis

Independent Component Analysis (ICA) is another popular technique used in artefact removal and features extraction from biomedical signals. Much research has been done and documented in EEG signal analysis and artefact removal from EEG signals using ICA (S. Bhattacharyya, 2013), (G. R. Naik, 2011), (A. Hyva¨rinen, 2000), (T. Jung, 2000).

2.5.1 Limitations of ICA

In real time and offline EEG signal processing, the major restriction in implementing ICA methods is the order of the independent components and that remains uncertain. This is due to the fact that the sources (i.e. EEG signals and artefacts) and the mixing matrix both are unknown.

Secondly, it is also not possible to calculate the energies or statistical variances of EEG signals and artefacts due to the same reason that these both and the mixing matrix are not known.

2.6 CO₂ blood gas tension in Preterm Babies

The arterial partial pressure of CO₂ indicates the amount of CO₂ dissolved in the blood; it may be considered as the balance between CO₂ production and consumption in the human body. It ranges from 4.6 – 6.0 kilo Pascal (kPa) in healthy infants.

In preterm infants on the first days after birth the effect of CO₂ blood tension on cerebral electrical activity and fractional oxygen extraction is very important. Studies have been conducted in an attempt to develop the relationship among measurable parameters from EEG signals of preterm infants (S.Wikstrom, 2011), (Wei Zhou, 2008), (S. Victor, 2005), (S. Victor, 2005). Studies of EEG signals from groups of preterm infants with different gestation age and birth weight show that for the first three days after birth, the total power in the EEG and the relative power in the delta (0.5–3.5 Hz) frequency band increase. In contrast, the relative powers in the alpha (8.0-12.5 Hz), beta (13-30 Hz), and theta (4.0-7.5Hz) bands decrease significantly for the first three days of birth. Furthermore, strong relationships between CO₂, EEG measurements and cerebral fractional oxygen extraction (CFOE) for the first two days were found. It was deduced that the relative power in the delta frequency band was an
inverse relationship with the CO\(_2\) level (mm Hg), while a direct relationship was established between IBI and CO\(_2\) level. The EEG with the highest power was found at CO\(_2\) level of 5.1 kPa. It is also reported that excessive CO\(_2\) in the blood, or hypercapnia, and a low glucose level increase the incidence of brain damage in preterm infants while moderate changes in both affect the EEG power and continuity (Wei Zhou, 2008).

2.6.1 Existing CO\(_2\) Blood Gas Determination

Software has been previously developed by the team at the University of Manchester and St. Mary’s Hospital that continuously estimates CO\(_2\) blood gas level in preterm infants from the EEG signals, as opposed to the conventional method of measuring CO\(_2\) from the blood samples taken from the infants, which, for obvious reasons, cannot be taken with any great frequency (S.Victor, 2013).

Digital recordings, one hour per week, with a sampling frequency of 200 Hz were conducted for four weeks. Nine disposable cup shaped silver-silver chloride electrodes with EEG paste were placed at Fp1, C3, T3, O1, Fp2, C4, T4, O2 and Cz. The NELO method defined in equation 2.36 followed by a smoothing window of 203 samples was used for the detection of burst and thus the ascertained IBI values. It is claimed that a strong relationship between IBI and the gestational age exists (S. Victor, 2014 (In Press)), (S.Victor, 2013).

\[
E(n) = x(n)x(n - 3) - x(n - 1)x(n - 2)
\] (2.36)

The NELO method defined in equation 2.37 followed by a smoothing window of 203 samples was used for artefact detection. Additionally, a 4th order Butterworth IIR band stop filter with a centre frequency of 50 Hz and a bandwidth of 2 Hz was applied to remove noise.

\[
E(n) = x(n)^2 - x(n + 1)x(n - 1)
\] (2.37)

A window of 400 samples with an overlap of 200 samples was used for spectral analysis. A Hanning window was convolved with each signal epoch to reduce spectral leakage between frequency bins. The relative powers were calculated by dividing the
value of their associated frequency range by the total of the frequency bins up to and including 30 Hz.

A linear regression equation defined in equation 2.38 was used for the prediction of the partial pressure of CO$_2$.

\[
PCO_2 = m + a. IBI - b. RP\Delta
\]  

(2.38)

Where \(m\), \(a\), and \(b\) are constants with values 6.32, 0.3, and 2.111 respectively. \(RP\Delta\) is the smoothed relative power in the delta frequency band (0.5-3.5 Hz) defined as:

\[
RP\Delta = \frac{\ln(RP\Delta_{int})}{(1 - \ln(RP\Delta_{int}))}
\]  

(2.39)

Where, \(RP\Delta_{int}\) is the actual relative power in the delta frequency band.
Chapter 3: CO₂ Determination Software

Description

There is always a real need for reliable, continuous and non-invasive neuromonitoring to sick preterm neonates as they are most vulnerable in first 48 hours after birth. Nearly all preterm infants of gestational ages less than 28 weeks need mechanical ventilation. To determine the level of agreement between partial pressure of blood CO₂ measured using blood gas analysis and CO₂ predicted by the automatic analysis of brain electrical activity in preterm neonates, a prospective observational study was performed at the Newborn Intensive Care unit, St Mary’s Hospital for Women and Children, Manchester.

