A Tool for Hemodynamic Data Analysis

by

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Abstract

Nearly 2% of all live births are very premature (gestational age less than 32 weeks), and 50% of all new cases of cerebral palsy occur in survivors of premature birth (gestational age less than 37 weeks). Because of their underdeveloped vascular structure, premature infants are especially vulnerable to brain injury caused by unregulated and erratic changes in blood pressure.

A challenge in the prevention of serious brain injury in premature infants is the inability to identify impending or recent hemodynamic events that might lead to injury of the newborn's brain. If events that indicate a propensity to experience brain injury can be identified, then such events can be monitored clinically, and steps can be taken to prevent them from occurring.

We designed and implemented a software tool, HemDAT, that can be used to test hemodynamics related hypotheses and to facilitate the discovery of interesting relationships among hemodynamic signals. HemDAT uses signal processing and statistical knowledge to provide clinical researchers a tool that can help develop a better understanding of how brain injury occurs in premature newborns.

HemDAT is capable of processing and navigating large data sets of blood pressure and cerebral blood flow. Large data sets are important because the events that cause brain injury are believed to be short-lived, possibly infrequent, and unpredictable. Additionally, since this is a relatively unexplored area in human infants, HemDAT provides flexibility in performing repeated analyses with different parameters modifiable by the user. HemDAT also provides convenient visualizations of results and does not demand signal processing or statistical expertise from the user.

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Chapter 1

Introduction

This document describes the design and implementation of a software tool, Hemodynamic Data Analysis Tool (HemDAT), that can be used in clinical research to extract and display information from previously gathered blood pressure and cerebral blood flow signals. HemDAT can also be used to perform some analyses, such as baroreflex and cerebral autoregulation assessment. The discussion presented here focuses on brain injuries, such as ischemia and intraventricular hemorrhage (IVH) in premature infants and on the use of this tool to analyze and compare physiological signals that may be indicators that an infant is particularly susceptible to brain injury. However, HemDAT can be used in other situations that require analysis of blood pressure and cerebral blood flow signals.

1.1 Motivation

Unregulated and erratic changes in blood pressure and cerebral blood flow can cause severe brain damage. Studies [8, 6, 9] indicate that premature infants are especially vulnerable to injury related to changes in blood pressure and cerebral blood flow, in part, because their vascular system is underdeveloped.

According to the National Center for Health Statistics, close to 12% of all live births are premature (gestational age less than 37 weeks), and 2% of all live births are very premature (gestational age less than 32 weeks.) Very premature and low birth weight infants are especially vulnerable to developing a form of brain hemorrhage called intraventricular hemorrhage (IVH). In preterm infants an area adjacent to the ventricles allows blood to enter the ventricles, which may put pressure on the neighboring nerve cells, causing damage to the existing brain tissue as well as retarding future development of the brain. Bleeding also damages other parts of the brain by depriving them of blood carrying needed oxygen.

Approximately 50% of all new cases of cerebral palsy occur in survivors of premature birth, and by school-age, 25-50% of those who were born prematurely exhibit learning, cognitive or behavioral

dysfunction [8]. Catastrophic events, such as rupturing of blood vessels, that can cause severe brain damage must be prevented if cerebral palsy is to be reduced. A challenge in the prevention of serious brain injury in premature infants is the inability to identify impending or recent events that might lead to brain damage before the injury becomes irreversible. The clinical signs of brain injury in an ill premature infant are often subtle or do not manifest themselves for hours to days. Despite several decades of research, the causes and signs of such events are still not completely understood. The investigation and understanding of causes of brain injury in premature infants has been difficult because of several factors.

The first factor is the clinical frailty of the study population. Newborn premature babies are physiologically delicate, and great care is necessary when studying them. Several studies have conducted experiments on healthy adults to evaluate the physiological systems whose failure is believed to play a role in brain injury. These experiments include inducing changes in subjects' blood pressure and heart rate using either drugs or physical activity. The subjects are then studied to assess how quickly their reference state is reestablished. Such studies cannot be conducted on fragile infants, nor can the results be directly applied to these infants since their systems are too underdeveloped to predict their response to stimuli based on data from adult experiments. Chapter 3, *Related Works*, discusses these experiments in more detail.

Secondly, physiological systems are affected by many factors. When studying a physiological system of a newborn, it is difficult to account for all the possible factors that might play a role in determining the functionality of that system. For example, when assessing the changes in cerebral blood flow, it is hard to simultaneously account for and model factors such as the amount of carbon dioxide in the blood, respiratory rate, and level of mental activity.

Finally, it is difficult to determine when the injury occurs, as it may not manifest for days or even months. As a result, various physiological systems cannot be studied at the time when the injury occurred. Moreover, there are no 'gold standards' that can be used to validate the findings of various studies.

Despite all of these challenges, researchers have proposed hypotheses that attribute brain-injury, in part, to hemodynamic factors. If events that indicate a propensity to experience brain injury can be identified, then these events can be monitored clinically, and steps can be taken to prevent them from occurring. To develop a better understanding of brain-injury causing mechanisms, we are developing tools to further investigate and test various hypotheses as well as to look for other possible features and relations that might advance our understanding.

1.2 Objective

The goal of this research is to design and implement a software tool that can be used to test hemodynamics related hypotheses, as well as to facilitate the exploration of blood pressure and cerebral blood flow data. The tool must combine medical concerns with signal processing and statistical knowledge to provide clinical researchers a tool that can help in developing a better understanding of how brain injury occurs in premature newborns.

There are three main challenges associated with developing such a tool.

First, the testing of hypotheses and exploration of new data requires analysis of large data sets. Events that cause brain injury are believed to be short-lived, possibly infrequent, and unpredictable. The understanding of these kinds of events necessitates analysis of large data sets. Thus, any tool capable of testing hemodynamics related hypotheses for the cause of brain injury must be able to process and navigate large data sets.

Secondly, this is a relatively unexplored area in premature human infants. Consequently, the utility of the proposed tool depends on its flexibility in performing repeated analyses with different parameters modifiable by the user and on providing multiple techniques of analysis.

Finally, the tool must provide convenient visualizations of results and must not depend upon signal processing or statistical expertise of the user.

1.3 Contributions

The research presented in this thesis makes following contributions:

- Provides an effective clinical research tool.
  - Combines multiple analysis techniques: HemDAT provides a suite of various approaches to analyze blood pressure and cerebral blood flow signals, which makes comparisons between analysis techniques easier.
  - Broadly applicable: This document uses the example of brain injury in premature infants to motivate the need for HemDAT and to demonstrate its functionality. However, HemDAT is a general tool that analyzes blood pressure and cerebral blood flow and can be used in multiple other situations requiring analysis of these hemodynamic signals.
  - Visual output: HemDAT outputs convenient visualizations of the output of the performed analysis.
  - Flexible: HemDAT provides flexibility in all of its computations. Users define relevant parameter values when performing various analyses. This flexibility makes HemDAT more usable and adaptable to its intended application.

  - Portable: HemDAT is portable and has been successfully tested on Windows and Linux operating systems.
  - Usability: HemDAT does not rely on expert knowledge or programming skills of the user. The graphical user interface eliminates the need for programming skills needed to use software packages such as Matlab.

- Provides a discussion of previous work in the field: This thesis includes a detailed discussion of the techniques that have been used to approach the problem of assessing the baroreflex and the cerebral autoregulatory systems.

1.4 Thesis Structure

This document starts with an introduction to the problem in Chapter 1. We briefly describe the problem of assessing hemodynamic signals of premature infants to learn more about the cause of brain injury. Additionally, chapter 1 discusses the goal of this research to develop a tool that facilitates analysis of physiological signals of interest. Chapter 2 provides a background of the problem and some possible approaches to the problem. Next, we discuss earlier works and some classical techniques for assessing the various systems believed to be related to brain-injury in Chapter 3. Chapter 4 describes our tool, HemDAT, that has been designed and implemented to assess hemodynamic signals. The use of HemDAT is demonstrated using an example data set in Chapter 5. Finally, Chapter 6 concludes the thesis and outlines future work.

Chapter 2

Background

2.1 Overview

The percentage of infants who suffer severe brain injury is significantly higher among those who were born prematurely than among those who were born at term. Brain injury may cause seizures, cerebral palsy, mental retardation, and even death. Many of these brain injuries are believed to be related to cerebral hemodynamic disturbances. This chapter reviews putative mechanisms of brain injury and their antecedents. In addition, this chapter discusses statistical and signal processing techniques that can be used to detect such events.

2.2 Brain Injury

In premature infants, brain injury can occur in two primary ways. First, the brain may not receive sufficient oxygen because of either low blood oxygen content or low blood flow. The second way an injury might occur is when the brain gets too much blood, causing rupture of the blood vessels.

Ischemia is caused when the brain, or regions of the brain, do not get sufficient oxygen. This can severely retard the development of the brain tissue and result in mental retardation or cerebral palsy, a condition characterized by impaired motor control.

Intraventricular hemorrhage (IVH) occurs when blood vessels in the brain rupture and bleed, usually into the ventricles of the brain. The bleeding puts pressure on the adjacent brain tissue and deprives parts of the brain of oxygen. Damage caused due to IVH often manifests itself as seizures, cerebral palsy, mental retardation or, in some cases, death.

2.3 Symptoms and Diagnosis

Usually, there are no external signs that brain hemorrhage has occurred or that parts of the brain are oxygen deprived. Premature infants who are at greatest risk for hemorrhage usually have a brain ultrasound in the first 3–10 days of life. This painless test uses sound waves to generate a picture of the baby's brain. Ultrasounds reliably detect the presence of blood, and thus, are used to diagnose IVH. MRI scans are also used as a diagnostic tool, however, these take longer to perform and cannot be performed in critically ill premature infants.

Unfortunately, there is no effective treatment for these brain injuries. Surgery cannot prevent or cure the bleeding or the oxygen deficiency. The improved overall care and monitoring of premature babies has decreased the rate of injury, but because many of the sickest infants now survive, brain injury remains an important problem. The lack of effective treatment for these severe brain injuries highlights the importance of understanding the cause of brain injuries, or conditions that indicate a susceptibility to injury, so that preventive measures can be taken.

2.4 Contributing Factors

Determining the causes of brain injuries is difficult, in part, because of the large number of potential factors involved. The exact causes are unknown, however, many mechanisms have been proposed. Blood pressure (BP) and cerebral blood flow (CBF) are related to three major factors that are thought to play significant role, often in concert, in the development of ischemia or IVH. These factors concern the maintenance of a constant blood pressure and blood supply, which are essential for the functioning of human organs. If the blood pressure is too high, the capillaries of the organs may rupture. If the pressure is too low, the organ will not get adequate oxygen, which may cause damage. Three major factors that may adversely impact the blood pressure and supply are:

- impaired baroreceptor reflex
- immature cerebrovascular structure
- impaired cerebral autoregulation

The baroreceptor reflex is a cardiac reflex system that minimizes the impact of short-term changes in the blood pressure. An increased pressure stretches the blood vessels and triggers the pressure sensitive nerve endings in the walls of the blood vessels. These nerve endings trigger the central nervous system to reduce the blood pressure by lowering the heart rate and thereby the cardiac output. Similarly, when the blood pressure decreases, the central nervous system is triggered to increase the cardiac output by increasing the heart rate, and as a result, raising the blood pressure.

Thus, the baroreceptor reflex is responsible for maintaining a constant blood pressure in the short-term. In doing so, the baroreflex provides powerful beat-to-beat negative feedback regulation of the arterial blood pressure, minimizing short term fluctuations [21, 14]. The techniques and experiments that have been used to measure how well the heart-rate responds to changes in the blood pressure are discussed in Chapter 3.

Premature infants have immature baroreceptor reflexes, which causes blood pressure fluctuations. Their immature vascular structure is not strong enough to endure major fluctuations in the blood pressure and may rupture when the blood pressure becomes too high.

The third factor that plays a significant role in brain injury development is impaired cerebral autoregulation. Cerebral autoregulation refers to the control system that maintains a constant blood flow despite changes in the blood pressure [8, 12], thereby ensuring that the brain receives adequate and constant blood flow and oxygen delivery. This homeostatic mechanism allows the blood supply to the brain to match the metabolic demand during daily activities, such as changes in posture [22]. In addition to providing protection against cerebral ischemia due to arterial hypotension, the autoregulatory mechanism also protects the cerebral vessels against excessive flow during transient or chronic arterial hypertension, which could damage the capillaries in the brain or lead to intracranial hypertension [18].

When the autoregulatory system is not functioning properly, the cerebral blood flow is not well regulated; the changes in CBF mimic the changes in blood pressure. The range of blood pressures over which autoregulation operates is called the autoregulatory plateau. The autoregulatory plateau in term neonates is narrower than it is in adults, and is even narrower in premature infants. Figure 2-1 shows a sample autoregulation curve.

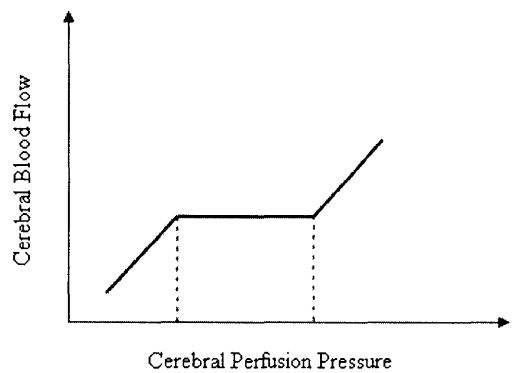


Figure 2-1: *Cerebral autoregulation curve*

When the blood pressure is too high or too low, the autoregulatory system fails and the cerebral blood flow changes passively with changes in the blood pressure. Each person has his individual

curve that changes temporally and may not correspond with another person's curve.

2.5 Signals Used

A hypothesized cause of brain injury is the change in cerebral blood flow, which is defined as follows [22]:

$$CBF \approx \frac{ABP - ICP}{CVR}$$

where CBF is the cerebral blood flow, ABP is the arterial blood pressure, ICP is the intracranial pressure, and CVR is the cerebrovascular resistance. This equation can be understood using the analogy of a tube: the flow of liquid is the pressure exerted by the liquid divided by the cross-sectional area of the tube. The total pressure is the blood pressure minus the pressure inside the brain, and the CVR reflects the resistance, or the elasticity of the blood vessels. The CBF is maintained constant in the face of blood pressure changes by changing the caliber of the blood vessels and thereby changing their resistance.

Under most conditions, the ICP has been shown to be sufficiently low relative to ABP [22], such that it can be ignored. However, in cases of severe head injury and hydrocephalus, the ICP may be elevated and must be taken into account [22].

If autoregulation is intact, we expect that when the blood pressure increases, the CBF will be maintained constant by increasing the CVR through contraction of the blood vessels. Thus, the functioning of the autoregulatory system can usually be assessed by measuring the relationship between the arterial blood pressure and the cerebral blood flow.

2.6 Signal Description

The two signals of interest in this study are the blood pressure and the cerebral blood flow. This section discusses some properties of these two signals.

2.6.1 Blood Pressure

Figure 2-2 shows a plot of a premature infant's blood pressure against time.

Blood pressure can be thought of as the amount of push the blood exerts on the walls of the arteries. The average blood pressure is referred to as the *baseline blood pressure*. The pressure against the walls of the arteries rises when the heart contracts to pump blood into the body; this peak in the blood pressure signal is called the *systolic pressure*. Similarly, the pressure drops when the heart relaxes, producing a trough, called the *diastolic pressure*. This occurs close to 80 times per minute in a healthy adult, and about 150-200 times per minute in a premature infant. Thus, for a premature infant, periodic rising and falling of blood pressure occurs 2-3 times every second. Each

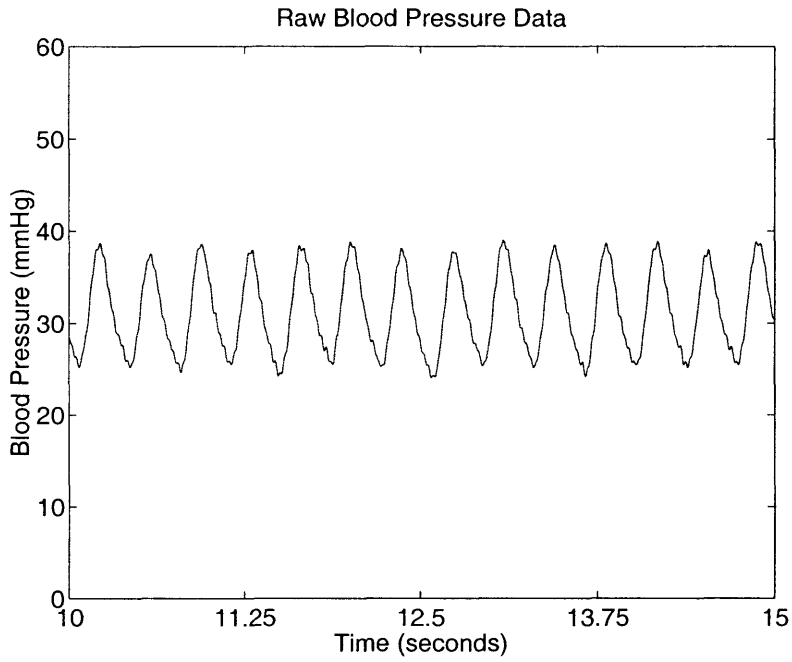


Figure 2-2: *Typical blood pressure signal of a premature infant*

such period is called a *cardiac cycle*, and the time difference between two adjacent cardiac cycles is called an *RR-interval*

As seen in the figure, the systolic pressure values are around 40mmHg and the diastolic pressure values are around 20-30mmHg. These values are higher for adults. The normal systolic pressure value for adults is about 120mmHg and the diastolic pressure value is about 80mmHg.

2.6.2 Cerebral Blood Flow

Because of the difficulty in measuring cerebral blood flow in clinically frail patients, many methods that provide a proxy for cerebral blood flow have been developed. Near Infrared Spectroscopy (NIRS) is a popular estimation method that measures changes in cerebral concentrations of the oxygenated and deoxygented hemoglobin. Another popular method uses Doppler ultrasound to measure the velocity of the cerebral blood flow.

There are a number of physiological factors that affect or change the cerebral blood flow (CBF). As in the case of blood pressure, cerebral blood flow cannot be negative, and is usually maintained at about 45-50ml/100g/min. However, since proxies are usually used for cerebral blood flow, features and expected values of CBF are not discussed in detail here.

2.7 Quantification of Similarity

The assessment of the baroreflex function, as well as the autoregulatory system requires quantification of how well the changes in one signal follow the changes in the other. In case of the baroreflex function, we are interested in how the heart rate responds to changes in the blood pressure. In case of autoregulation, we are interested in how the cerebral blood flow changes as the arterial blood pressure changes. This section describes two ways of quantifying the similarity between signals.

2.7.1 Statistical Correlation

The statistical correlation describes the strength of an association between variables. An association between variables means that the value of one variable can be predicted, to some extent, by the value of the other. In particular, correlation is concerned with a linear relation between the values of the variables.

For a set of variable pairs, the correlation coefficient gives the strength of the relationship between them. It is defined as:

$$Correlation(X,Y) = \frac{Covariance(X,Y)}{\sigma_X * \sigma_Y}$$

where standard deviation, σ is the square root of the variance, which is the square of the average value of all the differences from the mean:

$$Variance(X) = E[|X - E[X]|^2]$$

Intuitively, variance indicates how much a variable differs from its mean, on average. Similarly, covariance of two variables is the mean value of all the pairs of differences from the mean for one variable multiplied by the differences from the mean for the other variable:

$$Covariance(X,Y) = E[(X - E[X])(Y - E[Y])]$$

If the two variables are not closely related to each other, they do not vary together. This makes the covariance small, and as a result, the correlation is small. However, if the two variables are closely related, they vary in conjunction, and their covariance will be almost the same as the product of their deviations, so the correlation is almost 1. The squared correlation coefficient indicates the fraction of the variance in one variable that can be explained by the variance in the other variable.

2.7.2 Coherence

If the relationship between the signals of interest can be assumed or approximated to be linear and time-invariant, then we can use linear systems analysis to examine their relation in the frequency

domain.

The similarity between two signals can be quantified by comparing the energy at various frequencies in the two signals. Since we are concerned with a physiological system, it is likely that the system responds only to changes in a certain frequency range. The analysis in the frequency domain can address this problem by comparing the energy in the input and the output in the frequency bandwidths of interest,

The remainder of this section briefly illustrates how the relationship between CBF and BP in the time domain can be converted to a relationship between the spectra of CBF and BP in the frequency-domain. We combine the frequency-domain relationship with the feedback model of autoregulation to relate these two signals via a linear time-invariant function. Finally, we use coherence to estimate this LTI system that relates cerebral blood flow and blood pressure. The following section has been derived largely from Panerai's review of autoregulation assessment techniques[22].

For the case of autoregulation, let us assume that F_0, P_0, and R_0 are the initial cerebral blood flow, perfusion pressure and cerebrovascular resistance, respectively. Then, we can relate the three variables as follows:

$$F_0 = \frac{P_0}{R_0} \tag{2.1}$$

If we let $\Delta F(t), \Delta P(t)$, and $\Delta R(t)$ be the fluctuations in the flow, pressure and resistance, respectively. Then, we can write:

$$F_0 + \Delta F(t) = \frac{P_0 + \Delta P(t)}{R_0 + \Delta R(t)}$$

If $\Delta P(t)$ is relatively small (less than 10% of P_0), $\Delta F(t)$ and $\Delta R(t)$ will be sufficiently small to neglect the product $\Delta F(t)\Delta R(t)$ in comparison to other terms in equation 2.1[22].

$$\frac{\Delta F(t)}{F_0} = \frac{\Delta P(t)}{P_0} - \frac{\Delta R(t)}{R_0}$$

Using f, p, and r to express the normalized changes and writing the same expression in the frequency domain, we get:

$$F(f) = P(f) - R(f) \tag{2.2}$$

However, according to the generally favored theory[18], changes in resistance are due to the feedback mechanism resulting from excessive or insufficient blood flow to balance the oxygen supply and demand. Following this theory, a rudimentary linear model can be expressed in terms of the transfer function between the resistance and the flow, $G(f)$ as:

$$R(f) = G(f)F(f)$$

Substituting the result from equation 2.2, we get

$$F(f) = \frac{P(f)}{1 + G(f)}$$

where $G(f)$ is the feedback gain. If it is small, relative changes in flow will follow the changes in pressure and autoregulation will be absent. At the other extreme, if the feedback gain is very large, the effects of pressure change will be quickly attenuated. Replacing $1 + G(f)$ with $1/H(f)$, we can write

$$F(f) = P(f)H(f)$$

$H(f)$, and thus, $G(f)$ can be determined by dividing the spectral estimates, $P(f)$ and $F(f)$. However, this technique must be approached with caution as noise in the signals can give misleading results. Moreover, the transfer function estimates are valid only for the frequencies that have a high coherence. Roughly, the magnitude of coherence indicates the percentage of variability in the output that can be accounted for by the input. If the changes in the output cannot be accounted for by the input, the gain at that frequency does not provide meaningful information.

The coherence between two signals is defined to be:

$$Coherence(X, Y) = \frac{S_{xx} * S_{yy}}{|S_{xy}|^2},$$

where S_{xx} and S_{yy} are the spectral estimates of the signals X and Y, respectively. S_{xy} is the cross-spectral estimate of X and Y. Intuitively, a spectral estimate provides information about the amount of energy at each frequency, and a coherence value expresses the fraction of output power that can be explained by the input at each frequency. The coherence values are between 0–1, and a coherence of 0.5 is generally adopted to represent a significant association between the input and the output. A coherence greater than 0.5 implies that the input can account for more than half of the output power.

2.8 Summary

The exact causes of brain injury still remain unknown, in part, because of the large number of potential factors involved. Three main factors believed to be related to brain injury in premature infants are impaired baroreceptor reflex, immature cerebrovascular system, and impaired cerebral autoregulation. The baroreceptor reflex relates the heart rate and the systolic BP to maintain a constant blood pressure in the short term. When the blood pressure increases or decreases, the central nervous system is triggered to reduce or increase the cardiac output to minimize the impact of the changes in blood pressure. The autoregulatory system is responsible for maintaining a constant

cerebral blood flow in face of changing perfusion pressure by changing the cerebrovascular resistance.

The assessment of both these systems requires a way to quantify how well two signals follow each other. This chapter discussed correlation and coherence as ways to quantify signal similarities in the time domain and in the frequency domain.

Chapter 3

Related Work

In spite of the developments in health care, severe brain-injury remains a major cause of neonatal death in premature infants. Of the infants who survive, many experience neurological disabilities. The improved survival rate of premature infants has highlighted the higher incidence of their developing brain injury and/or learning disabilities.

Baroreceptor reflex and cerebral autoregulation are believed to be related to brain injury. Both phenomena have been studied extensively to develop a better understanding of how they function. This chapter discusses some of the popular techniques used in the analysis of baroreflex and autoregulation functions.

3.1 Baroreceptor Reflex

The baroreflex is one of the most powerful control mechanisms of blood pressure homeostasis. Its structure may be described as follows: baroreceptors, which are stress sensors placed in the carotid arteries and at the aortic arch, continually detect arterial wall dilation induced by BP. This information is sent through neural fibers to the control centers located in the brain-stem. These control centers process the baroreceptor inputs, with the aim of counteracting possible deviations of the blood pressure from the reference point by modulating the heart rate and the peripheral vascular tone accordingly [14].

A major property of the baroreflex is the time-variance of its gain. This characteristic is the result of continuous influences exerted by the centrally mediated mechanisms. In many instances, it provides a proper adaptation for the cardiovascular system to specific behavioral conditions. For example, during physical exercise or under emotional stress the blood pressure should rise from its reference level. Given the intrinsic high efficiency of the baroreflex, this pressure rise can be obtained only through a reduction in the baroreflex gain. Indeed, should the baroreflex gain remain stable at its maximal level, no pressure increase would be allowed [14].

Because of the primary role played by the baroreflex in cardiovascular control, an impairment of the baroreflex function usually results in significant deregulation of the blood pressure. Given its crucial role, the baroreceptor reflex function has been studied in the time domain, as well as in the frequency domain.

3.1.1 Time Domain

Di Rienzo *et al* [15] introduced a baroreflex effectiveness index to asses how well the baroreflex is working. They studied 14 healthy adult volunteers over a period of 24 hours. For each subject, the blood pressure signal was recorded at 200Hz. This measurement was used to identify consecutive beats and the time intervals between them. The authors identified sequences of consecutive beats in which progressive increases or decreases in systolic blood pressure (SBP) are followed by a progressive lengthening or shortening in pulse interval, with a one-beat delay. The slope of the regression line between the SBP and the pulse interval values included in each sequence is taken as an index of the sensitivity of the baroreflex control of the heart. One reason for the popularity of this approach is that all the information can be derived through the analysis of the systolic blood pressure. However, to give a meaningful index, this approach requires a large amount of data that includes many changes in the SBP followed by changes in the RR-intervals.

3.1.2 Frequency Domain

In the frequency domain, the baroreflex can be thought of as a control system linking the blood pressure and the heart rate. Multiple models of the baroreflex have been proposed, including a closed loop feedback system with two transfer functions, one governing the effect of the blood pressure on the heart rate and the other one governing the effect of the heart rate on the blood pressure. If this model is further simplified, it can be viewed as one system relating the blood pressure and the heart rate, which can be evaluated from the ratio of the RR interval spectrum and the blood pressure spectrum [28]. Multiple studies have followed this approach, but used different methods of calculating spectrum.

Clayton *et al* [28] provide a review and a comparison of four different approaches to calculating spectra: FFT, zero-padded FFT, windowed autocovariance, and maximum entropy. The authors reported little difference in the results obtained using the same data but different methods of analysis. The ECG and the arterial blood pressure measurements were gathered from ten adults of average age 67 years. Five minute segments of the RR-interval sequences and the systolic blood pressure were derived from this data and analyzed using the following four techniques.

The first technique found the spectrum of the data using FFT. Each 5-minute epoch was divided into nine segments of 512 points and windowed with a Hanning window. The spectrum was calculated using an FFT with a spectral resolution of 1/128Hz.

Kay & Marple [30] and Challis & Kitney [27] improved upon the previous method by extending the length of the epochs by padding them with zeros. The procedure for spectral estimation with the zero-padded FFT was similar to that for unpadded FFT. Each 5 min epoch was divided into 9 overlapping segments of 512 points. Each segment was padded with an equal number of zeros on each side to increase its length to 1024. The padded epochs were windowed with a Hanning window and the transform was calculated with a spectral resolution of 1/256Hz.

The third method used to estimate the spectral content uses the autocovariance function, which is the autocorrelation of a sequence with a zero-mean. The autocovariance function is calculated for each 5-minute epoch and then truncated to 512 points. Each of these is windowed with a Parzen window and transformed with a spectral resolution of 1/128Hz. The fourth method used an autoregressive model to fit each 5-minute data set.

The effect of blood pressure on heart rate variability, α was calculated from the ratio of RR-interval and blood pressure spectra. Estimates for α were obtained for each discrete frequency. Clayton's study found that the average value of α in the frequency-bands that had a high coherence agreed well for all four spectral estimation methods. This study showed that the use of different spectral estimation techniques to obtain the RR-interval and the blood pressure spectra does not have a major influence on the calculation of the transfer function gain.

Andriessen *et al* [19] used spectral power and transfer function analysis to study the baroreflex function in stable premature infants. They studied 10 infants of gestational age less than 34 weeks. The low frequency (LF) bandwidth was defined to be 0.03–0.2Hz, and the high frequency (HF) band was determined on an individual basis based on the respiratory frequency of the infant. For all infants, a LF peak occurred close to 0.1Hz and was attributed to baroreflex. A HF peak occurred close to 1Hz and was attributed to the respiratory frequency. The power in low and high frequency bands was compared. The authors found that the ratio of the power in low and high frequency bands of the RR-interval, LF/HF, was higher in studied infants than had been found in adults [29, 2]. The higher ratio can be interpreted as the predominance of sympathetic influence or immature parasympathetic activity. Gestational age was also found to be correlated with decreasing LF/HF ratio in the RR-interval. The decreasing ratio could be consistent with an increase of parasympathetic influence. A low parasympathetic influence in preterm infants could lead to a situation in which the relatively fast respiratory-induced blood pressure changes cannot be buffered by modulations of the RR-interval, because only the parasympathetic system is fast enough to influence the cardiovascular variables in the frequency range of respiration in premature infants.

The phase of the transfer function provides information about the delay in the response of the system. In their study, Andriessen *et al* found a phase shift of 96 degrees corresponding to 0.07Hz, which is where the peak attributed to baroreflex occurred. This phase corresponded to a delay of 3.8 seconds. In human adults, the delay between the BP and the RR-interval has been found to

be close to 2 seconds. These findings suggest that preterm infants have a dominant sympathetic response and a longer time delay of the baroreceptor loop.

3.2 Autoregulation

Autoregulation refers to the body's mechanism of maintaining a constant cerebral blood flow in face of changes in the perfusion pressure. This homeostatic mechanism allows the blood supply to the brain to match the metabolic demand during daily activities [22]. In addition to providing protection against cerebral ischemia due to arterial hypotension, the autoregulatory mechanism also protects the cerebral vessels against excessive flow during transient or chronic arterial hypertension, which could damage the capillaries in the brain or lead to intracranial hypertension if it caused a corresponding increase in the cerebral blood volume [18].

The above definition of autoregulation was developed based on Fog's experiments in 1939[17]. Fog used cats to study the changes in the diameters of blood vessels. He created an opening in the skulls of cats to directly observe how the diameter of vessels changed in response to various stimuli. Fog decreased the systemic blood pressure of these cats and observed an immediate vasoconstriction of the vessels, which was followed by a secondary vasodilation to restore the blood pressure [3].

Since Fog's experiment, many animal, as well as, human studies have been conducted to develop a better understanding of autoregulation. The assessment of the functioning of the autoregulatory system requires measuring and analyzing changes in the CBF when the blood pressure is known to be changing. Research in the area has advanced since the 1970's when studies used Xe and Kr isotopes to estimate the cerebral blood flow . Most studies now use transcranial Doppler ultrasound to measure the velocity of the cerebral blood flow. Another popularly used technique is near-infrared spectroscopy, which measures the changes in the cerebral concentrations of oxygenated and deoxygenated hemoglobin, which has been shown to correlate strongly with volemic CBF [11].

Past research has compared changes in the blood pressure and the cerebral blood flow in time domain as well as in frequency domain.

3.2.1 Time-Domain Autoregulation Assessment

In the time domain, analysis of autoregulation can be further characterized as either static or dynamic. Static analysis attempts to evaluate the overall effect of the autoregulatory action: how does the cerebrovascular resistance, as reflected in the cerebral blood flow, change in response to a change in the arterial blood pressure. The static measurements do not address the time in which this change occurs. Dynamic analysis of autoregulation, in contrast, attempts to measure the transient response of the cerebral blood flow when the blood pressure changes: how does the cerebral blood flow respond to changes in the blood pressure soon after the change occurs.

Static Analysis

Static autoregulation analysis attempts to determine where an individual lies on the autoregulation curve, as shown in Figure 2-1.

For static analysis, there are two parameters that can be used to assess the static performance of autoregulation: the regression slope and the correlation coefficient.

Panerai *et al* [26] measured the cerebral blood flow velocity with Doppler ultrasonography in one middle cerebral artery for 5-minute periods in 33 babies of gestational age less than 33 weeks. They used linear regression analysis of the blood flow velocity on the blood pressure. The records were classified as showing loss of autoregulation if the regression slope was greater than a critical value. As shown in Figure ??, the autoregulating part of the autoregulatory curve has a shallow slope, indicating that a change in blood pressure does not change the cerebral blood flow significantly. The non-autoregulating parts of the curve indicate that a change in blood pressure causes a significant change in the cerebral blood flow. A minimum change in the mean arterial blood pressure of 5mmHg and maximum slope of 1.5%/mmHg was used to classify records as autoregulating. Similar methods were used by Pryds *et al*[23] and Cowan *et al* [1] to assess autoregulation. Various studies have used different thresholds to classify data. The range of thresholds extends from as low as 0.5%/mmHg [5] to as high as 4.4%/mmHg [23].

A linear regression can be performed on any set of two variables, and a slope can be obtained. However, this numerical quantity is meaningless if the regression is not significant. Instead of the slope, many other researchers use the correlation coefficient as an indication of the relation of cerebral blood flow changes to changes in the cerebral perfusion pressure. As in the prior case of using the regression slope, multiple thresholds have been proposed to distinguish between intact and impaired autoregulation.

Czosnyka *et al* [13] studied 82 patients with head injury. The intracranial pressure (ICP), arterial pressure, and transcranial Doppler flow velocity were captured during 2-hour periods. The time-averaged mean of the flow velocity was calculated. The correlation coefficient between the cerebral perfusion pressure and the mean flow velocity was calculated during 3-minute epochs, and the correlation coefficients were averaged over all epochs. A positive correlation between flow velocity and cerebral perfusion pressure was assumed to indicate pressure passivity. The study reported a significant correlation between pressure passivity and the outcome after head injury.

Several other studies have proposed other correlation thresholds to define autoregulation. Lam *et al*[10] proposed a threshold of 0.5 for correlation to distinguish between autoregulation and pressure passivity. Buijs *et al* [7] reported that in their study population of infants undergoing cardiopulmonary bypass, the mean correlation for pressure-passivity was 0.88.

While correlation coefficients provide a convenient way to quantify how well values of two variables track, it does not necessarily provide a good measurement for autoregulation assessment. High

values of correlation do not provide any information about the slope between the two variables. As a result, it is possible for the correlation between the cerebral perfusion pressure and the cerebral blood flow to be large, but have a negligible slope, indicating that the patient is actually autoregulating, contrary to what the information about the correlation alone would have suggested. Information about the correlation coefficient as well as about the slope between the two variables is needed to make a more accurate assessment of the autoregulatory system.

Panerai *et al*[26] proposed a combination of correlation coefficient and regression slope to assess autoregulation. In their study of 33 premature newborns, they collected 5-minute recordings of the mean arterial pressure and the cerebral blood flow velocity. The recordings were classified as either autoregulating or lacking autoregulation by applying a threshold test to correlation and slope values of each recording. The thresholds selected in their work were 0.3 for correlation and 0.5%/mmHg for slope. The recordings below these thresholds were considered to be autoregulating. In addition to these two thresholds, the authors imposed another condition. Only recordings that show a change in the mean arterial blood pressure of more than 5mmHg could be analyzed to assess autoregulation. This condition is reasonable because if the blood pressure does not change sufficiently, the slope between cerebral flow and blood pressure does not provide enough information to assess the autoregulatory system.

While static analysis provides information about the state of the autoregulatory system, its major drawback is that it considers only the steady-state response of the cerebral blood flow to a change in the blood pressure. Static analysis gives no information about how the cerebral flow changes, or how quickly it rises or falls.

Dynamic Analysis

The mechanisms responsible for vasomotor control of the cerebral circulation require time to affect changes in the cerebro-vascular resistance. This implies that when the blood pressure changes suddenly, the CBF also changes in response, but then returns to its original level as the CVR is changed. It is this transient response of CBF's return to its initial level that dynamic analysis examines [22].

Aaslid *et al* [24] introduced the 'thigh cuff' method to produce a step-like change in blood pressure as a standard stimulus to study the temporal evolution of the CBF response. A step change of approximately 20mmHg was induced by rapidly deflating a thigh blood pressure cuffs following a 2-minute inflation above the systolic blood pressure. The instantaneous arterial blood pressure was measured using this servo-cuff method, and the cerebral blood flow changes were assessed by transcranial Doppler recording of middle cerebral artery blood flow velocity. The authors analyzed the blood pressure and the cerebral blood flow immediately following the step-like change in blood pressure. The slope of the cerebral blood flow with respect to time indicates how quickly cerebral

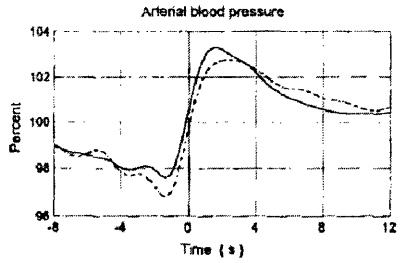
blood flow returns to its original level and is often used to grade autoregulation.

Information over a very short period of only about 20 seconds is needed for dynamic analysis. This assumes that changes in metabolism and brain activation, which effect the cerebral blood flow, are not likely to have a major influence during the time of measurements. However, with thigh cuff inflations lasting between 2–4 minutes and causing discomfort, this method cannot be seen as neutral to mental activation and changes in metabolic demands. Furthermore, several cycles of inflation/deflation are needed to gather sufficient amount of data, causing the procedure to last close to 10 minutes. During this time other factors might also contribute to a change in baseline metabolism and cerebral blood flow demands.