3.1 Consent and Ethical Approval

Parents were approached and provided adequate information if the mother was present in early preterm labour. All attempts were made to provide adequate time to get consent prior to birth. Due to difficult and stressful situation for parents who have a very sick preterm neonate to make quick decisions, routine EEG recordings were done. At all stages it was made clear to the parents that they remain free to withdraw their consent at any time. The study was approved by the Oldham Local Research Ethics Committee.

3.2 Criteria

The preterm neonates inducted for the study were less than 30 weeks gestational age and less than 24 hours old. Babies were ventilated through an endotracheal tube (a plastic breathing tube used to assist a patient in breathing) and admitted to the Newborn Intensive Care Unit, St Mary’s Hospital Manchester. Preterm neonates with postnatal diagnosis of congenital brain malformation were excluded.

3.3 Digital EEG Recordings

Digital EEG recordings were carried out soon after birth and lasted for 24 – 36 hours for all preterm neonates who met the criteria, using a sampling frequency of 200 Hz. In accordance with international 10-20 system, seven electrodes were placed on the scalp at Fp1, C3, O1, Fp2, C4, O2 and Cz positions by a trained neurophysiologist. To avoid pain and distress to the preterm neonate, disposable cup-shaped silver-silver chloride electrodes with EEG paste were used instead of needle electrodes. A Commercially...
available XLTEK EEG breakout head box (Natus) with 16 bit resolution and LabVIEW software (National Instruments) were used. A 6-channel configuration i.e. Fp2-C4, C4-O2, Fp1-C3, C3-O1, C4-Cz, and Cz-C3 was formed from the 7-electrode configuration. The same configuration is currently in use for further recordings.

3.4 Block Diagram of the Software

![Block Diagram of the Software](image)

3.5 Data Segmentation

For time domain analysis, a matrix \( M \) was formed by sliding a rectangular window of 0.25 sec (50 samples) using each channel. The number of columns of the matrix represented the segment length of each channel and the number of rows of the matrix was equal to the number of channels.

\[
M = c \cdot w_N
\]  

(3.1)

Where \( c \) is the channel vector.

\[
c = [c_1 \cdots c_N]^T
\]

(3.2)

\( T \) represents the transpose operation and \( w_N \) is the rectangular window of 0.25 second length.

For time domain analysis, a smaller window was chosen due to the non-stationary nature of the burst and artefact. For frequency domain analysis, multiple channels were
combined into one channel $CH$ by summing instantaneous amplitudes across all channels.

$$CH = \sum_{j=1}^{N} c_j$$  \hspace{1cm} (3.3)

Where, $c_j$ is the $j^{th}$ channel and $N$ is the total number of channels.

The channel $CH$ was then segmented by multiplying a rectangular window of 4.0 seconds (800 samples). The longer window was chosen to get the appropriate frequency resolution \((200/800 = 0.25 \text{ Hz})\) and ultimately to separate the closely spaced frequencies.

**3.6 Artefact Removal**

Every row of the matrix $M$ was pre-filtered with a $4^{th}$ order high pass Butterworth filter with a cut off frequency of 0.5 Hz to remove slow transients. This was followed by a discrete wavelet noise removal technique to filter out low amplitude noise. Due to its orthogonal and symmetrical properties, a Db02 mother wavelet with a decomposition level of 4 was used. Furthermore, a Db02 results in the minimum number of taps (i.e. 4 taps) for high and low pass filters used in analysis and reconstruction of the signal of interest (figure 3-2).

![Figure 3-2 Low and High Pass Filter Characteristics](image)

In figure 3-2, the x-axis show the coefficient number e.g. 0, 1 and the y-axis indicates the value of the respective coefficient. Therefore, an equation representing the filter can be obtained.
\[ H(Z) = 0.5 + 0.8Z^{-1} + 0.2Z^{-2} - 0.1Z^{-3} \]  
\[ G(Z) = -0.1 - 0.2Z^{-1} + 0.8Z^{-2} - 0.5Z^{-3} \]

Where \( H(Z) \) and \( G(Z) \) represent the low pass and high pass filter respectively.