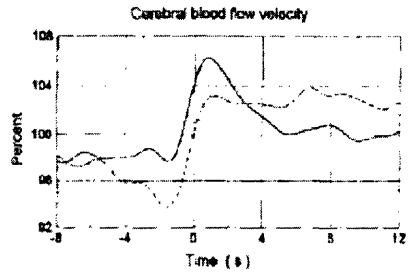
If the metabolic activity and the cerebral blood flow demands are assumed to not change significantly, the method described above tests the autoregulatory system by inducing a step change. However, such methods cannot be used for analyzing patients of stroke or head-injury or premature infants. Panerai *et al* [26] propose an alternative that can be used for patients who require delicate care. Instead of inducing step-like changes, which can cause severe damage, the authors studied the increases in blood pressure that occurred naturally. They detected transient increases in blood pressure and extracted the signal starting 8 seconds before and 12 seconds after the transient. All such 20 second signals were averaged for each recording. The instant corresponding to maximum rate of rise in BP was used as the point of synchrony to average the blood pressure and the blood velocity transients for all recordings. Such averaging is termed *coherent averaging.*

Figure 3-1 shows plots of coherent averaging for a population of autoregulating premature infants and for a population of non-autoregulating premature infants. In both parts of the figure, solid lines are used to represent graphs for the autoregulating population and dashed lines are used for the non-autoregulating population. Part (a) shows the average of spontaneous transients in blood pressure. For the autoregulating, as well as the non-autoregulating, population the blood pressure rises suddenly and then starts to come back towards its original baseline. Part (b) shows the response of the cerebral blood flow to these transitions in BP. For the autoregulating patient, the CBF initially rises. This rise is expected, because the autoregulatory system requires a finite amount of time to respond to BP changes. However, after the initial rise, the CBF begins its descent towards its original level. This is not the case for the non-autoregulating population. After the initial rise of CBF in the non-autoregulating population, the blood flow does not even start its descent in the following 12 seconds. This implies that even if autoregulation is not entirely impaired, it is significantly delayed compared to the autoregulating population.

The slope of the CBF after the initial rise can be used to grade autoregulation. The quicker the blood flow returns to its original level, the better the autoregulation function. A slope close to zero indicates that after the initial rise in CBF due to change in BP, the blood flow stayed close to the new higher level. Thus, a small slope implies pressure passivity. Figure 3-1 suggests that



(a) A spontaneous sustained increase in blood pressure



(b) The corresponding cerebral blood flow at the time of the increase in blood pressure

Figure 3-1: *A sample dynamic assessment of autoregulation. The solid lines show the data for an autoregulating patient and the dashed lines show data for a non-autoregulating patient [26].*

autoregulation was taking place within 1 to 2 seconds. This pattern was not observed in records that were believed to be pressure-passive.

Tiecks *et al* [4] compared the static and the dynamic analyses of autoregulation for 10 adults undergoing elective orthopedic surgery. All the data was gathered from patients with intact autoregulation during propofol anesthesia. For static analysis, phenylephrine was used to raise the blood pressure, and for dynamic analysis, rapid deflation of blood pressure cuff around one thigh was used to reduce the blood pressure suddenly. Transcranial Doppler ultrasonography was used to measure the cerebral blood flow velocity. The authors found the results of static autoregulation and dynamic regulation showed good correlation, with r=0.93. Such high correlation might suggest that static and dynamic assessments are comparable.

However, the authors point out that static and dynamic analysis could potentially be testing different mechanisms. During static testing, the stimulus consisted of an increase in the arterial blood pressure, which should induce vasoconstriction of the resistance vessels to account for the autoregulatory response. During dynamic testing, however, the arterial blood pressure is lowered, which should lead to vasodilation of the blood vessels. Vasoconstriction and vasodilation could depend on different mechanisms of action, which could vary individually or could be affected to a different extent if autoregulation is impaired. Even if the underlying mechanism were the same, the ability to dilate or constrict the cerebral vessels shows some variability within individuals [4].

3.2.2 Frequency Domain Autoregulation Assessment

The frequency domain analysis of autoregulation analyzes blood pressure and cerebral blood flow in terms of frequencies. One of the premises that frequency analysis of autoregulation is based on is that autoregulation may respond to blood pressure changes of certain frequencies but not others.

Tsuji *et al* [16] used coherence to study autoregulation in the frequency domain. The authors studied 32 very low birth weight premature infants (gestational age: 23–31 weeks and birth-weight:

605–1870 grams). NIRS was used to measure the cerebral blood flow, and the mean arterial pressure was measured invasively by an arterial catheter pressure transducer. The authors studied the response of the autoregulatory system to very slow changes (occurring over several seconds) in blood pressure. Coherence was used to study the bandwidth of 0–0.1Hz. The authors reported concordant changes (coherence scores greater than 0.5 in HbD and MAP), consistent with impaired cerebrovascular autoregulation in 17 of the 32 infants. Eight of the 17 infants (47%) developed severe intraventricular hemorrhage (IVH) or periventricular leukomalasia (PVL) or both. Of the 15 infants with intact autoregulation, as indicated by coherence scores less than 0.5, only 2 (13%) developed severe brain injury. Thus, for the entire study population, 8 out of 10 infants who developed severe brain injury, exhibited high coherence scores [16]. These results imply that autoregulation, as assessed by coherence, is closely related to occurrence of brain injury.

Arterial blood pressure is known to vary spontaneously over a wide range of time scales, and cerebral autoregulation is known to respond to changes in blood pressure in several seconds [22]. Zhang *et al* [25] used transfer function analysis to study the response of the autoregulatory system when blood pressure changes abruptly. Acute hypotension was induced by thigh cuff deflation in ten healthy volunteers. Mean arterial pressure was measured in the finger and mean blood flow velocity was measured in the middle cerebral artery during supine rest. Transfer function gain, phase, and coherence function between changes in arterial pressure and CBF velocity (CBFV) were estimated. The impulse response function, calculated as the inverse Fourier transform of this transfer function, enabled the calculation of transient changes in CBFV during acute hypotension, which was compared with the directly measured change in CBFV during thigh cuff deflation. The authors report that the transfer gain increased substantially with increasing frequency from 0.07 to 0.20Hz in association with a gradual decrease in phase. In healthy adults, the coherence function was greater than 0.5 in the frequency range of 0.07-0.30Hz and less than 0.5 for frequencies less than 0.07Hz. These results suggest that coherence is high for frequencies greater than 0.07Hz even when autoregulation is intact.

The calculated transfer function was also used to predict changes in CBFV. The prediction was similar to the measured CBFV during thigh cuff deflation. This data suggests that changes in the cerebral blood flow that occur at the frequency range of 0.07-0.30Hz are related strongly to changes in arterial pressure and, furthermore, that short-term regulation of cerebral blood flow in response to changes in arterial pressure can be modeled by a transfer function with the quality of a bandpass filter in the frequency range of 0.07-0.30Hz.

Transfer function and coherence methods have been used by several researchers to estimate a model for the system that responds to changes in autoregulation. However, since the autoregulatory system changes not only from person to person, but also from time to time for each person, the estimation of the model parameters may not be useful a few minutes after the measurements are

made. Moreover, frequency domain analysis in a low frequency band requires more data than the time analysis methods.

3.3 Summary

Assessment of the baroreceptor reflex requires quantification of how well RR-intervals respond to changes in blood pressure. In the time domain, correlation coefficient and regression slope are used to estimate the tracking between the two signals. In the frequency domain, multiple studies have used spectral analysis and transfer function analysis to estimate and assess the baroreceptor function.

As in the case of baroreceptor analysis, autoregulation assessment can be performed both in the time and the frequency domains. Autoregulation assessment concerns the quantification of how well CBF follows the changes in BP. In the time domain, researchers have proposed static and dynamic autoregulation analyses. Static analysis focuses on assessing the overall response of the autoregulatory system: how does the cerebral blood flow change in response to a change in arterial blood pressure. Static analysis does not address the time in which this change occurs, and can be thought of as analyzing the steady state response. Dynamic analysis, in contrast, focuses on assessing the transient response of cerebral blood flow when blood pressure changes: how does the cerebral blood flow respond to changes in blood pressure soon after there is a spontaneous change in blood pressure.

Techniques for frequency domain analysis of autoregulation are similar to the ones used for baroreceptor analysis. Researchers have proposed the use of spectral analysis to calculated transfer function and coherence between the signals to assess autoregulation.

Chapter 4

Tool Description

4.1 Overview

Hemodynamic Data Analysis Tool, *HemDAT*, is a software tool created in Matlab to facilitate exploration of prerecorded physiological data that is believed to relate to brain injury in premature infants. This tool provides means to assess the conditions that are believed to predispose a pre-term infant to developing brain injuries such as intraventricular hemorrhage and ischemia. In addition to exploration of features of physiological signals, HemDAT can be used to assess the baroreceptor and the autoregulatory systems.

4.2 Input

HemDAT accepts files, or folders containing files, that contain representations of BP and CBF data as inputs. Each file is a header followed by a sequence of floating point values in a single column. The header contains the following information:

- sampling frequency in Hz
- length of the file in minutes
- type of data in the file
- starting time of the data
- stopping time of the data

An automated data preprocessor formats the data to relieve the user of having to remember statistics about the data. Such preprocessing proves useful because, for example, the user is no longer required to provide the sampling frequency of the data each time it is processed. Mistakenly

entering the incorrect sampling frequency can produce misleading results. Such misleading results are made unlikely by embedding the sampling frequency in the data itself. HemDAT includes a data preprocessing tool and an artifact eliminator.

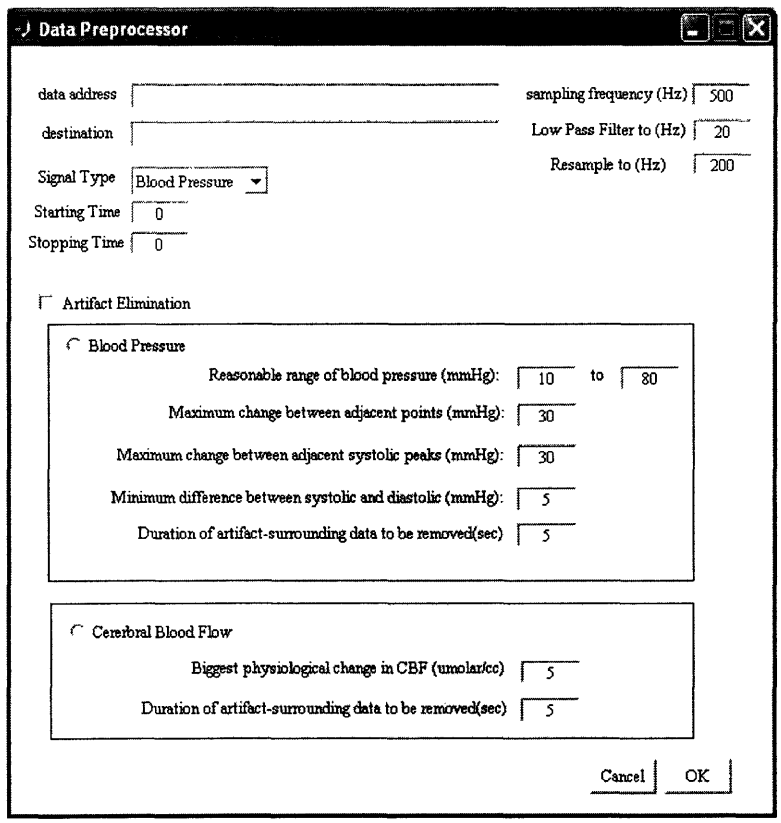


Figure 4-1: *A screenshot of the data preprocessor*

4.2.1 Data Preprocessing

Figure 4-1 shows a screen shot of the preprocessing utility. Input to the preprocessor is expected to be floating point values in a single columned text file. The data preprocessor provides four functions:

- Prepend data information: This function collects the information about the data that the user provides and prepends it to the data file in the order listed below:
  - Sampling frequency of the signal after it has been resampled at the rate specified by the user.
  - Length of the data in minutes, as calculated by the data preprocessor.
  - Type of data, which indicates whether the data is a blood pressure signal, a cerebral blood flow signal or neither.

- Starting time of the data.
- Stopping time of the data.

- Low pass filtering the data. While HemDAT supports any sampling frequency, for the purposes of the calculations performed, sampling frequencies of BP and CBF data do not need to be greater than 20Hz. Assuming the data has been sampled following the Nyquist theorem, it can be low pass filtered to the desired frequency. Low pass filtering the data to some frequency f_1 removes all frequency content greater than f_1 from the signal, thus removing information that changes more quickly than f_1. Using a low pass filter also addresses the removal of noise and jitter that might be present in high frequency data.

  Low pass filtering the data removes higher frequency content from the data, but it does not change the sampling frequency of the signal. If a signal was originally sampled at F_s and was then low pass filtered to f_1, it will still have the sampling frequency F_s, i.e. there will still be F_s sample points for each second of data.

- Resample to the desired frequency. The objective of resampling a signal is to change its sampling frequency. Assuming the signal had originally been sampled following the Nyquist criterion, its sampling frequency can either be increased (upsampled) or decreased (downsampled) without loss of information as long as the Nyquist criterion is still met.

  Downsampling is advantageous because if the data has been sampled at a much higher rate than required, it can be decimated to a lower frequency without loss of useful information. Doing so reduces a large data set to a more manageable size, which reduces the required storage space as well as the processing time. For example, if the data had been sampled at 500Hz, and we are interested only in frequency content below 20Hz, it can be resampled to as low as 20Hz without loss of information. The data is low pass filtered prior to decimation to avoid frequency aliasing.

  Upsampling is also advantageous in situations where a time resolution finer than the sampling frequency is required. Since the original data followed the Nyquist criterion, no new information is needed to increase the sampling frequency of the signal. A higher time resolution might be needed for detecting the instance when a peak occurs or identifying the instance of greatest derivative. HemDAT uses both of these identifications in several functions.

- Artifact Elimination. This function seeks to exclude from analysis the data that cannot be physiologically plausible. The criterion used to detect such data is described in the following section.

The data preprocessor low pass filters the data prior to resampling it. Artifacts are then eliminated from the data if the user chooses the option to do so. Finally, information about the data is

prepended to the data.

4.2.2 Artifact Eliminator

Artifacts are portions of data that do not correspond to meaningful physiological data. For example, in premature infants, blood pressure is usually measured using a catheter in the umbilical artery. When blood tests need to be conducted, blood supply to the catheter is cut off while blood is collected from the umbilical artery. This can cause a non-physiologically related change in the blood pressure level. Moreover, in the absence of real data, noise might be recorded.

To identify such artifacts, we use our knowledge of the physiologically relevant features of the signals. Artifact elimination must be done prior to analyzing the signals because unless these artifacts are removed, HemDAT will analyze them and produce potentially misleading results. Once identified, data surrounding the identified time is replaced with NaNs (Not a Number) to indicate the removal of an artifact. As shown in Figure 4-1, users can specify the duration of data to be replaced. NaNs are used to replace artifacts because they do not assign a false value to data during an artifact. Even if an unlikely false value is used to replace artifactual data, it can mistakenly be used in data analysis and can produce misleading results. Alternatively, the data during the times of artifacts can be completely removed. However, if this is done, the user will have no way of knowing that an artifact at that time was removed, and this might lead to confusion.

Blood Pressure

The artifact eliminator uses the following criteria to detect physiologically unlikely data in blood pressure signal. The criteria are described in the order they are checked. All the points that meet a certain criterion are detected and eliminated before the artifact eliminator checks the next criterion.

- Criterion I: Blood pressure must be in a reasonable range. We choose a conservative range of 10-80mmHg to be reasonable. Most premature infants have blood pressure values in the range of 20-50mmHg. Blood pressure must always be positive. Moreover, if the blood pressure is close to zero, the infant will not experience sufficient circulation. NICU staff would attend to such a situation urgently before the blood pressure dropped as low as 10mmHg. 80mmHg is too high a blood pressure for premature infants with immature vascular system. The NICU will treat the infant and lower the blood pressure before it gets as high as 80mmHg.

  Figure 4-2 shows a sample of blood pressure data containing artifact. From our knowledge of the properties of blood pressure signals, we know that data on the right half of the figure is most likely artifactual.

  The above described criterion will detect where the blood pressure is negative, which is physiologically implausible. This criterion will also detect the data to the right of the negative blood

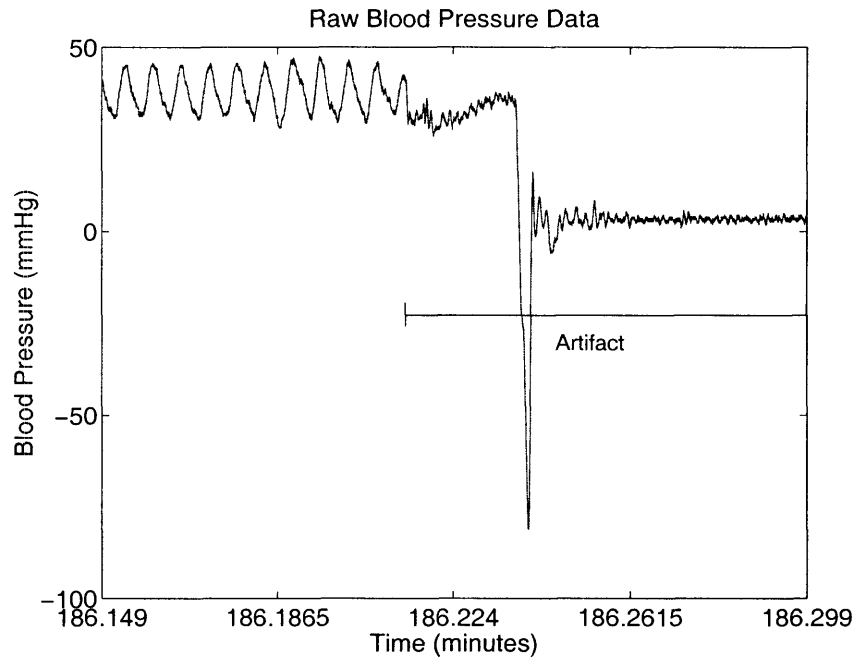


Figure 4-2: *An example of physiologically unreasonable values for blood pressure.*

pressure point in Figure 4-2, because it is close to zero. However, it will not detect the data to the left of the negative BP, which we know to be artifactual. This artifact will be detected by Criterion IV, described later in this section.

- Criterion II: Difference in pressure between adjacent points must be less than 20mmHg. The recommended sampling frequency for HemDAT is at least 20Hz. It is physiologically unlikely for the blood pressure to rise or fall more than 20mmHg in 1/20th of a second.

  Figure 4-3 shows blood pressure data with artifact. Once again, from our prior knowledge of blood pressure signals, we can visually tell that the marked region is an artifact. There are two types of artifacts in this figure. The first is where blood pressure values are negative, which, as discussed earlier, will be detected under Criterion I. The other artifact, which occurs on either side of the negative values in this figure, is a large change in blood pressure. Such large changes are physiologically implausible and will be detected under Criterion II.

- Criterion III: Difference between adjacent systolic peaks must be less than 30mmHg. In premature infants, systoles occur at a rate of 2-3Hz. It is physiologically unlikely for adjacent peaks to change by more than 20-30mmHg. 30mmHg threshold is used as a conservative value.

- Criterion IV: Difference between systolic and diastolic pressure must be at least 5mmHg. If there isn't enough variation in the data, it is likely to not be legitimate blood pressure data. If the difference is less than 5mmHg, it is considered an artifact.