Discrete wavelet transform multiresolution analysis (MRA) was used on every pre-filtered row of the matrix \( M \) to remove artefacts and preserve the information. A Db02 wavelet with a decomposition level of four was used (figure 3-3).

\[
\begin{align*}
\text{In figure 3-3, } h[n] & \text{ and } g[n] \text{ is the low pass and high pass filters respectively. An arrow pointing downwards (\downarrow) indicates down sampling of the incoming signal or array by a factor of 2. This is why the use of a discrete wavelet results in dyadic frequency resolution (spacing) in contrast to the linear frequency spacing of the Fourier transform i.e. } \Delta f = f_s / N. A_4 \text{ and } D_4 \text{ represent the approximation and detail coefficients obtained at each level respectively.} \\
\text{During the reconstruction, all the detail coefficients were discarded and only approximation coefficients were retained. The final frequency of the clean signal for further processing i.e. calculation of burst and IBI was therefore } 200/2^4 = 12.5 \text{ Hz. As per the analysis, the maximum power in the EEG signals of preterm infants was found 60\% - 90\% in the delta frequency band and 2\% - 20\% in the other frequency bands (mostly in alpha frequency band). Therefore, any further increase in the MRA level may suppress the real burst or due to the frequency dependence of the NLEO, the threshold setting may require readjustment. When an artefact is not localized, the artefact removal capability of MRA may be compromised.}
\end{align*}
\]
3.7 Burst and Inter-Burst Interval (IBI)

The NLEO defined in equation 3.6 was used to calculate the energy of every artefact-free row of the matrix $M$.

\[
E(n) = c_i(n)c_i(n-3) - c_i(n-1)c_i(n-2), \forall i = 1, \cdots, N \tag{3.6}
\]

Where, $c_i$ is the $i^{th}$ channel that corresponds to the $i^{th}$ row of the matrix $M$ and $n$ indicates the sample number of the $i^{th}$ channel. To obtain the overall value of the energy, the NLEO output was smoothed by a window of length equal to the number of columns of the matrix $M$.

\[
E(n)_{\text{smooth}} = \sum_{n=1}^{50+n-1} |E(n)| \tag{3.7}
\]

If the signal $E(n)_{\text{smooth}}$ was greater than or equal to the threshold of 50000, present in at least 50% of the available channels and lasted for at least 2.0 seconds it was considered as a burst. All events of less than 2.0 seconds between two consecutive bursts were also counted as a part of the burst and thus both bursts were considered a single event. During an IBI the EEG activity was normally very low in magnitude compared to the burst and therefore $E(n)_{\text{smooth}}$ was below the threshold. All spikes of less than 2.0 seconds between two consecutive IBIs were counted as a part of the IBI and thus were joined together into one (figure 3-4).
The start of the burst and the end of the following IBI was called the burst-IBI cycle (figure 3-5).

A threshold of $10^7$ was used to detect any residual artefact. $E(n)_{\text{smooth}}$ crossing the threshold on any of the channel was called a residual artefact (i.e. not cleaned by pre-filtering and MRA processing). In the presence of any residual artefact all the temporal and spectral calculations were paused for the whole of its duration.

The start of the burst ($BS$) and the end of the burst ($BE$) was calculated using the Boolean operation defined in equation 3.8.

$$\begin{align*}
    n(BS) &= (BP(n) \oplus BP(n - 1)).BP(n) \\
    n(BE) &= (BP(n) \oplus BP(n - 1)).BP(n - 1)
\end{align*}$$

(3.8)

Where $n$ is the sample number and $BP$ is the Boolean state indicating the presence of a burst.
The burst and IBI durations were based on the number of samples, defined in equation 3.9 and 3.10.

\[
IBI_{\text{duration}} = (n + +) - n(BE) \forall BS
\]  
\[
Burst_{\text{duration}} = (n + +) - n(BS) \forall BE
\]

Each of the burst and IBI durations obtained from the above equations were divided by the sampling frequency to yield the duration in seconds.

### 3.8 Spectral Analysis

To reduce the spectral leakage, a Hanning window was convolved with each array (800 samples) of the channel CH. The total absolute power i.e. power in all the frequency bins (2-120) from 0.5 Hz to 30 Hz and all the relative powers i.e. relative power in delta (0.5-3.5 Hz), theta (4.0-7.5 Hz), alpha (8-12.5 Hz), and beta (13-30 Hz) frequency bands were calculated. For the duration of every burst-IBI cycle, all relative powers were arithmetically averaged. Equation 3.11 was used to compute the normalized power spectrum.

\[
S_{xx} = \frac{|F(X)|^2}{n^2}
\]

Where, \( n \) is number of samples and the length of \( X \) is the valid power of 2. \( F(X) \) represents the Fourier spectrum of the signal \( x[n] \).

### 3.9 Linear Regression Equation

Due to the lack of mathematical model(s) to describe the preterm neonate’s EEG signals, a truth table was constructed containing blood gas analysis and 2-minute arithmetic average values of all the EEG parameters produced by the software (IBI length and relative powers in all frequency bands). Only good quality EEG signals of 36 hours obtained from low electrode impedance (typically below 5.0 Ω) having a wide range of blood gas values were selected for the analysis. The quality of the EEG trace was determined and validated by a team of expert neurophysiologists at St Mary’s Hospital. The selected signals were used to develop a linear regression equation using
the Statistical Package for the Social Sciences (SPSS) software package. It was observed that the relative power in alpha frequency band has the highest significance in relation to the blood gas CO$_2$. The software developed the linear regression equation (equation 3.12) and excluded all the parameters of low significance.

\[
PCO_2 = C + 38.718RPA
\]  

(3.12)

Where \( RPA \) indicates the relative power in the alpha frequency bands and \( C \) is a constant of 2.297.
Chapter 4: Results and Discussion

The results of four individual but interrelated areas of the research i.e. artefact removal, detection of burst and IBI, relationship between the spectral and temporal parameters of premature EEG and blood gas CO₂, and finally the estimation of CO₂ blood gas are presented in this chapter.

4.1 Artefact Removal

The effectiveness of discrete wavelet MRA and a discrete wavelet de-noising technique following a 4th order high pass Butterworth filter in removing artefacts from the EEG signals of preterm neonates is presented. These techniques were implemented in the LabVIEW environment using the advanced signal processing toolkit. Figure 4-1–4-4 indicates the effectiveness of these techniques as the majority of artefacts (circled red) and high frequency artefacts (noise) present on channel C4-Cz are filtered out. The presence of these artefacts was confirmed by the expert neonatologist with vast experience in premature EEG at Newborn Intensive Care Unit, St Mary's Hospital for Women and Children.

Figure 4-1 Raw one minute premature EEG trace-1
Figure 4-2 Processed one minute premature EEG trace-1

Figure 4-3 Raw one minute premature EEG trace-2
4.2 Detection of Burst and IBI

Bursts were detected using the signal $E(n)_{smooth}$; a burst was considered valid if it was greater than or equal to the burst threshold, present in at least 50% of the available channels and lasted for at least 2.0 seconds. All events of less than 2.0 seconds between two consecutive bursts or between two consecutive IBIs were also counted as a part of the burst or the IBI respectively.
For the validation of these results, eight fifteen minute segments of artefact free premature EEG signals were randomly selected from the available traces, each of 24 – 36 hours. From the selected traces, two two-minute traces were randomly chosen for marking by an expert neonatologist. Figure 4-5 indicates the detection of bursts and IBIs in a 60 second segment by the software and the expert neonatologist.

![IBI Detection Graph](image)

Figure 4-6 Two Independent Detections of IBIs

Figure 4-6 shows the IBI detection by the software and marked by an expert neonatologist from randomly selected, two minutes artefact-free traces. At event (IBI) number 7 a much longer IBI was marked by the expert by joining two separate IBIs i.e. IBI number 7 and 8. Similarly IBI number 2 and 5 remained undecided by the expert. The discrepancy between the IBI detected by the software and marked by the expert can be minimized by splitting the two minute trace into two one minute traces.
4.3 Relationship of Premature EEG Parameters with Blood CO₂

A good quality EEG trace of 36 hours duration having a wide range of blood CO₂ values, determined and validated by an expert neonatologist was analysed. A two minute arithmetic average of IBI was used in developing a relationship between blood CO₂ and the IBI. SPSS was used for the analysis, which confirmed a direct relationship (with correlation coefficient of 0.71) between the IBI and CO₂ (figure 4-7). Similar relationships between blood CO₂ and the IBI have been developed in two independent observational studies (S. Victor, 2005), (S. Wikstrom, 2011). In the first study all ten minute IBIs were manually marked while in the second study all ten minute IBIs were automatically marked by the software. Ten minutes manual averages of IBIs were then analysed.

![Figure 4-7 Relationship between Blood CO₂ and the IBI](image)

Longer IBIs are indicative of low EEG activity and the accumulation of blood CO₂.
For spectral analysis, two minute arithmetic averages of burst-IBI cycle relative power in the delta, theta, alpha and beta frequency bands were used.