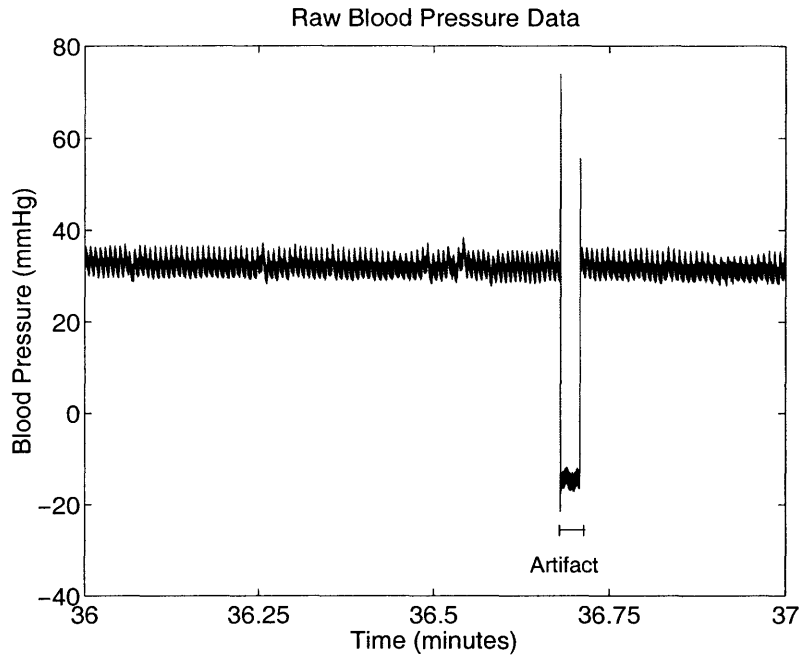


Figure 4-3: *An example of physiologically unreasonable change in blood pressure*

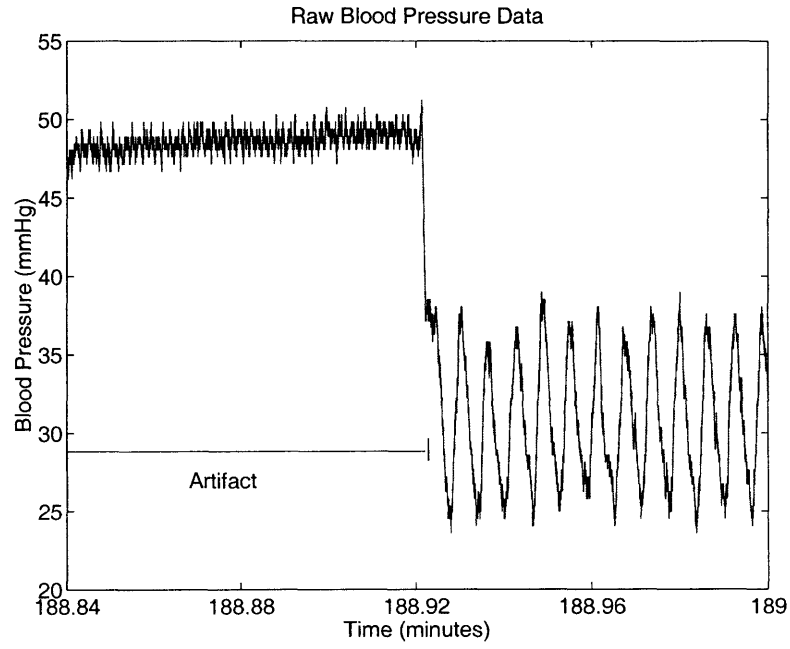


Figure 4-4: *An example of a lack of sufficient variation in blood pressure*

Figure 4-4 shows portion of data with such an artifact. Once again, we can visually label the left half of the figure to be artifactual. The data on the left does not show the pulse structure and the variations that the right half does. This criterion detects such artifacts.

As mentioned earlier, this criterion also catches the artifact on the left of the negative blood pressure in Figure 4-2.

Cerebral Blood Flow

As in the case of blood pressure, artifacts in cerebral blood flow are values in the signal that are physiologically implausible. Following criterion is used to detect an artifact. Physiologically, the flow of blood in the brain cannot change by more than a few micromolar/cc over the course of a second. If a CBF signal has been measured following the Nyquist criterion, adjacent points cannot vary by more than a few micromolar/cc. Thus, for CBF signals, an artifact is said to occur when values of CBF for adjacent points varies by more than 5micromolar/cc. There are two situations that arise with such an artifact:

- One point artifact: A one point artifact occurs when in the midst of physiologically plausible data, there is one point that it either too high or too low compared to the rest of the data. The data suddenly rises or falls at one point and then returns to the baseline at the next point. Such artifacts can be 'mended' by substituting a more likely value for that point, such as the average of the neighboring points. Even though the substituted value will most likely not be the true value of the signal, it will not cause as much deviation in the result as the artifact value would have.

- Sustained deviation: A sustained deviation occurs when the value of the signal suddenly changes, as in the earlier case, but does not return to the baseline value at the next point. The higher or lower baseline is maintained for several point, or several seconds. Such artifacts cannot be 'mended' as we would have to attribute false values to a long duration of signal. In these cases, the artifact must be removed.

The default values used in elimination of artifacts in cerebral blood flow and blood pressure are conservative and based on data from premature infants. As shown in Figure 4-1, the thresholds used in the artifact detector can be changed using the preprocessing utility. The above criteria for identifying artifacts are based on what is physiologically expected. This approach will not identify the artifacts that fall in the physiologically expected range, which may skew the analysis produced by HemDAT.

The instances that are detected by one of the above criteria are replaced with NaN's. However, it is likely that the time instance that the artifact eliminator detects as an artifact is not the only instance of artifactual data. Data before and after is likely to be artifactual too, even if it meets

the physiological criterion. Again, consider blood pressure measurement when the blood supply to the catheter is blocked because blood is needed to conduct a blood test; the blood supply will not drop instantaneously. In fact, the change in blood supply might occur over several seconds as the supply is slowly turned off. The blood pressure will slowly decrease, but might still meet the above described physiological criterion. However, this is not a true measure of the infant's blood pressure and must be excluded from analysis. Thus, the artifact eliminator replaces user-specified duration of data before and after each instance of detected artifact.

4.3 HemDAT: Hemodynamic Data Analysis Tool

HemDAT can be used to explore various features of the physiological signals of interest. Figure 4-5 shows a screenshot of HemDAT when it is started. As seen in the figure, HemDAT is divided into four parts.

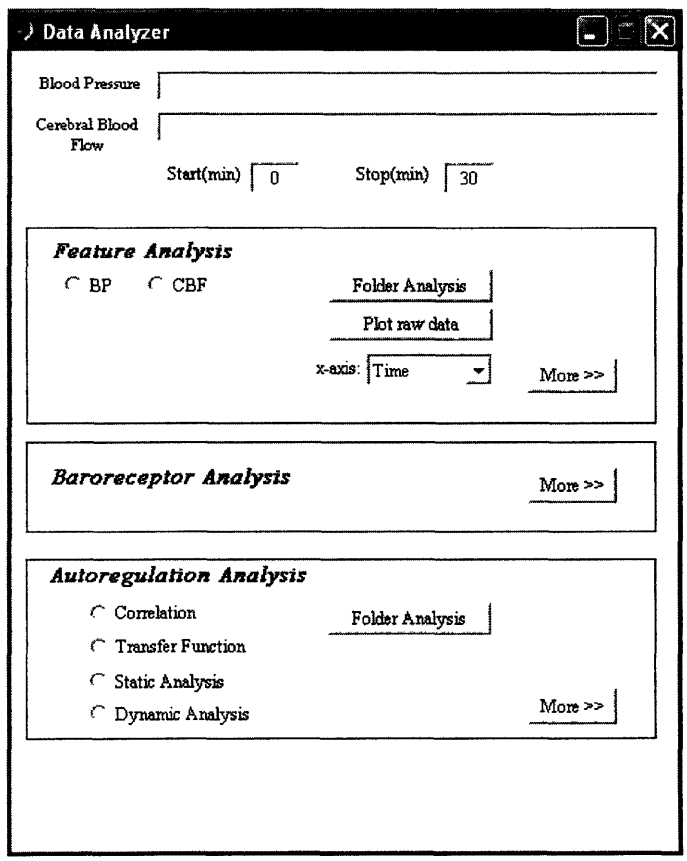


Figure 4-5: *A screenshot of HemDAT*

The top part of HemDAT serves to collect information about input data to be analyzed. The next three parts each assist in the exploration of three factors thought to contribute to susceptibility

to brain injury:

- features of blood pressure and cerebral blood flow
- state of the baroreceptor reflex
- state of the autoregulatory system

4.3.1 Parameters

One of the features that HemDAT offers in the analysis of blood pressure and cerebral blood flow signals is the ability to change the parameters used in calculations. This section describes the parameters that are common to multiple calculations. The parameters that are unique to a certain type of analysis or feature calculation are discussed when that feature is described.

Following are some of the parameters that the user can alter:

- *Window Length:* Each signal is segmented into small windows, and calculations occur over each window. The user specifies the size of window in time. The bigger the window size, the more averaged the results are. However, if the windows are too small, calculations will be computationally expensive, and salient features might be missed if the window length is not large enough to capture them sufficiently. For example, if we are interested in calculating variation within a window of systolic blood pressure, we should not choose a one second window because it would include only 2–3 systolic peaks and not give a good estimate of the average variation in blood pressure at that time. A 30–60 second window would provide sufficient systolic peaks to estimate the variability reliably. Windows as big as 5–10 minutes can be used if the user is interested in long term averaged information.

- *Overlap Length:* The overlap length determines how much adjacent windows overlay. If the overlap is non-zero, the signal will be segmented into non-mutually exclusive windows. However, overlap length of zero makes the windows mutually exclusive. Overlapping is especially useful in the situations where an interesting feature might appear near the end of a window, or might be split between two windows. In such a case, it is possible that neither of the two windows will capture the feature sufficiently, and it will go unanalyzed. However, if the windows are overlapped, that feature is more likely to be sufficiently captured. Typically, overlap is half the window size.

A second set of user specified parameters is related to the calculation of coherence, which is used to assess the baroreflex and the autoregulatory functions. Coherence is calculated using the welch-algorithm, which divides the data into overlapping segments to calculate an N-point Fast Fourier Transform of each window. This transform is used to calculate the power spectra and the

cross-spectra of the two signals in each window. These spectra are used in calculating the coherence between the two signals. Following are the parameters that the user can set on HemDAT:

- *NFFT:* is the number of points to be used when calculating the FFT of the segmented data. This number must be a power of 2 and at least as large as the FFT window length parameter explained below. Coherence is calculated at 1 + NFFT/2, equally spaced frequency starting from 0Hz until the bandwidth of the signals. This implies that if the bandwidth of the signals is large, but the frequency bandwidth of interest is narrow, we would need to use a large NFFT to ensure that coherence is calculated at multiple frequencies in the bandwidth of interest. However, if the NFFT is large, the time segment that is analyzed must also be large, thus, we trade time resolution for frequency resolution.

- *FFT Window Length:* FFT window length is not the same as the time window length described earlier. Once, the entire data set has been segmented into smaller windows, each window must be processed to find its frequency content. This requires that each window be further segmented into smaller FFT windows. The FFT window length refers to the further segmenting of the windows. Each window is divided into segments of FFT window length and FFT is computed on each. This number must be a power of 2. Moreover, since Fourier Transforms are computed on windows of this size, this number should be large enough to allow a reliable estimate of its frequency content. Recommended values are in the neighborhood of 1024, but strictly less than the number of points in the time window.

- *FFT Overlap:* When the data is divided into segments, the segments overlap by this number of points. Typically, overlap is half the window length. This ensures that the calculations do not miss an interesting feature because the data of interest was split between two windows.

4.3.2 Input

Input to HemDAT can be addresses of either files containing signal data or folders containing such files. Folder analysis can be performed on only some of the features included in HemDAT. This section discusses the use of HemDAT for files as inputs. The *Folder Analysis* section discusses analysis of folders of multiple files.

Entering the addresses of both, blood pressure and cerebral blood flow signals, is not necessary if the user intends to explore only one of the two signals. If the files/folders cannot be found at the specified address, HemDAT will give an error message and allow the user to correct the address.

The users must also enter the duration of the signal to be analyzed. Each input file is assumed to start at minute 0. The users can specify where in the data to start and stop the analysis by specifying the starting and stopping points, respectively. The users can also use `end` as a stopping

point to indicate that the data between the specified starting point and the end of the file should be analyzed.

4.3.3 Signal Feature Analyzer

The second part of the tool, labeled 'Feature Analysis' is used to facilitate the analysis of individual input signals. Figure 4-6 shows a screenshot of this part.

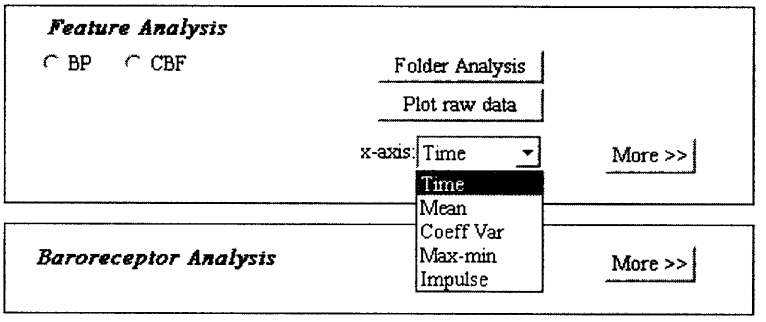


Figure 4-6: *The Feature Analysis section of HemDAT*

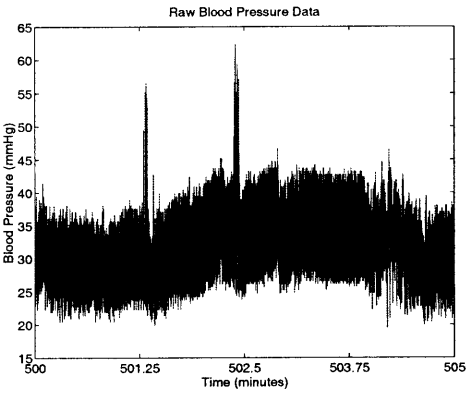
Plotting Data

The *Plot Raw Data* button plots data directly from the specified source. The sampling frequency is extracted from the data, and the data in the specified file is plotted against time without any processing. Plotting the data prior to any processing can help in understanding of trends in the data, the quality of the data, and in visually identifying events of interest.

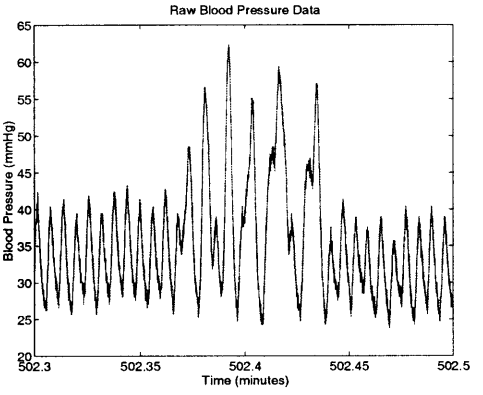
Figures 4-7 and 4-8 show samples of blood pressure and cerebral blood flow, respectively, over a 5-minute period. Blood pressure data shown here was originally sampled at 500Hz. It was low pass filtered and resampled to 20Hz using the preprocessing tool. We see in part(a) that there are two instances when the blood pressure suddenly increases, stays high for a few seconds and then returns to its previous baseline. If the user is interested in such events, the signal can be studied in more detail near the time of the sudden changes. A zoomed in version of one of the sudden peaks is show in part(b). The zoomed figure shows that the increase in blood pressure lasted for 3–4 seconds and then the blood pressure returned to normal.

Cerebral blood flow was sampled at 6Hz and is shown in Figure 4-8 prior to any processing. We see a sharp rise followed by a quick fall between minute 11 and minute 12. We can zoom in to investigate the beginning of this peak in more detail. A zoomed-in figure is shown in part(b).

Additionally, we notice that the range of cerebral blood flow plotted in these figures goes from -10–10 micromolars/cc. These clearly cannot be true cerebral blood flow because blood flow cannot

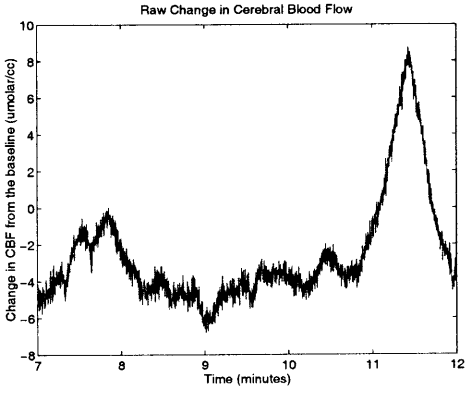


(a) Plot of sample blood pressure data. Users can zoom in to inspect regions of interest more closely.

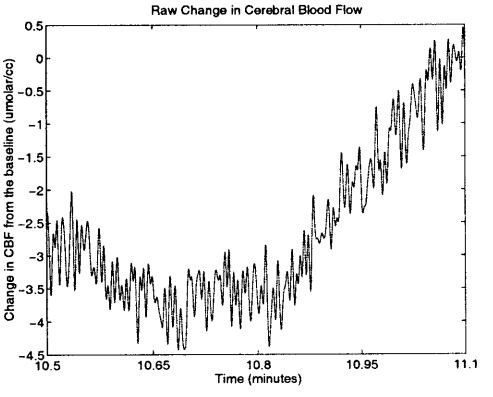


(b) Plot of an interesting region where blood pressure increases abruptly and then returns to normal level

Figure 4-7: *Sample blood pressure data.*



(a) Plot of sample cerebral blood flow. Users can zoom-in to inspect regions of interest more closely.



(b) Plot of an interesting region where the blood flow start to rise sharply.

Figure 4-8: *Sample cerebral blood flow data.*

be negative. The skewed values of CBF can be attributed to the measurement technique used. The plotted data was measured using Near-Infrared Spectroscopy (NIRS). NIRS can measure the change in cerebral blood flow from when the measurement was started, but it cannot measure the absolute value of cerebral flow when measurement starts. As a result, CBF at time 0 is used to choose the '0' point of the y-axis, and the plotted data is the change in CBF since time 0.

Signal Features

This part of HemDAT allows additional ways of exploring various features of individual signals. Following are the features that are included in HemDAT:

- Mean: For BP, the mean systolic pressure is calculated by finding the values of the peaks in the blood pressure signal and averaging them over each window.

  For CBF, the mean is the average of CBF values in each window.

- Coefficient of Variance: For BP, this coefficient is calculated by finding the average difference between adjacent systolic peak values in each window. This gives a better understanding of how much the pressure changes, or 'jitters', than calculating standard deviation. Classically defined variance,

  $$E[(X - E[X])^2],$$

  is a probabilistic measure. As a result, any two signals that have the same distribution of values will have the same variance. For example, consider two signals, A and B, that can take only two values, either 0 or 1, and they each have equal number of 0's and 1's. Further suppose signal A is a sequence of all 1's followed by a sequence of all 0's, and signal B is a sequence of alternating 1's and 0's. With the exception of change in signal from 1's to 0's, values in signal A are stable and do not change. Signal B, however, is not as stable and its values vary considerably. According to the classical definition of variance, both the signals will have the same variance. However, following the definition used by HemDAT, signal A will have a variance close to 0, indicating that the values in the signal do not change much, and signal B will have variance of 1, indicating that on average, adjacent values of the signal vary by 1. HemDAT's result better capture the notion of volatility in the signal.

  For CBF, the difference between adjacent values are averaged over each window.

- Max-Min: This is the difference between the maximum and the minimum value of BP or CBF in the window. This feature gives a sense of the range of variability in a window.

- Impulse: This function calculates the number of sudden changes. These 'sudden changes' are defined by the users by providing values for threshold change in signal, *dsig*, and threshold

change in time, *dtime*. A sudden change is said to occur whenever the signal changes by *dsig* or more in time *dtime* or less.