Figure 4-8 indicates an inverse relationship (with correlation coefficient of -0.82) between blood CO₂ and the relative power in delta frequency band. It was observed that most of the bursts and total power (75%-97%) in the premature EEG reside in the delta frequency band. Therefore, it can be concluded that the relative power in the delta frequency band depends on the length of the burst or the IBI indicating an inverse relationship with the IBI’s length and a direct relationship with the burst length. Furthermore, the relative power of the delta frequency band was negatively correlated with all the other frequency bands (table 4-1). The maximum negative correlation was established between relative power in the delta frequency band and relative power in the alpha frequency band.
Table 4-1 Correlation ($R^2$) among Spectral Parameters

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<th>RP THETA</th>
<th>RP ALPHA</th>
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<td>0.86</td>
<td>0.81</td>
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Figure 4-9 indicates a direct relationship (with correlation coefficient of 0.75) between blood CO$_2$ and relative power in the theta frequency band.
A direct relationship between blood CO$_2$ and relative power in the alpha frequency with highest correlation coefficient of 0.8.4 was achieved (figure 4-10).

This correlation between blood CO$_2$ and relative power in the alpha frequency band confirms the development of the regression equation used to estimate the blood CO$_2$. All the spectral measurements were burst-IBI cycle based; the majority of bursts contained energy in the delta frequency band, with small contributions from the theta and alpha frequency bands. Only residual artefacts and a few bursts may fall in the beta frequency band. Therefore, no correlation was found between blood CO$_2$ and relative power in the beta frequency band (figure 4-11).
4.4 Blood CO₂ Estimation

The results shown in table 4-1 are based on the offline EEG (24 – 36 hours) signal processing of preterm neonates of different gestational ages. Table 4-1 shows the CO₂ measurements (kPa) obtained from ABL800 FLEX blood gas analyser-radiometer (a blood gas machine) and the CO₂ estimation by the software along with other premature EEG parameters. The measurement range of the analyser is 0.67 – 33.3 kPa.
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Longer IBIs (e.g. table 4-2, subject cj-19 at 11/09/2013 5:29) may be indicative of loose electrode connections. From figure 4-12 it is confirmed that the IBI (extremely long) is correctly detected by the software. The trace contains the large amount of residual artefacts (circled red) and spikes (less than 2.0 seconds) circled blue.

All blood gas points with higher relative power in the alpha frequency bands (typically greater than 10%) are indicative of small spikes and glitches, typically less than 2.0 seconds. All blood gas points with higher relative power in the beta frequency bands (≥ 5%) indicate some type of unwanted energies.
It is concluded that the software effectively removed majority of the artefacts. All artefacts with very high energy compared to the burst energy were only detected (could not remove). The detection of the events (IBI) was consistent with the expert marking. Burst-IBI cycle spectral measurements were aligned with the events detected (IBI, burst). Due to the 50% availability criteria for the burst, small spikes and glitches less than 2.0 seconds did not affect the detection of the IBIs. These spikes always yielded in high relative power in the alpha and beta frequency bands. Therefore, these spikes and glitches adversely affected the correlation coefficients between the temporal and spectral parameters (e.g. correlation between the IBI and relative power in the delta frequency band) of the preterm EEG. This may lead to the wrong estimation of blood CO₂.

For artefact-free premature EEG signals, the overall predictability of the software (table 4-2) is acceptable and can be clinically used.
Chapter 5: Summary

This novel research, conducted in four interrelated areas i.e. artefact removal, detection of burst and IBI, spectral quantification of premature EEG signals, and finally the estimation of blood CO₂, has significantly contributed to the field of preterm neonate EEG signal analysis.

5.1 Conclusion

Signal segmentation with a small window size significantly improved temporal event (e.g. IBI) detection; in contrast, signal segmentation with a large window size effectively improved the accuracy of spectral measurements. The combination of a conventional high pass Butterworth filter and discrete wavelet MRA considerably removed high instantaneous energy artefacts typically with frequencies below 0.5 Hz and above 12.5 Hz; thereby the temporal accuracy of IBI and burst detection increased. This was validated by an independent expert neonatologist with vast experience in premature EEG at Newborn Intensive Care Unit, St Mary's Hospital for Women and Children. The novel approach of burst-IBI cycle spectral measurements yielded precise spectral measurements representing the actual segment of the premature EEG signals. The degree of correlation between the spectral and temporal parameters showed a very significant effect of relative power in the alpha frequency band on CO₂ estimation. Consequently, the number of independent variables in the linear regression equation describing the CO₂ level reduced to one parameter. Analytically, relative powers in the alpha and beta frequency bands at some CO₂ points indicated the presence of short transients (e.g. bursts and IBIs of less than 2.0 seconds). It was analysed that the limitation (if any) of the work points towards the regression equation describing the CO₂ level. Therefore, future research work can resolve it by implementing more novel and effective algorithms and techniques.

5.2 Future Work Recommendations

The research can be advanced in two areas, i.e. fast and accurate measurement of all the parameters of premature EEG signals and the development of a mathematical model or an equation describing the premature EEG signals. The real-time and offline processing time of the software can be considerably reduced by calculating both the temporal and spectral parameters using the discrete wavelet transform MRA. The detail coefficients represent the signal energy at the respective level (equation 5.1).
Where, $E_j$ is the energy in $j^{th}$ scale/level. $C_j(k)$ represents detail or wavelet coefficients. The sum of all detail coefficients represents the total signal energy (equation 5.2).

$$E_j = \sum_k |C_j(k)|^2$$

Therefore, the signal energy at a particular decomposition level or the wavelet entropy can be used directly for the detection of burst events in premature EEG signals. For a sampling frequency of 200 Hz, the wavelet coefficients at decomposition level of 5 represent the burst energy. In doing so, it is no longer necessary to perform inverse signal reconstruction in the time domain. The spectral power of the signal is the sum of all detail and approximation coefficients. Therefore, the sum of detail and approximation coefficients at 5th decomposition yields the power in the delta frequency band. Similarly, the power in all other frequency bands can be achieved by summing the coefficients at the correct decomposition level. It is to be noted that the discrete wavelet MRA produces dyadic frequency resolution in contrast to the linear frequency resolution of the DFT. To get the exact frequency bands pre discrete wavelet MRA filtering is recommended.

The regression equations developed in SPSS are statistical in nature. Therefore, either attempts can be made to develop a model describing the premature EEG signals or efforts can be taken to clean bursts and glitches less than 2.0 seconds to get accurate spectral measurements.

5.3 Concluding Remarks

The research effectively implemented all the necessary techniques/ algorithms used to accurately measure the spectral and temporal parameters of the premature EEG signals. Statistical analysis and the expert opinion validated the outcomes of the techniques. Thus, the software core to estimate CO₂ is technically acceptable and further validated from the readings produced by the blood gas machine. It is therefore concluded that for the clean premature EEG signals, the software can be used to estimate CO₂.
Bibliography


Appendix A: Experimental Protocol

Title: The automatic analysis of brain electrical activity and its prediction of partial pressure of blood carbon dioxide in premature newborn babies

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UMIP (The University of Manchester Intellectual Property)

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PeCO₂ using EEG- levels of agreement with PCO₂_v1_24/09/2012
Objective
Our objective is to study the changes in brain electrical activity during the first 36 hours after birth in preterm newborn babies in relation to specific events including hypo/hypercarbia. The primary aim of the study is to determine the levels of agreement between partial pressure of blood carbon dioxide (PCO₂) measured using blood gas analysis and the carbon dioxide (PeCO₂) predicted by using automatic analysis of brain electrical activity in premature newborn babies.

Background
There is a real need for reliable, continuous, non-invasive bedside neuro-monitoring specific to sick preterm babies. In the UK, 7% of births are premature, and one in five of those babies less than 26 weeks’ gestation develop severe disabilities. 86% of babies born before 26 weeks’ gestation have some form of moderate to severe neurodisability at 6 years of age. With improved survival, the number of babies with poor neuro-developmental outcome is on the rise.

Premature babies are most vulnerable in the first 48 hours after birth. Nearly all babies born before 28 weeks’ gestation have surfactant deficiency and need to be supported by mechanical ventilation and surfactant administration. This places them at risk of hypo/hypercarbia from soon after birth. Low blood carbon dioxide (hypocarbia) and high blood carbon dioxide (hypercarbia) has been associated with the development of brain and lung damage, intraventricular haemorrhage, periventricular leucomalacia and even death. Close monitoring of PCO₂ in the newborn premature baby is therefore important.

The current gold standard of monitoring PCO₂ in preterm newborn babies is by blood gas analysis performed on average every four hours. This technique has its drawbacks such as blood loss which may lead to anaemia and more blood transfusions. The procedure is invasive and if the baby is unstable this would mean blood sampling being performed more frequently. If the blood sampling is performed from an indwelling arterial catheter, ischemia and arterial spasms are also a risk.