The data is first divided into segments of length *dtime*/4. The change in signal in each segment is calculated. If this change is greater than or equal to *dsig*, then, by definition, an impulse has occurred. The point of impulse occurrence is stored. Next, changes in windows of length *dtime*/2 are obtained by adding the changes in adjacent *dtime*/4 windows:

If the combined changes are greater than *dsig*, the point of impulse occurrence is stored and the process is repeated for lengths 3*dtime*/4 and *dtime*. Final points of impulse occurrences are the union of impulse occurrences for various length segments. The following pseudo-code illustrates the algorithm used.

```
impulses = [ ];
for i = 1:num_windows
    difference = diff(window(i)); % derivative of the window.

    diff_in_0.25dtime = [ ];
    for j = 1:floor(length(window(i))/(0.25*dtime))
        diff_in_0.25dtime = sum(difference(0.25*dtime*j:0.25*dtime*(j+1)));
        % cummulative derivative in 0.25*dtime long segments.
    end
    impulses = find(diff_in_0.25dtime >= dsig);
    % impulse if the change in dtime/4 is greater than dsig

    diff_in_0.5dtime = [ ];
    for j = 1:length(diff_in_0.25dtime)-1
        diff_in_0.5dtime = diff_in_0.25dtime(j:j+1);
        % cummulative derivative in 0.5*dtime long segments.
    end
    impulses = union(impulses, find(diff_in_0.5dtime >= dsig));

    diff_in_0.75dtime = [ ];
    for j = 1:length(diff_in_0.25dtime)-2
        diff_in_0.75dtime = diff_in_0.25dtime(j:j+2);
        % cummulative derivative in 0.75*dtime long segments.
    end
    impulses = union(impulses, find(diff_in_0.75dtime >= dsig));

    diff_in_dtime = [ ];
    for j = 1:length(diff_in_0.25dtime)-3
        diff_in_dtime = diff_in_0.25dtime(j:j+3);
        % cummulative derivative in dtime long segments.
    end
    impulses = union(impulses, find(diff_in_dtime >= dsig));

end
```

Signal features can be analyzed in two ways.

- The first way is to understand the change in feature values over time. For example, as shown in Figure 4-6, the x-axis of the final intended plot can be chosen from the drop-down menu.

- The second way to analyze features is to understand the relationship between changes in two features. For example, HemDAT can be used to analyze how the variation in CBF changes as the mean of CBF changes.

Feature vs. Time

To understand the evolution of a certain feature value over time, a graph of feature values versus time can be created by choosing time for the x-axis. Next, the user can choose up to two features to be plotted on the y-axes on the same graph. After the features have been selected, HemDAT requests further information about window and overlap lengths for each feature, as shown in Figure 4-9.

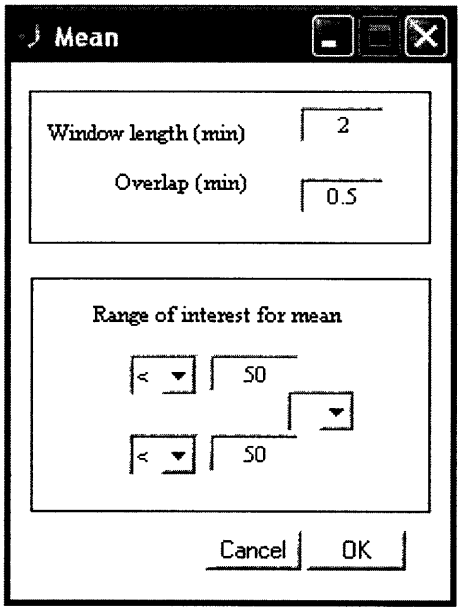


Figure 4-9: *A window requesting parameters for calculating the mean of a signal*

The signal is divided into windows of the specified length with the specified overlap, and features are calculated and averaged over each window. Additionally, the user can define ranges of interest for each feature value. This allows the user to see which windows meet the threshold criterion, and what percentage of the windows up to that point in time, meet the criterion. Figure 4-10 shows an example.

For example, if we are interested in blood pressure, we can plot the mean of blood pressure against time. Suppose we want to find out how often blood pressure is between 41mmHg and 43mmHg. We can use the comparators and combinator in the window shown in Figure 4-9 to select this range of interest. The output is shown in Figure 4-10. The curve in '*' carries information about the first criterion, the curve in '+' carries information about the second criterion, and the curve in 'o' carries information about the conjunction of the two criteria. Looking at the rightmost point of

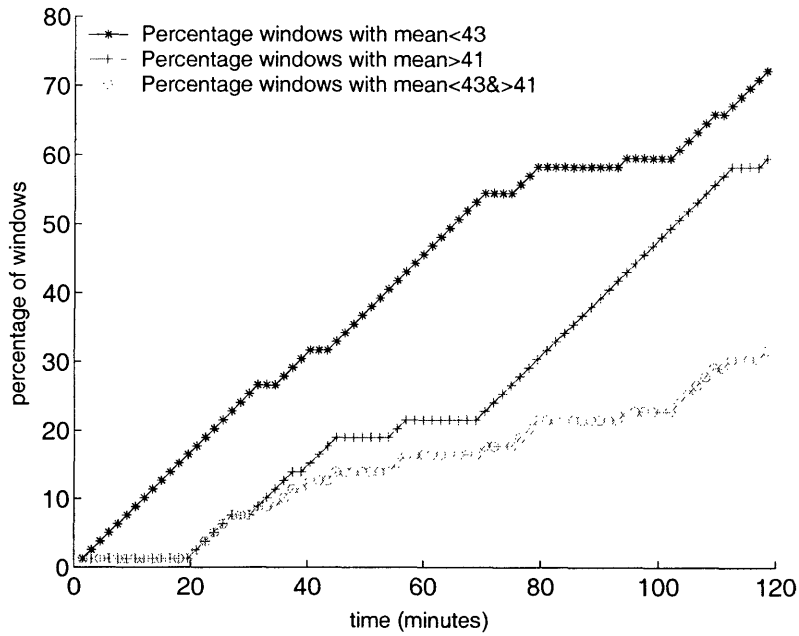


Figure 4-10: *Plot of percentage windows that meet the specified threshold criterion*

the three curves, we learn that the first criterion was met by about 73% of all windows. Similarly, the second criterion was met by about 60% of all windows, and both criteria were met by about 32% of all windows. Moreover, no windows meet the second criterion for the first 20 minutes of the data. Similarly, we see that at minute 40, about 11% of the total number of windows have met the conjunction of the two criteria. This tells us that of the 32% of the total windows that eventually meet both criteria, 11%, or close to a third, occur before minute 40.

In addition to the threshold curve, the output includes a graph of feature vs. time as well as a histogram of the values that the feature takes, as shown in Figure 4-11.

Feature vs. Feature

To understand how one feature relates to another feature, a graph of one feature against another one can be created. As in the previous case, such a graph can be created by choosing the appropriate features for the x-axis and the y-axis. The user specifies the window and overlap lengths to be used for both the features. Figure 4-12 shows an example of a scatter plot showing how the max-min in a window relates to the mean in the window.

4.3.4 Baroreceptor Analysis

The baroreceptor reflex is the system that minimizes the impact of short-term changes in the blood pressure. When the blood pressure increases, the blood vessels are stretched, which triggers the

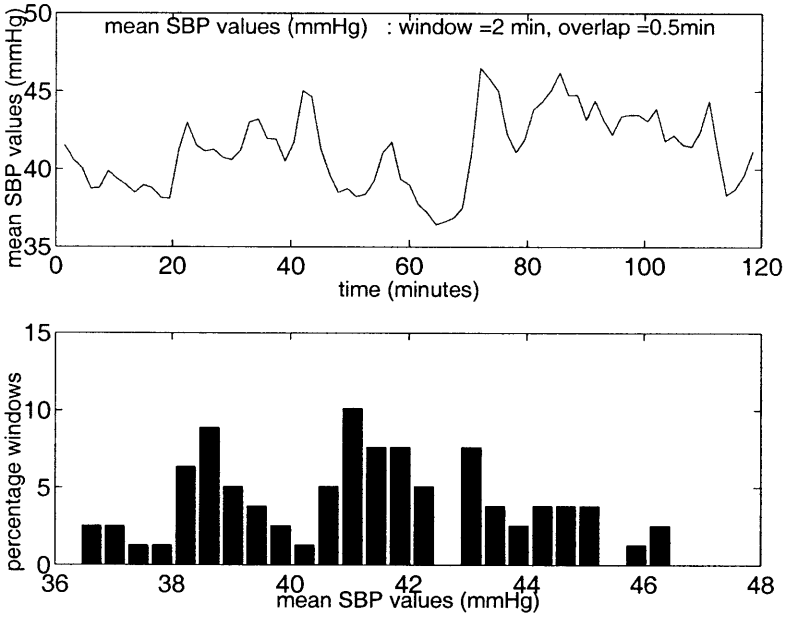


Figure 4-11: *The output of calculating the mean systolic blood pressure over time in 2-minute windows with 30-second overlap.*

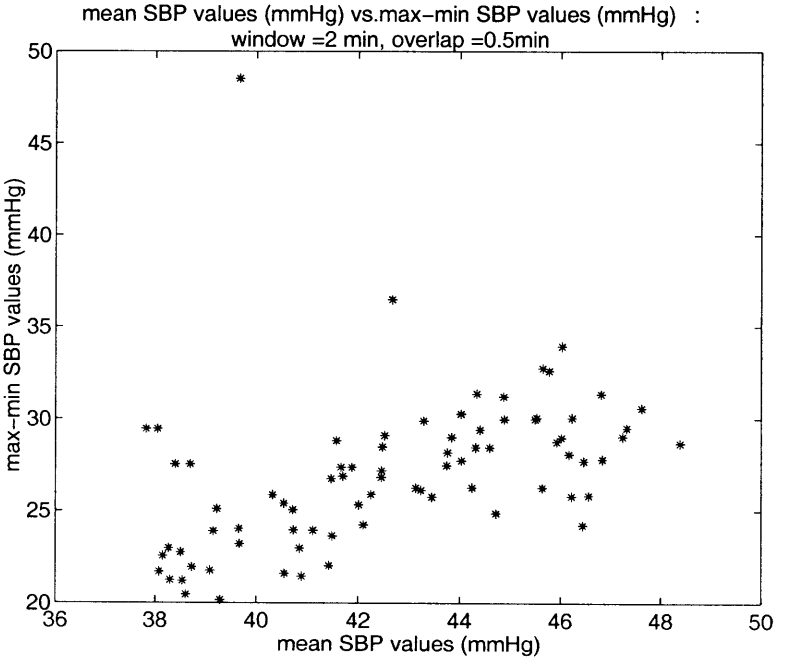


Figure 4-12: *The output of analyzing a max-min against the mean blood pressure*

central nervous system to reduce the cardiac output and restore the blood pressure. Similarly, when the blood pressure decreases, the central nervous system is triggered to increase the cardiac output. The baroreceptor reflex is crucial in maintaining constant blood pressure in the short-term.

If the baroreceptor reflex is not functioning correctly, there will be many short-term changes in the blood pressure. In premature infants, these changes can cause stress on the underdeveloped and fragile blood vessels and lead to their rupture. Thus, assessment of the baroreceptor function is essential to the assessment of an infant's propensity to develop brain injury.

Baroreceptor assessment is concerned with the relation between the systolic pressure and the time difference between successive systolic peaks. If the baroreceptor reflex is functioning, an increase in the blood pressure will trigger a reduction in the cardiac output, thus increasing the *RR-interval*, which is the spacing between successive pulses. The pulses are spaced closer together if the blood pressure reduces.

HemDAT provides an assessment of the baroreceptor reflex using coherence analysis. The data is first low pass filtered to 5Hz, and then resampled at 200Hz. As discussed in chapter 3, the baroreceptor reflex responds to frequencies lower than 1Hz. Thus, by low pass filtering and resampling, we do not lose any important information. The resampling rate is restricted by the time resolution needed for the RR-interval, which is 1/resampling-rate. In premature infants, 2–4 cardiac cycles occur in one second, making the RR-interval span the range of 250–500msec. However, the changes in the RR-interval in response to the changes in the blood pressure are expected to be in the range of 5–10msec. The time between successive data points must be sufficiently small to allow the detection of changes as small as 5msec. If the resampling frequency is 20Hz, for example, the time resolution for the RR-interval will only be 1/20Hz = 50msec. By using a resampling rate of 200Hz, the resolution is improved to 5msec.

The next step is to detect peaks in the blood pressure data. The peak detection algorithm searches for the indices where the derivative of the blood pressure changes from being positive to negative. However, this approach catches small bumps in the signal that are not the peaks of a cardiac cycle. This problem is solved by checking that the next two points following every detected point where the derivative changed signs have a negative derivative and two points preceding the detected point have a positive derivative.

Systolic blood pressure is the value of blood pressure at the peaks of blood pressure signals, and the RR-interval is the time difference between successive peaks. The systolic pressure and the RR-interval signals are created by identifying the peaks in the blood pressure signals. Both of these are defined only at the beginnings of the cardiac cycles and are unequally spaced. They are interpolated using a cubic function to synthesize equally spaced signals in time. The synthesized signals have the same sampling frequency as the original blood pressure signal.

The objective of this analysis is to determine whether RR-interval changes in response to blood

pressure. Coherence analysis is used to quantify the relationship between the RR-interval and the blood pressure. Figure 4-13 shows the screenshot of a window requesting the parameters to be used in this analysis. As seen in the figure, the user provides three sets of parameters. The first set is the window and overlap lengths, which have already been discussed.

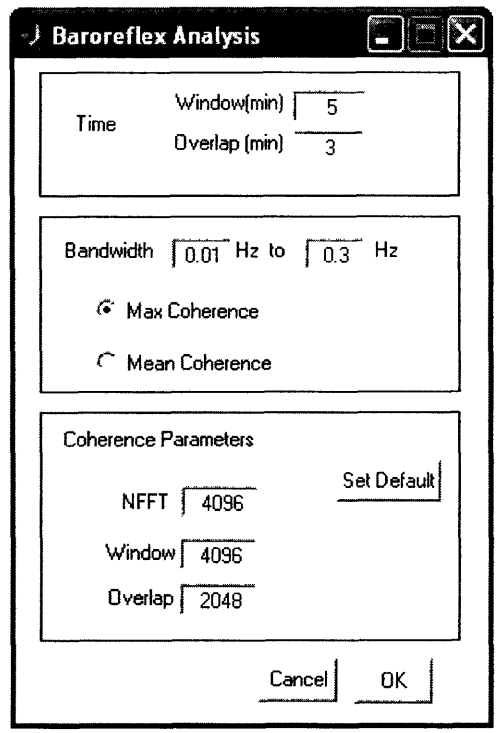


Figure 4-13: *A window requesting parameters for baroreceptor function analysis*

The second set of parameters specify the frequency bandwidth. HemDAT allows analysis of any frequency band between 0Hz and $F_s/2$. For baroreflex analysis, the frequency band where we expect to see meaningful tracking between the BP and the RR-interval is in the 0–1Hz range [20]. Additionally, the user can analyze either the maximum or the mean coherence in the chosen bandwidth of each window. While maximum coherence tells the highest possible tracking of the two signals, the mean coherence is a more robust and reliable indication of tracking between two signals.

The third set of parameters allows the user to choose the parameters to the Matlab function *cohere*, which is used to calculate coherence. These parameters were discussed in an earlier section.

Figure 4-14 shows the output of the Baroreceptor Analysis part of HemDAT. Baroreceptor Analysis produces a graph that shows how the systolic blood pressure changes over time, and another graph that shows how the RR-interval changes over time. In addition to these plots, HemDAT also outputs the coherence between the two signals. Durations of high coherence suggest that the RR-interval changes when the blood-pressure changes, which suggests functioning baroreflex. Durations of low coherence indicate that the RR-interval changes did not match the blood pressure changes.

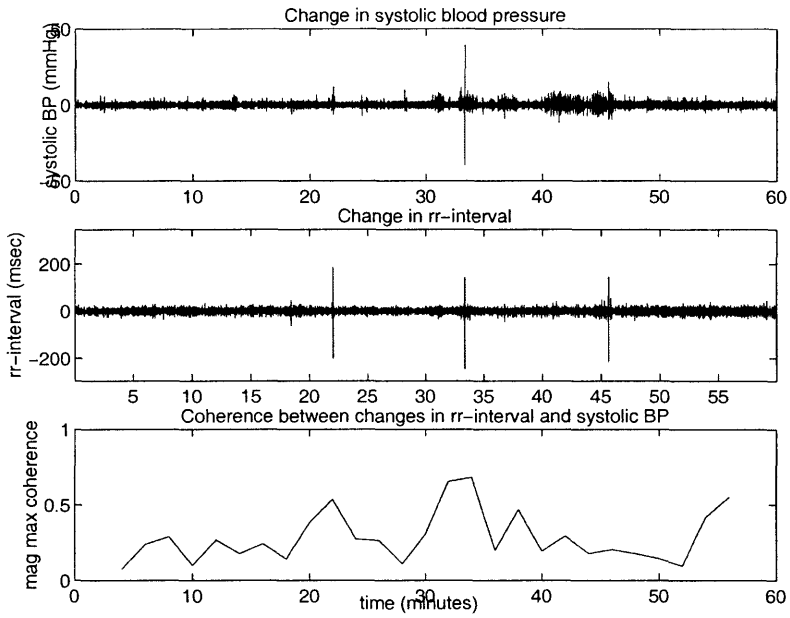


Figure 4-14: *Sample output of analysis of the baroreflex function*

The functionality of the baroreceptor reflex cannot be determined by observing the coherence values alone. The baroreflex is tested only when the blood pressure changes. When the blood pressure is not changing, or changing by a small amount, high coherence between the RR-interval and the blood pressure is not necessarily indicative of preserved baroreceptor function. Similarly, low coherence may not be an indicator of failed baroreflex if the blood pressure is not changing sufficiently. Thus, the coherence between the blood pressure and the RR-interval is an indicator of functioning of the baroreflex only when the blood pressure is changing. Moreover, there are multiple other factors besides blood pressure change that affect the RR-interval. These factors have not been taken into consideration here. As a result, we cannot conclusively assess the functioning of the baroreceptor reflex.

4.3.5 Autoregulation

The autoregulatory system maintains a constant physiological state. For our study of how brain injury is caused in premature infants, we are interested in the autoregulation in the brain. The cerebral autoregulatory system is responsible for maintaining a constant blood flow in the brain even when the blood pressure changes. Some change in CBF is normal. CBF often changes in response to change in mental activity, amount of carbon dioxide and oxygen in the blood. In these situations, CBF changes in response to a change in demand for oxygen in the brain. However, a risky situation arises when the CBF changes not because of a change in the demand for oxygen, but

because of the failure of the autoregulatory system to adjust the cerebrovascular resistance when the blood pressure changes. Therefore, to assess the condition of the autoregulatory system, we must observe CBF as well as BP, and quantify the similarity in changes in BP and CBF.

HemDAT provides four ways of assessing the autoregulatory system:

- *Correlation :* The statistical correlation function quantitatively describes how well two sets of data relate. Correlation of 1 or -1 indicates that the two sets of data are linearly dependent, while a correlation of 0 indicates that the two sets are linearly independent. The correlation between BP and CBF is calculated using the *corrcoef* function in Matlab. The data is divided into user-determined constant length segments. The correlation of BP and CBF in time is calculated by calculating the correlation in successive data segments. Figure 4-15 shows a sample output of this function.