Non-invasive techniques currently available to monitor carbon dioxide in newborn babies are transtcutaneous monitoring and end-tidal carbon dioxide monitoring. Both these techniques are currently not used in clinical practice. Transtcutaneous monitoring measures partial pressure of oxygen (PO₂) and partial pressure of carbon dioxide (PeCO₂) at the skin surface to provide an estimated arterial partial pressure of oxygen and carbon dioxide. The device provokes hyperperfusion by local heating of the skin and measures the partial pressure of oxygen and carbon dioxide electrochemically. This tool can be difficult to use effectively, due to the requirement of frequent position changes of the probe to prevent burns, sensor calibration and preparation. It has also been found that poor tissue perfusion and acidosis can alter their values. End tidal carbon dioxide monitoring measure the partial pressure of carbon dioxide in exhaled breath (PetCO₂). However this technique can be difficult in sick neonates who often have a rapid respiratory rate and small tidal volumes resulting in a wide variation in end tidal carbon dioxide values. There is therefore an urgent need for continuously monitoring carbon dioxide in newborn preterm babies.
Electroencephalography (EEG), a record of the electrical activity of the brain, can be used for brain monitoring in newborn preterm babies. Previous research has established the usefulness of recording preterm EEG. EEG can detect changes in oxygenation, carbon dioxide, and blood pressure in preterm babies. The degree of discontinuity of the EEG trace has been shown to be predictive of neuro-developmental outcome in premature babies. Hence, there is sufficient evidence to recommend continuous EEG monitoring routinely in preterm newborn babies.  

Despite this EEG monitoring is not routinely performed in newborn preterm babies as qualitative EEG reporting is highly specialised and time consuming. We have recently developed software that can automatically analyse preterm EEG recordings. The software is capable of:

1. Consistently quantifying the degree of discontinuity (interburst interval) and frequency of EEG trace (relative power of delta EEG band)
2. Automatically removing artefacts
3. Continuously predicting carbon dioxide (PeCO₂) using a regression equation and
4. Presenting the analysis continuously in a mode easily interpretable by the clinicians

The software is compatible with commercially available EEG head box device which will be used to acquire EEG. The software now facilitates continuous EEG monitoring routinely in preterm newborn babies.

Furthermore, we have obtained proof of principle that preterm EEG can be used to predict PCO₂. Using 1-hour EEG recordings done on 22 preterm babies born before 30 weeks gestation a strong correlation was demonstrated between interburst interval and PCO₂ (R square = 0.695).

Figure 1: The correlation between interburst intervals (ibi) measured in seconds and blood carbon dioxide (pcO2) measured in mm Hg from 22 EEG recordings done on the first day after birth.

Further proof that EEG can be used to predict blood carbon dioxide has been obtained by comparing the trends of predicted PeCO₂ and transcutaneous PetCO₂. A strong correlation between continuously PeCO₂ and PetCO₂ has been demonstrated as shown in Figure 2. More importantly PeCO₂ was obtained consistently without tissue injury.
in all participants, while PtcCO₂, currently used in some neonatal units, caused tissue hyperemia and needed after an hour to avoid skin burns.

Figure 2: Trends comparing transcutaneous PtcCO₂ and predicted PeCO₂ using EEG. Figure 2a: Example of transcutaneous PtcCO₂ measurement

Figure 2b: Simultaneous predicted PeCO₂ measurement using EEG in the same

Our prior experience is that the device is most accurate when recordings are conducted during the first 36 hours after birth. This is a critical period in the life of a premature baby when mechanical ventilation, surfactant administration and several invasive procedures are performed. The consequences of what happens during this period can be long lasting and significantly affect prognosis. We therefore aim to commence EEG recording from soon after birth.

The purpose of this study is to determine the level of agreement between PeCO₂ and PCO₂ in preterm babies born before 30 weeks gestation during the 24 to 36 hours after birth.

**Aims of the study**

**Primary aim:** To determine the level of agreement between partial pressure of blood carbon dioxide (PCO₂) measured using blood gas analysis and the carbon dioxide (PeCO₂) predicted by using automatic analysis of brain electrical activity in premature newborn babies.

**Secondary aim:** To identify and study EEG changes during other events that are likely to affect brain electrical activity (e.g. hypotension, decreased oxygenation/desaturation, procedures such as endotracheal suction, surfactant administration, painful procedures and apnoea of prematurity).

**Methods**

This will be a prospective observational study

**Inclusion criteria:**

1. Born before 30 weeks’ gestation and
2. Less than 24 hours old and
3. Ventilated through an endotracheal tube
4. Admitted to Newborn Intensive Care Unit, St Mary’s Hospital, Manchester

**Exclusion criteria**

1. Antenatal or postnatal diagnosis of congenital brain malformation
Data collection

Digital EEG recording
Digital EEG recording will be routinely commenced from soon after birth and continued until 36 hours of age in all babies who fit our inclusion criteria.

Seven electrodes will be placed on the scalp at Fp1, C3, O1, Fp2, C4, O2 and Cz positions according to the International 10-20 system. We will use non-invasive techniques that do not cause pain or distress to the baby for fixing electrodes. Needle electrodes will not be used to avoid painful procedures.