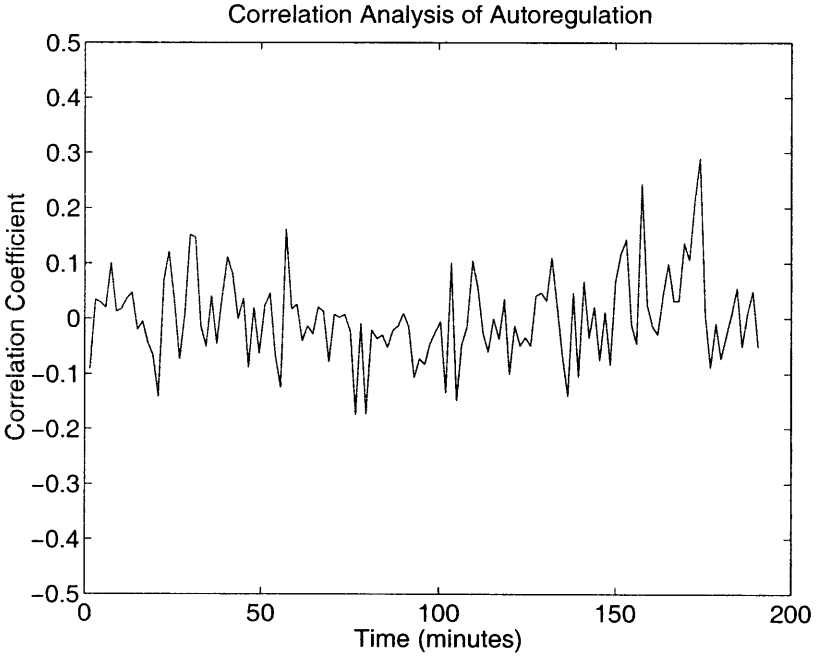


Figure 4-15: *Sample output of correlation analysis of the autoregulatory system, with window size of 2 minutes and overlap length of 0.5 minute.*

In this figure the correlation coefficient is consistently small. However, we must be careful in our interpretation of this graph. This graph does not necessarily mean that the autoregulatory system is functioning. The autoregulatory system is tested when blood pressure varies. If the blood pressure does not vary and the correlation is low, we do not gain information about the functioning of the autoregulatory system.

Additionally, the autoregulatory system requires some time to respond to changes in the blood pressure. When the blood pressure starts to change, the cerebral blood flow might also change

initially, until the autoregulatory system responds. As a result, the correlation between the two signals will be high when the blood pressure starts to change, and might lead to the misinterpretation that the autoregulatory system is impaired.

Another delay that can lead to misinterpretation of correlation results is the time taken by the changes in blood pressure to propagate to the brain. When the blood pressure changes, there is a delay before the CBF experiences the effects of the change. If autoregulation is impaired, the CBF will change in response to changes in the blood pressure with a time lag. The correlation between the two signals will be small due to this delay, and might lead to the misinterpretation that the autoregulatory system is intact.

Furthermore, there are multiple other factors that affect changes in CBF and that have not been considered here.

- *Transfer Function Analysis:* Another way of assessing the autoregulatory system uses transfer function analysis. In Chapter 2, we discussed how autoregulation can be viewed as a system and expressed in the form

$$F(f) = P(f)H(f)$$

where $F(f)$ is the Fourier Transform of cerebral blood flow, $P(f)$ is the perfusion pressure, and $H(f)$ is a model for autoregulation that describes how pressure relates to flow in the frequency domain. Figure 4-16 shows the parameters that users can specify when using transfer analysis to assess autoregulation. With the exception of one parameter, all the others are the same as those used for Baroreceptor Analysis.

The exception is the threshold of coherence. Recall from chapter 2 that transfer analysis is valid only when the coherence between the signals is significant. As explained in more detail earlier, coherence is a measure of how well variation in one signal corresponds with variation in another signal at each frequency. The coherence threshold allows the users to choose the level of coherence considered significant. For frequencies where the coherence is less than the specified threshold, no transfer gain and phase is calculated. Figure 4-17 shows an example of the output of transfer function analysis. The points marked by '+' are the points where gain and phase were calculated. However, for windows that had coherence less than the threshold, no gain and phase were calculated, which explains the gaps in the figure.

- *Static Analysis:* Static analysis analyzes periods of blood pressure and blood flow that show tracking. This function low pass filters and resamples the data following the user's specifications. Thereafter, the data is divided into windows of user-specified length and overlap. For each window, the mean arterial pressure and the mean cerebral blood flow is calculated for each cardiac cycle. The absolute value of the correlation coefficient between the mean arterial

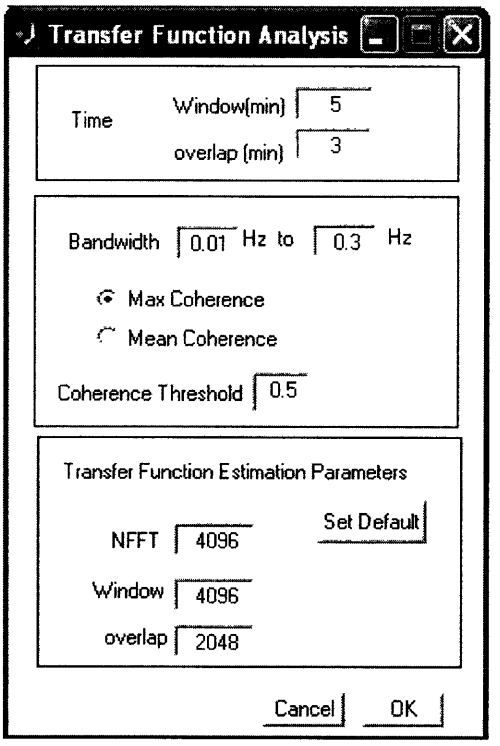


Figure 4-16: *Parameters for transfer function analysis of the autoregulatory system*

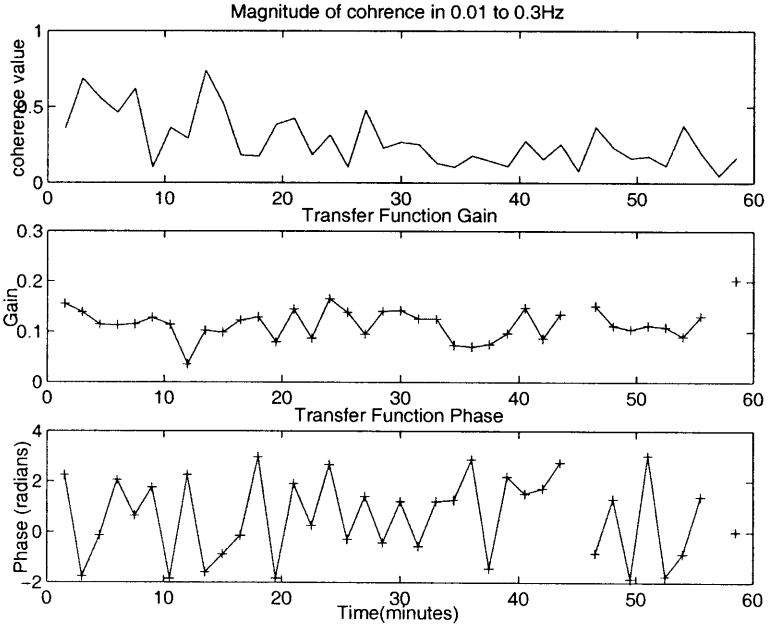


Figure 4-17: *Example of transfer function analysis of the autoregulatory system, using a threshold coherence on 0.05*

pressure and the mean cerebral flow is calculated. If the correlation is lower than the specified threshold, the autoregulatory system is assumed to be functioning because the values of blood flow do not follow the values of blood pressure. However, if the correlation coefficient is higher than the threshold, the slope of the regression is calculated. A large slope indicates that for a small change in blood pressure, cerebral blood flow changed by a large amount, which indicates lack of autoregulation. However, a small slope implies that a large change in blood pressure caused the cerebral blood flow to change by only a small amount, indicating an intact autoregulatory system. Figure 4-18 shows the parameters that users can choose when using static analysis. As before, window and overlap parameters determine how the data is segmented. Intact autoregulation can require several seconds to respond to changes in blood pressure. Therefore, the window chosen for this function should be large enough to capture the change in blood pressure as well as the response of the autoregulatory system. However, if the window is too large, the correlation in a short duration will be hidden by lack of correlation in the rest of the window. 20–40 seconds provide a fair compromise.

Finally, users can specify the threshold correlation coefficient. Regardless of the correlation coefficient between two signals, a slope for their linear regression can be obtained. However, this slope is meaningful in relating the two signals only if the correlation between them is high. Thus, the interpretation of the output must take the threshold into account.

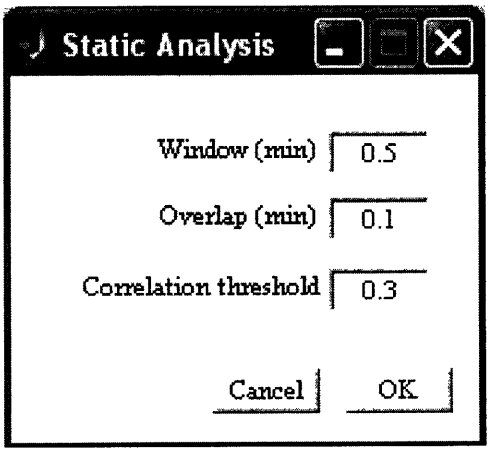


Figure 4-18: *Parameters for static analysis of the autoregulatory system*

Figure 4-19 shows an example of the output of performing static analysis. Sudden gaps in the output indicate coherence lower than the threshold in those windows. During the analyzed 60 minutes, the slope is close to -0.075micromolars/cc/mmHg. Whether this slope is big enough to cause alarm will depend on the patient and the application.

- *Dynamic Analysis:* As discussed in chapter 3, dynamic analysis attempts to assess the tran-

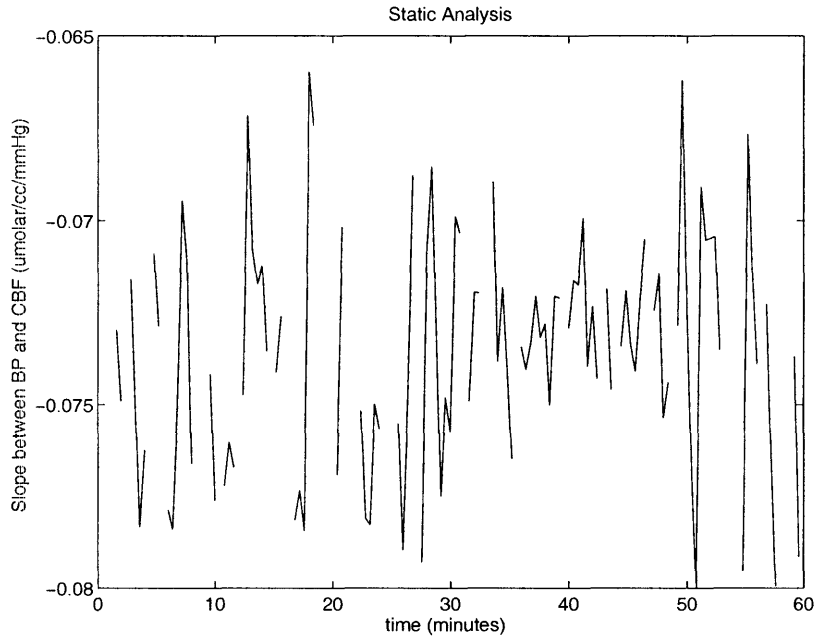


Figure 4-19: *An example of static analysis of the autoregulatory system*

sient response of the autoregulatory system to a change in blood pressure. The implementation of dynamic analysis in HemDAT closely follows the method used by Panerai et al [26]. The blood pressure and the cerebral blood flow signals are first low pass filtered to 5Hz, and re-sampled at 50Hz. The diastolic and systolic peaks are then identified. Identification of the peaks is the reason behind low pass filtering the data. The low pass filter removes small bumps and jitters in the data that might be mistakenly detected as peaks. Furthermore, the data is resampled at a frequency higher than the low pass filter so that peaks can be detected more accurately in time.

A cardiac cycle is assumed to start half-way between diastolic and systolic peaks. The mean blood pressure, defined to be (1/3)*systolic + (2/3)*diastolic, and the mean cerebral blood flow over each cardiac cycle is calculated. As in the case of baroreflex assessment, this results in two unequally spaced signals. The mean blood pressure and cerebral blood flow signals are both defined at the start of a cardiac cycle. To obtain equally spaced signals that can be processed, these signals are interpolated with a cubic function. The user defines the lowpass filtering and resampling frequencies for the interpolated signal. As discussed in chapter 3, dynamic analysis seeks to assess the response of the autoregulatory system to changes in the blood pressure. The system requires several seconds to respond, which implies that the data can be low pass filtered to close to 0.5–1Hz without loss of the information needed for dynamic assessment. Low pass filtering the interpolated signals can also be thought of as smoothing

the signal, which prevents the dynamic analysis algorithm from being potentially misguided by higher frequency changes. Once again, we are interested in resampling rates of close to 10–15Hz so that time resolution can be preserved. As shown in Figure 4-20, these parameters are user defined.

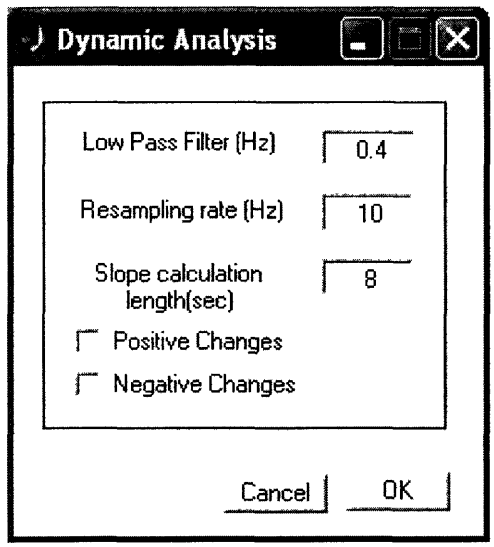


Figure 4-20: *Parameters for dynamic analysis of the autoregulatory system*

As discussed in chapter 2, dynamic analysis studies the changes in mean BP and the mean CBF. Users can choose to study positive or negative (or both) changes in the blood pressure. Once equally spaced mean blood pressure is obtained, changes in the signal are detected. If these changes meet a certain criterion, they can be used as changes in blood pressure that test the autoregulatory system. The first criterion is that the change in blood pressure must be at least 2% of the baseline blood pressure. This condition ensures that the change being studied is not a small bump that does not test the autoregulatory system. The second criterion is that the change in blood pressure must be maintained for at least 3 seconds. This condition checks that the change in blood pressure is not too quick for the autoregulatory system to respond. This is an important criterion because the dynamic assessment seeks to measure how quickly the blood flow returns to the reference level despite a high blood pressure. The last criterion is that the peaks must be at least 8 seconds apart so that the response of cerebral blood flow to each peak can be studied in isolation.

Once such changes are identified, the point of synchrony, which is defined to be the point between the foot and the top of the peak where the largest change occurs [26], is determined. When the blood pressure changes, the cerebral blood flow will also change initially since the vessels require time to respond to a change in blood pressure. Dynamic assessment measures how quickly the cerebral blood flow returns to its reference value. Once the point of synchrony

has been determined, a window of cerebral blood flow data starting a quarter of a second after the synchrony point is studied. The length of this window is determined by the user and is discussed more later in this section. To quantify the response of cerebral blood flow, the slope between the highest and the lowest points in the window is calculated. The slope indicates how quickly the cerebral blood flow changes.

The final parameter that users can specify in Figure 4-20 is the duration of CBF to be analyzed. This duration should be long enough to allow the cerebrovascular resistance to change in response to changed blood pressure and for the cerebral blood flow to be regulated accordingly. We are interested in understanding the transient response of the system. The period after the synchronization point should not be too large. In their proposal of this technique, Panerai et al [26] used a length of 12 seconds after the point of synchrony.

Figure 4-21 shows an example of dynamic analysis output for positive changes. The figure shows the slope of CBF following a spontaneous rise in the blood pressure. This plot illustrates the results using a sample and hold technique in which the CBF slope value obtained from a spontaneous transient is illustrated on the graph until the next transient occurs. A negative change in the CBF indicates that after the initial rise in the flow, the cerebral blood flow decreases towards its original reference level. However, a positive slope or a slope close to zero indicates that after the initial rise, the blood flow remains high or climbs even higher, which might indicate that the autoregulatory response is considerably delayed.

One must be careful in the interpretation of such graphs. As with the other means of analyses discussed in this section, the output does not provide conclusive evidence about the functioning of the autoregulatory system. The slopes graphed in Figure 4-21 only indicate the behavior of the blood flow in a short duration. This figure suggests that autoregulation is functioning better in minutes 40-60 than in the first 15 minutes. However, this does not provide conclusive evidence of autoregulation impairment in the first 15 minutes. Moreover, there are many other factors that affect autoregulation that have not been considered here.

4.3.6 Folder Analysis

The purpose of *Folder Analysis* is to allow analysis of many files together. *Folder Analysis* provides averaged information and gives an idea of trends that might be common among the files in the folder. This feature can be useful in two situations. The first situation arises when one patient's information is contained in multiple files. Folder analysis can be used to gain an overview of the patient's data. Another situation arises when there is information from multiple patients. In this case, folder analysis can be used to study a population of patients. HemDAT provides this ability in the *Feature Analysis* and in the *Autoregulation Analysis* sections.

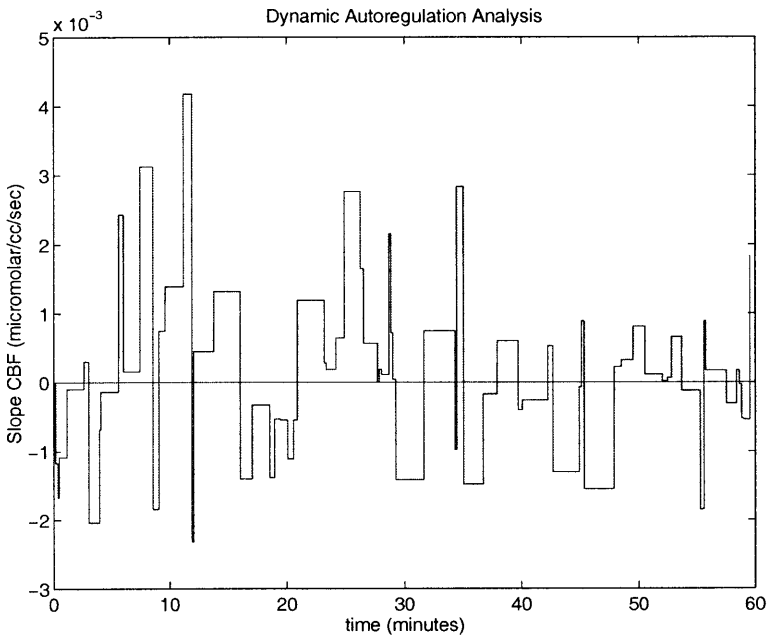


Figure 4-21: *An example of dynamic analysis of the autoregulatory system*

Folder Analysis of Features

There are two types of graphs that can be created to examine features of the files in the folder. First is the graph that shows the distribution of the selected feature values. For this graph, each file in the folder is segmented into windows of specified size and overlap, and the specified feature is calculated for each window. Figure 4-22 shows the parameter window for Folder Analysis.

The output is an averaged histogram of the values that the feature takes. Histograms are averaged over all the files and weighted by the length of the file. In the implementation, the feature values for all the files are collected in a single vector and a histogram is created using this vector. Because a large file will have more windows and thus more feature values, this has the same effect as taking a weighted average of all the feature values. Figure 4-23 shows a sample output of calculating the mean systolic blood pressure using folder analysis.

The second type of graph shows how two features in the files relate to each other on average. This type of plot can be chosen by picking 'feature vs. feature' option in the drop-down menu shown in Figure 4-22. When constructing this type of a graph, the user can specify the percentage of windows to be used in calculating the features, as shown in Figure 4-24.