A combination of techniques using hydrogel electrodes, silver-silver chloride electrodes secured with collodion and other non-invasive techniques will be used. The quality of EEG recordings is best with silver-silver chloride electrodes. The application of the hydrogel electrodes can be performed by any member of the clinical team. Placement of silver-silver chloride electrodes will require a member of the research team or a neurophysiologist trained at placing silver-silver chloride electrodes. The choice of electrode application technique will depend on skin integrity, timing of delivery and availability of trained staff.

Electrodes will be connected to a commercially available Xtek EEG head box. The head box is then connected to a laptop on which the developed software will analyse and display the EEG.

PeCO₂, interburst interval and relative power of delta EEG band will be continuously displayed and stored on the encrypted laptop. The impedance, a measure of the quality of electrode contact will be measured automatically at the start of the recording and at 1-hourly intervals for the duration of the recording.

Other monitoring
Capillary and or arterial blood gases measurements for monitoring PCO₂, pH, and PO₂ will be performed as per clinical requirements. Continuous heart rate, blood pressure, respiratory rate and peripheral oxygen saturation will be monitored as per standard care. The nurses caring for the baby will be asked to document any procedures, activity or handling involving the baby on a paper CRF to help identify events and artefacts.

Events of interest
The following events will be studied:
1. Surfactant administration
2. Endotracheal intubation
3. Endotracheal suction
4. Painful procedures – capillary blood sampling; peripheral venous cannulation
5. Hypotension requiring fluid boluses, commencement of inotropes, increase in inotropic support
6. Apnoeas, bradycardia and desaturation requiring stimulation and/or mask ventilation.

PeCO₂ using EEG- levels of agreement with PCO₂ v1_24/09/2012
Demography
We will record demographic details including prenatal care and conditions with regards to CTG’s, fetal blood samples, evidence of maternal chorioamnionitis, prenatal steroids. Also we will document the Apgar information and the resuscitation at delivery, gender, birth weight, gestational age, mode of delivery, CRIB score and cranial ultrasound scan findings.

Sample size
The study will be conducted over a two-year period during which recruitment will be performed for 18 months. Around 100 babies a year who fit our inclusion criteria are admitted to the Newborn Intensive Care Unit, St Mary’s Hospital, Manchester. Each baby on average will have four to six blood gas measurements. With a 75% consent rate we will have 300 – 450 sufficient data points to determine levels of agreement.

Data analysis
For levels of agreement between PeCO₂ and PCO₂ we will compare stable baseline PeCO₂ data of five minutes duration within 0.5 hour prior to the measurement of PCO₂. Bland Altman levels of agreement and correlations will be used.

For events that are likely to alter baseline EEG activity we will compare steady baseline EEG activity of at least five minutes duration within 0.5 hour prior to and after the event to the EEG activity during the event. Two group comparisons using Mann-Whitney test or Students t test will be performed.

Consent and recruitment
Parents will be approached antenatally and provided adequate information if the mother presents in early preterm labour. All attempts will be made to provide adequate time so that informed consent can be taken prior to birth. However, this can not always be achieved due to the unpredictable nature of preterm labour.

We are particularly interested in the immediate period following birth when babies receive surfactant and mechanical ventilation is commenced. Babies are most vulnerable to hypo/hypercarbia during this period. The usefulness of measuring PeCO₂ is therefore highest during this period. We also want to study a large number of babies delivered at different levels of sickness. Often it can be difficult and stressful for parents who have a very sick newborn baby to make quick decisions. We therefore want to commence EEG recordings routinely in all babies who satisfy the inclusion criteria from soon after birth prior to parents giving consent. We will use only non-invasive sticky electrodes (hydrogel electrodes) to commence the EEG recordings.

Parents will be approached from soon after birth by a member of the research team and given information about the study. Written information in the form of a leaflet will be given to parents to take away and study. Parents will be requested consent for using EEG and clinical data already being acquired for the purpose of the study. Consent will be taken prior to changing the electrodes to silver-silver chloride electrodes which although are non-invasive require more skin preparation, handling and expertise than hydrogel electrodes. At all stages it will be made clear to the parents that they remain free to withdraw at any time.
Data handling and storage

All study data will be entered into a customised electronic database in which the baby will be anonymised using a study number. The paper consent form containing baby’s name, hospital number and study number will provide the link. Electronic data will be stored securely in appropriate data storage devices in accordance with the local policy.

Regulatory issues

This study is sponsored by the University of Manchester. Research ethics approval and site specific approval from Central Manchester University Hospital NHS Foundation Trust will be obtained prior to commencement of the study. Indemnity arrangements will be provided for by the University of Manchester as the sponsor of the study.

Ethics

This research is designed to advance the care and treatment given for premature babies. Consequently this study will be performed on this specific patient population. Consent procedures developed from previous studies has been used.

Dissemination and publication policy

Dissemination of the study results will be conducted in peer reviewed journals and conferences.

Reference List