A user-specified percentage of windows are randomly selected from all the windows. The percentage of windows parameter is useful because if all the windows are used, the plots may be too crowded to reveal useful information. For each window, the two selected features are calculated and plotted against each other. Figure 4-25 shows an example of such a plot.

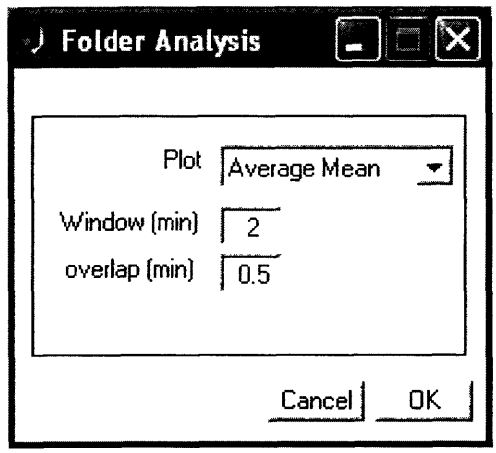


Figure 4-22: *Parameters for Folder Analysis of features*

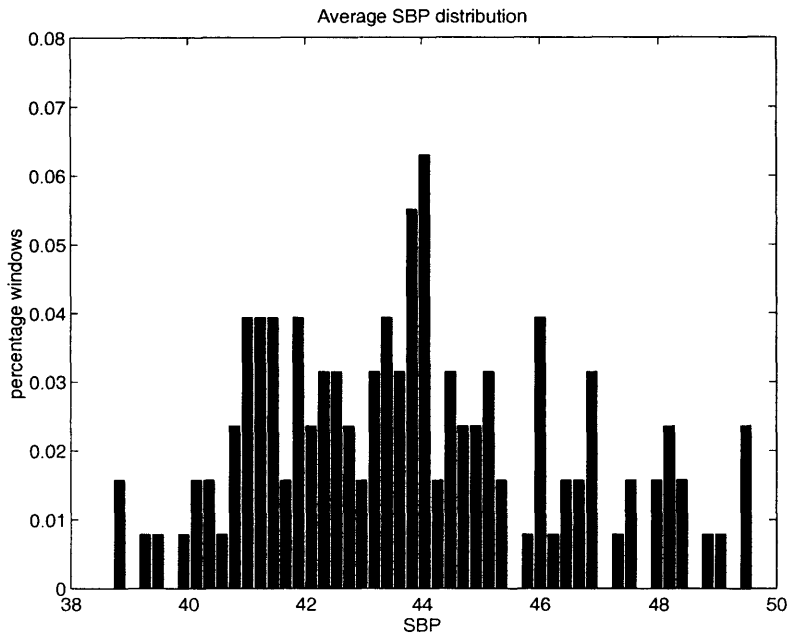


Figure 4-23: *The output of analyzing the average mean of blood pressure in a folder of multiple blood pressure data files*

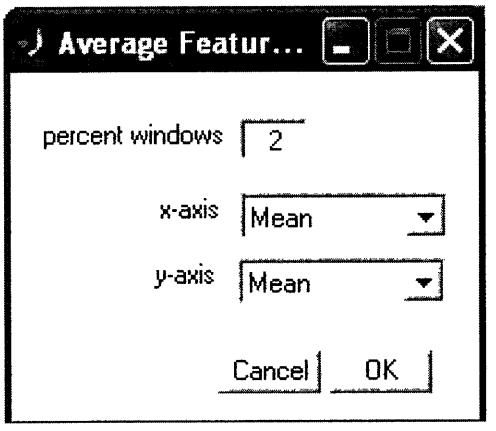


Figure 4-24: *Parameters for folder analysis of two features against each other*

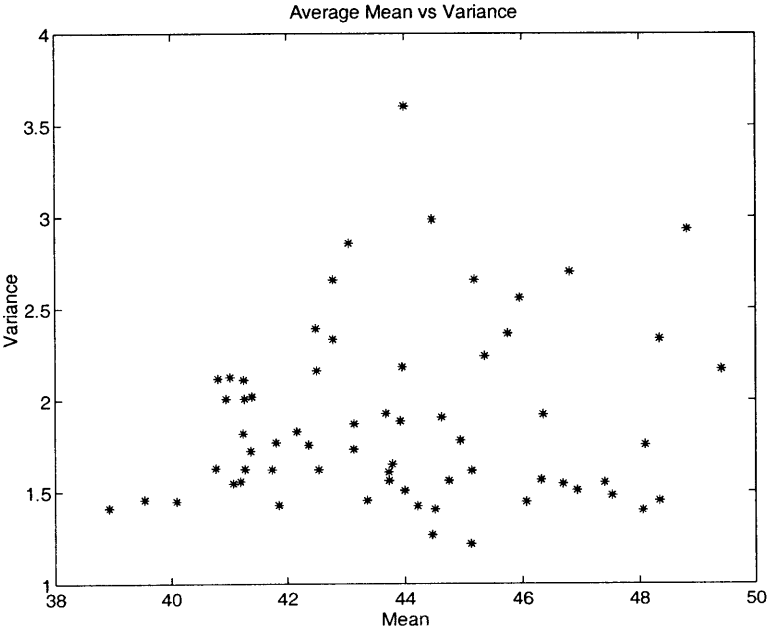


Figure 4-25: *The output of Folder Analysis of the mean of blood pressure against the variance in blood pressure*

Folder Analysis of Autoregulation

This function intends to provide an overview of the tracking of blood pressure and cerebral blood flow from multiple files. Multiple ways have been proposed to assess the autoregulatory system in humans. However, as discussed in chapter 3, these ways are diverse. As a result, there is no consensus on how the autoregulatory system should be assessed. Moreover, every person's autoregulatory system works differently. Individuals have varying delay in response, as well as a varying response. Thus, one must be cautious when comparing the autoregulatory systems of multiple patients.

Folder Analysis in this section provides averaged measure of correlation and coherence in the signals, not an averaged measure of autoregulation function . These graphs must be interpreted with caution and should not be assumed to reflect the functioning of the autoregulatory system.

The input for Folder Analysis is the address of a directory that contains subdirectories. Each subdirectory contains signals that were collected at the same time, and each must contain one preprocessed blood pressure signal and one cerebral blood flow signals. The blood pressure and cerebral blood flow input fields are used to enter the directory address.

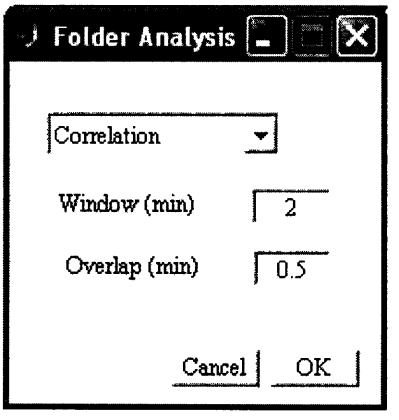


Figure 4-26: *Parameters for folder analysis*

As shown in Figure 4-26, the user can choose the window and overlap lengths to be used in the analysis. The chosen function is computed for each set of blood pressure and blood flow signals. The output is a distribution of values of the chosen function. Figure 4-27 shows an example of the output.

If coherence is chosen as the function to compute, the user defines the parameter values such as the length of the FFT, and the window and the overlap lengths to be used.

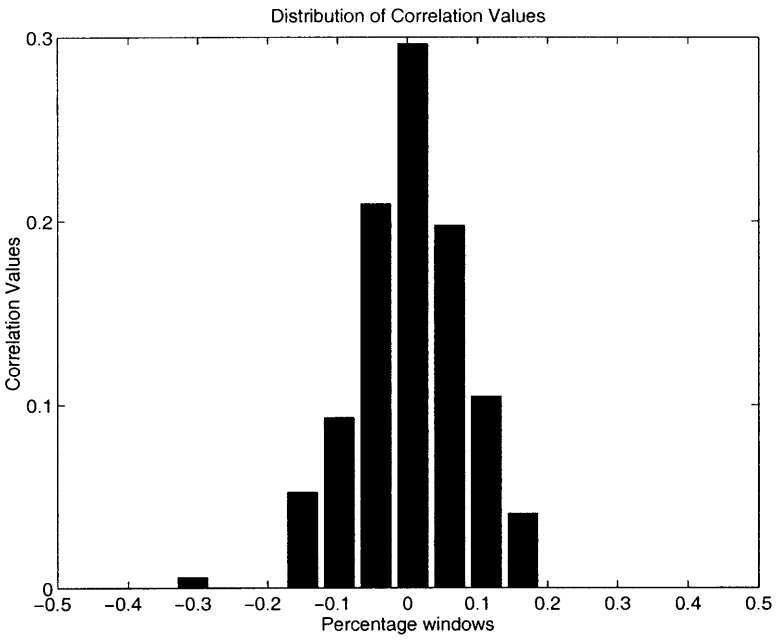


Figure 4-27: *The output of using Folder analysis to calculate distribution of correlation*

4.4 Summary

HemDAT provides means to analyze three of the factors believed to be related to brain injury. HemDAT can be used to analyze features of signals, the baroreceptor reflex and the autoregulatory function. This chapter discussed the analysis methods that HemDAT provides and the parameters that users can choose when performing various analyses.

Chapter 5

Sample Analysis

5.1 Overview

This chapter uses data collected from a very premature infant in the neo-natal ICU of Brigham and Women's Hospital, Boston, to demonstrate the use of HemDAT. The blood pressure data was collected from the umbilical artery of the infant at 500Hz, and CBF was recorded using NIRS at 6Hz.

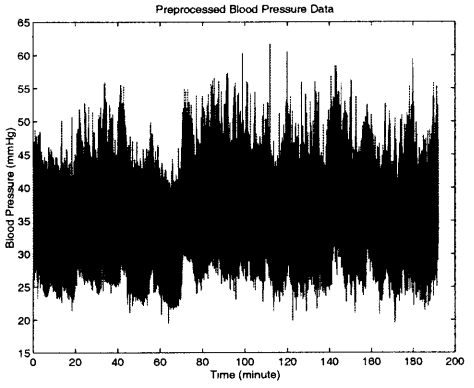
5.2 Preprocessing

The first step towards the analysis of this data is preprocessing. The blood pressure data is low pass filtered to 20Hz and resampled at 50Hz. Plots of filtered and resampled BP and CBF data are shown in Figure 5-1.

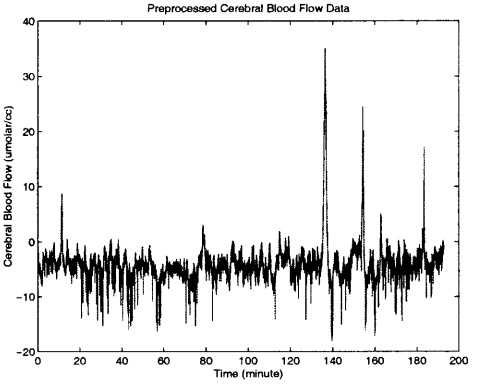
For the remaining of this chapter, the first 60 minutes of blood pressure and cerebral blood flow data is used to perform example analysis.

5.3 Feature Analysis

The *Feature Analysis* part of HemDAT provides the ability to analyze various features of the signal. As an example, we analyze the variance in blood pressure and discuss the effect of changing the window and the overlap. Figure 5-2 shows the output of calculating variance of the first 60 minutes of data with a 2-minute window and an overlap of 1 minute. As seen in the figure, for the most part, the variance before minute 30 stays between 1 and 1.5mmHg. Thereafter, the variance starts to rise, and there are two sharp peaks near minute 40 and minute 45. The histogram of variance values shows that close to 90% of the variance values are below 2mmHg.



(a) Plot of filtered blood pressure data.



(b) Plot of cerebral blood flow data gathered using NIRS

Figure 5-1: *Preprocessed data plots.*

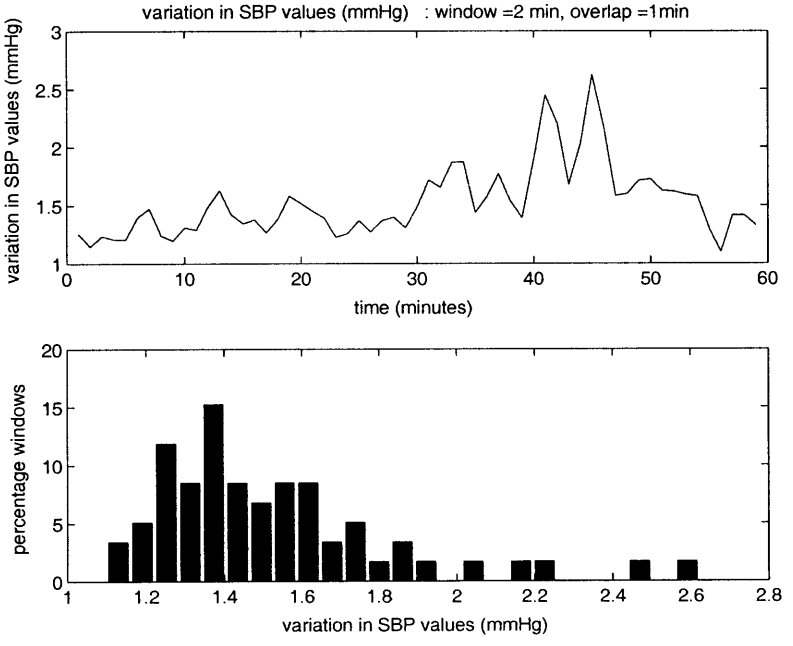


Figure 5-2: *The output of analyzing variation using Feature Analysis, window=2min, overlap=1min. Plot of variance in blood pressure over time and distribution of variance values*

In Figure 5-3, the window for variance analysis is changed to 5 minutes, but the overlap of 1 minute is maintained. Since fewer windows are analyzed, the result is coarser than the graph shown in Figure 5-2. Both the figures show low variance in the beginning and then start to rise near minute 30. As in the earlier figure, here too, there is a bump near minute 45. However, there are no longer two distinct variance spikes, as in Figure 5-2. Instead, there is only big bump.

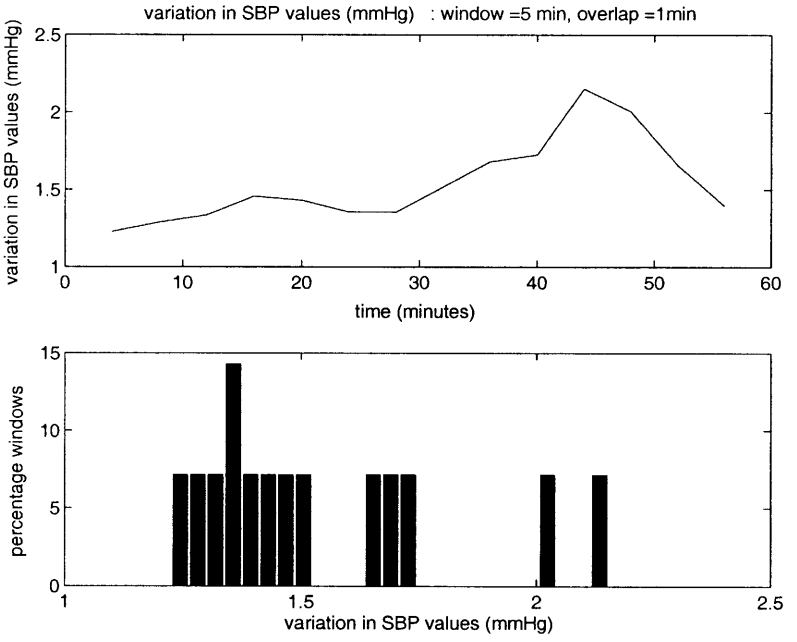


Figure 5-3: *The output of analyzing variation using Feature Analysis, window=5min, overlap=1min. Plot of variance in blood pressure over time and distribution of variance values*

Figure 5-4 plots the variance in the same data. The windows are maintained at 5 minutes, but the overlap is increased to 4 minutes. This means that every window shifts over by only 1 minute, sharing the first 4 minutes with the previous window. This figure is different from Figure 5-3 in that this figure has a better resolution since more windows were analyzed. Comparing Figures 5-3 and 5-4, we see that they share the same underlying shape. However, while 5-3 gives only a general idea of how the variance changes over time, 5-4 includes more detail.

It is interesting to compare Figures 5-2 and 5-4. The two figures have the same general trend of low variance in the beginning, then rising and then falling back. However, the two distinct peaks in Figure 5-2 are lost when the window size is increased. Instead, we see just one big hump located close to where the two peaks occur.

Furthermore, when the overlap size is increased the values of variance change more slowly. Since adjacent windows change by only one minute out of five, that is, the window changes by only 20%, the values of variance are unlikely to change dramatically from one window to the next. This explains

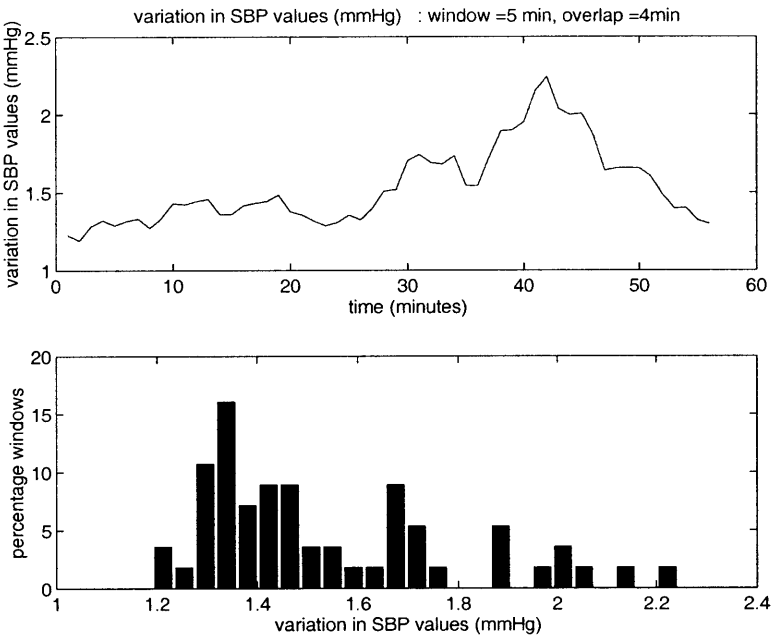


Figure 5-4: *The output of analyzing variation using Feature Analysis, window=5min, overlap=4min. Plot of variance in blood pressure over time and distribution of variance values*

why there are peaks in the graph when the window size is 2 minutes, but only a hump when the window size is increased.

The appropriate window and overlap sizes are determined by the application of this analysis. When using HemDAT and analyzing the results, users must remember that changing values of the parameters can change the results significantly. For example, when testing the hypothesis that long durations of consistently high blood pressure leads to brain injury, long windows that match the hypothesized duration would be appropriate of analysis. However, for a hypothesis that suggests that sharp short-lived changes cause brain-injury, smaller windows would be appropriate for analysis.

5.4 Baroreceptor Analysis

Baroreceptor analysis seeks to provide an assessment of how well the heart-rate, as represented by the time between systolic peaks, corresponds to change in the blood pressure. If the baroreceptor reflex is intact, an increase in the blood pressure should cause the RR-interval, the time between systolic peaks, to increase, and conversely, the RR-interval should decrease when the blood pressure decreases. Figure 5-5 shows the output of performing baroreceptor analysis on the first 60 minutes of the data, using the default parameters values.

Figure 5-6 zooms in at an arbitrarily chosen interval of minute 33–34 for a more detailed look at

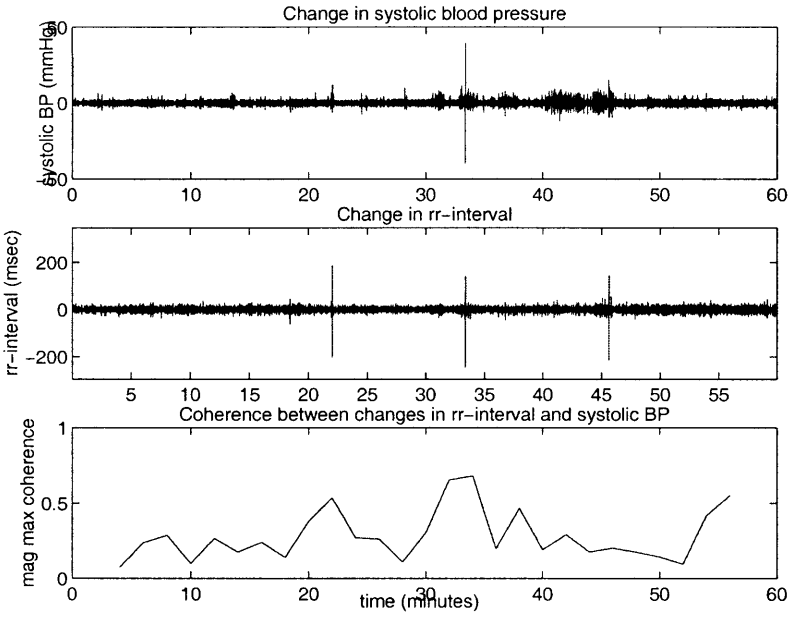


Figure 5-5: *The output of baroreflex analysis, using default parameters*

the changes in blood pressure and the RR-interval.

The effects of window and overlap sizes were discussed in the previous section apply here as well. Additionally, the trade-off between precision in the frequency and the time domains comes into play. Specifically, if baroreceptor analysis is performed on small windows, we can assess the baroreflex in that small window, and thus obtain a better time resolution than we would by using larger windows. However, frequency analysis and coherence calculations are only estimates. As the amount of data used to make these estimates reduces, so does the quality of the estimates. As a result, the estimates for the small windows will be imprecise. These estimates can be improved if the window size is made larger. However, by doing so, the precision in the time domain is lost.

Recall that coherence computation divides the data into equal-sized segments and computes an average of normalized cross-spectra. Moreover, if the coherence function is used on two linearly related signals with a single, non-overlapping window, the output for all frequencies is 1, indicating perfect coherence. Thus, it is crucial that the window of data that is used for coherence is long enough to be divided into at least two segments, preferably, 8–10 segments.

Figure 5-7 shows the coherence when default options are chosen, but the bandwidth of interest is changed to 0.01–1Hz. Thus, the plotted values are the maximum values of coherence in each window in the 0.01–1Hz bandwidth. As discussed in chapter 3, the bandwidth of interest for baroreflex analysis is likely to be below 1Hz.

The user can also choose to plot either the maximum coherence in the specified bandwidth or the

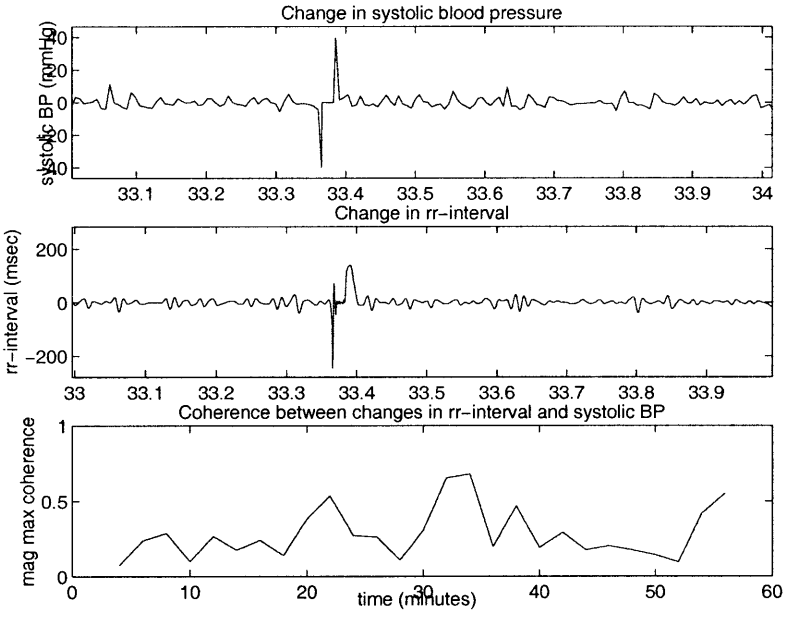


Figure 5-6: *A zoomed-in version of the example output in Figure 5-5*

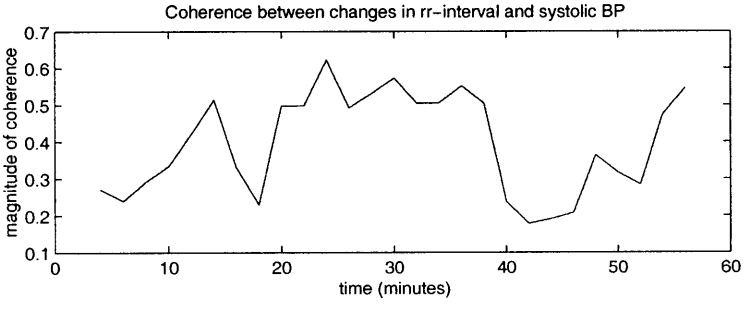


Figure 5-7: *Baroreceptor Analysis output: maximum coherence between RR-intervals and blood pressure in 0.01–1Hz bandwidth*

mean coherence in the bandwidth. Calculation of coherence is an estimation process. Thus, taking a mean over the bandwidth would reduce the error associated with the estimation process.

Concerning the interpretation of correlation, recall that correlation does not necessarily indicate the functioning of the autoregulatory system because the system is tested only when the blood pressure changes. Moreover, the response of the system to change in blood pressure is delayed, which may cause the correlation to be low even when cerebral blood flow follows blood pressure.

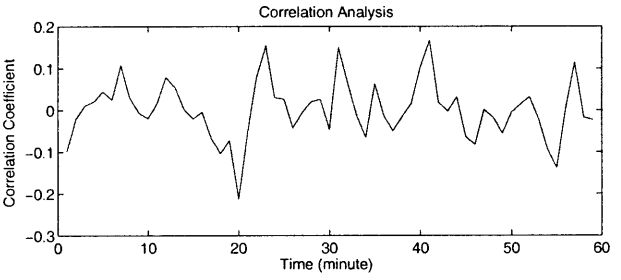
In Figure 5-7, the coherence in minutes 20–40 is high, and the coherence in minutes 40–50 is low. As cautioned, these coherence values alone cannot be used to judge the functioning of the baroreceptor reflex. However, the coherence values for this figure can be used in conjunction with other plots produced using HemDAT to gain a better understanding of the baroreflex functioning during these times. In particular, the high coherence in minutes 20–40 seems to suggest that the changes in RR-interval followed the changes in blood pressure, thus, suggesting a functioning baroreflex. However, Figure 5-2, which shows the variance in blood pressure, shows that the variance in blood pressure is small during minutes 20–40. As a result, the baroreceptor reflex is not tested during this time, and the high coherence values cannot be used to judge the functioning of the baroreceptor reflex.

Similarly, the low coherence in minutes 40–50 can be analyzed in conjunction with Figures 5-2 and 5-5. Figures 5-5 shows that the blood pressure changes considerably during minutes 40–50. This observation is confirmed by Figure 5-2, which shows high variance in minutes 40–50. The low coherence in face of changing blood pressure suggests an impaired baroreceptor reflex. Additionally, Figure 5-5 can be used to visually check that the RR-interval did not change in response to changes in the blood pressure.

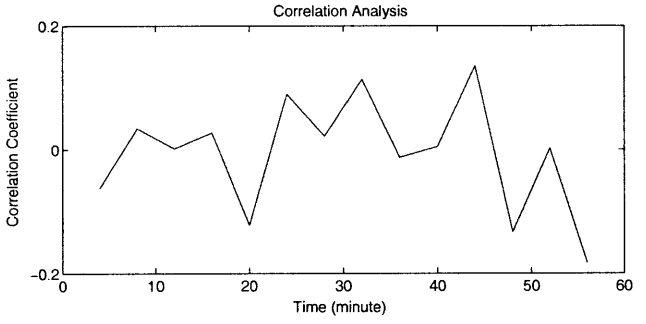
5.5 Autoregulation Analysis

HemDAT provides four ways of assessing the relationship between blood pressure and cerebral blood flow. The first way is to calculate the correlation between blood pressure and cerebral blood flow. Figure 5-8 shows three plots of correlation. Each plot was created using the same data, but a different window and overlap size.

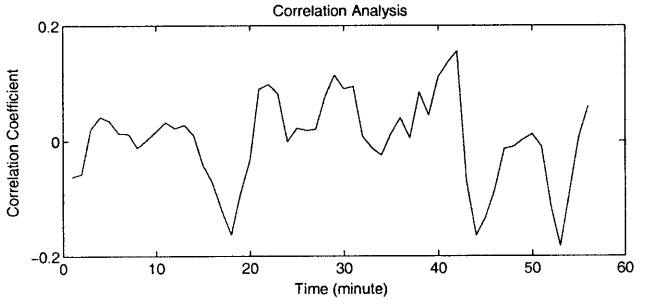
Part(a) uses windows of 2 minutes and overlaps of 1 minute. Part(b) uses window and overlap lengths of 5 minutes and 1 minute, respectively. Finally, the correlation in part(c) is calculated using windows of 5 minutes and overlap length of 4 minutes. As in our earlier discussion of window and overlap length, increasing the size of windows while keeping the overlap constant makes the result more coarse. Comparing parts (a) and (b) shows that when window length changes, the underlying shape of the curve may not be preserved well. However, when only the overlap is changed, as in parts(b) and (c), the shape is well preserved. Increasing the overlap increases the number of windows



(a) *The correlation between mean blood pressure and cerebral blood flow in 2 minute windows with overlap of 1 minute.*



(b) [*The correlation between mean blood pressure and cerebral blood flow in 5 minute windows with overlap of 1 minute.*



(c) [*The correlation between mean blood pressure and cerebral blood flow in 5 minute windows with overlap of 4 minute.*

Figure 5-8: *The Output of Autoregulation Analysis using correlation, for varying parameters*

analyzed and shows the changes in more detail.

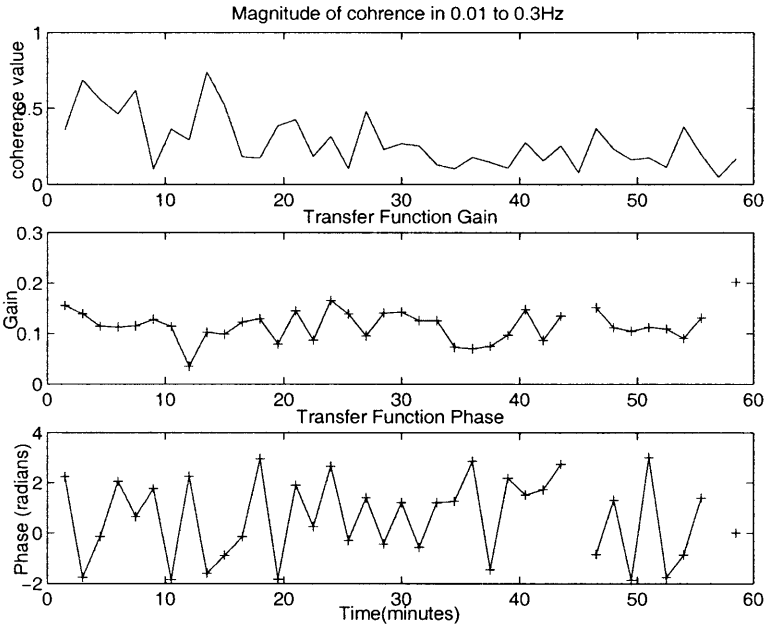


Figure 5-9: *The output of transfer function analysis, using threshold coherence of 0.1*

The second way HemDAT uses to relate blood pressure and blood flow is transfer function analysis. Figure 5-9 shows an example of transfer function analysis, using the default parameter values, with the exception of coherence threshold, which is lowered to 0.1. The parameters used in transfer function analysis are similar to the ones used in baroreceptor analysis, and thus, are not discussed here.

The third approach to studying blood pressure and blood flow is static analysis. Figure 5-10 shows the output of static analysis on the first 60 minutes of data, using the default parameters. The effect of window and overlap parameter values have already been discussed. The correlation threshold is used to determine for which windows the slope value should be calculated. The slope of the line that best fits two sets of data is shown in the figure. No slope was calculated for windows that showed a correlation less than the threshold.

The final approach to relating blood pressure and blood flow is using dynamic analysis, which studies the transient response of blood flow when blood pressure spontaneously increases. Figure 5-11 shows three results of dynamic analysis, calculated for positive changes in the signal, but with different parameters values.

Part(a) uses default parameter values of 0.4Hz and 10Hz for low pass and resampling frequencies, respectively. After each spontaneous change in blood pressure, 8 seconds of cerebral blood flow was analyzed. Part(b) of the figure uses low pass and resampling frequencies of 0.4Hz and 10Hz,

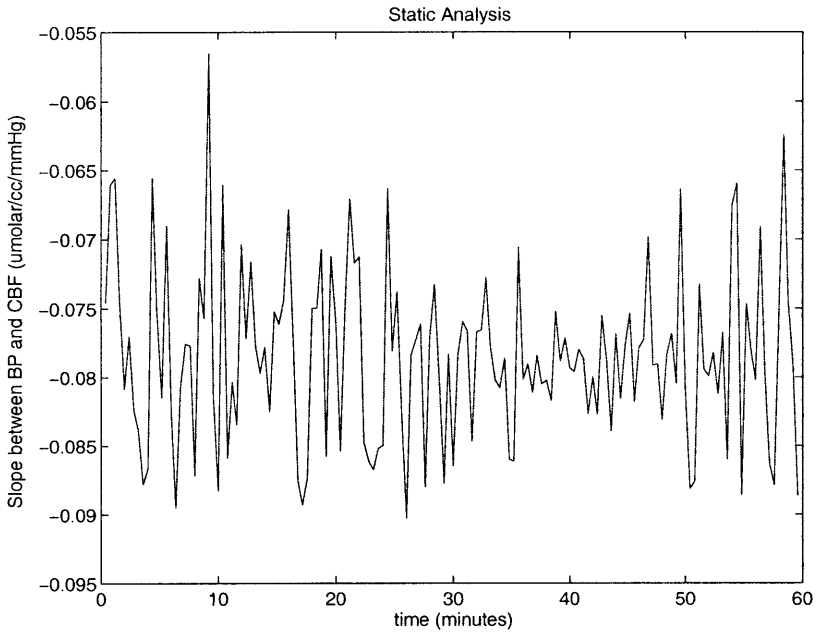
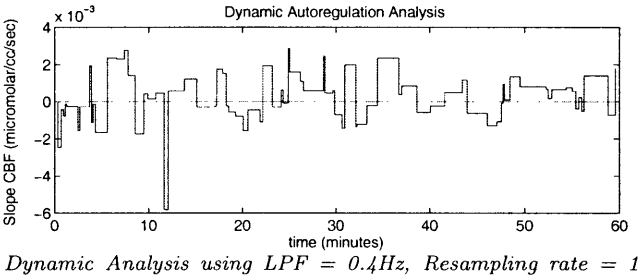


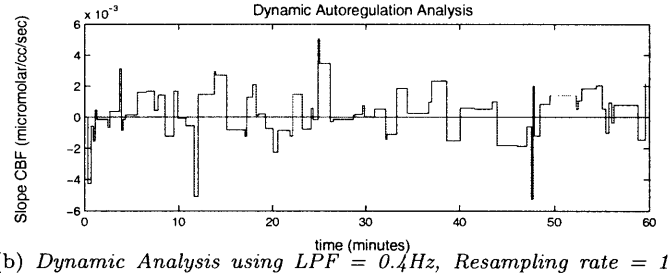
Figure 5-10: *The output of static analysis using the default parameters*

respectively. However, only 4 seconds of cerebral blood flow following a change in blood pressure is analyzed. As evident from the figure, this results in different output. Many of the general features of the output, for example the times of positive and negative slopes, are preserved, but the values of slope at particular times changed dramatically at several instances. The appropriate parameter value for the duration of analysis following a change in the blood pressure depends on the expected duration of the response. If the chosen duration is too small, the results of dynamic analysis will not be meaningful and might be misleading. Conversely, if the chosen duration is too long, the transition response will be averaged out with the steady state response.

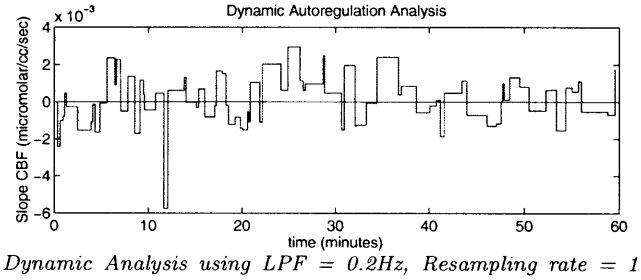
Part(c) uses a low pass frequency of 0.2Hz and resampling rate of 10Hz, and studies 8 seconds of cerebral blood flow after a change in BP. Once again, comparing parts (a) and (c), the values at particular time instances vary considerably. The choice of the low pass frequency is closely related to the expected transition time. Low pass filtering the signal to 0.2Hz, as in part(c), preserves only the changes that occur over longer than 5 seconds. If the transition time is smaller than 5 seconds, information might have been lost.



(a) *Dynamic Analysis using LPF = 0.4Hz, Resampling rate = 10Hz, post-BP-change duration analyzed = 8sec*



(b) *Dynamic Analysis using LPF = 0.4Hz, Resampling rate = 10Hz, post-BP-change duration analyzed = 4sec*



(c) *Dynamic Analysis using LPF = 0.2Hz, Resampling rate = 10Hz, post-BP-change duration analyzed = 8sec*

Figure 5-11: *The output of dynamic analysis for varying parameter values.*

Chapter 6

Conclusion

This chapter provides an overview of the goal of our research and the contributions made in meeting that goal. Additionally, we propose possible improvements to the work presented in this thesis.

6.1 Goal

The goal of this research was to design and implement a software tool that facilitates the analysis of blood pressure and cerebral blood flow signals, both of which are believed to be related to brain injury. The tool must combine medical concerns with signal processing and statistical knowledge to provide clinical researchers a tool that can help develop a better understanding of how brain injury occurs in premature newborns.

This lead us to impose three main requirements on the tool. First, the tool must be able to process and navigate large data sets, because events that cause brain injury are believed to be short-lived and possibly infrequent, making analysis of large data sets necessary. Secondly, the tool must provide flexibility to allow the user to modify search parameter values. This requirement allows the user to navigate the exploration space, which is large and complicated. Finally, the tool must provide convenient visualizations of the output and must not depend upon signal processing or statistical expertise of the user.

We designed and implemented HemDAT, Hemodynamic Data Analysis Tool. HemDAT is a tool that facilitates signal processing based analysis of blood pressure and cerebral blood flow. Specifically, HemDAT facilitates analyses of signal features and the baroreceptor reflex function and provides multiple techniques for autoregulation analysis.

6.2 Contributions

The research presented in this thesis makes the following contributions:

- Provides an effective clinical research tool. Following are some of the features of HemDAT that make it a valuable tool:
  - Combination of multiple analysis techniques: HemDAT provides a suite of various approaches to analyzing blood pressure and cerebral blood flow signals, which makes comparisons between analysis techniques easier.
  - Broadly applicable: This document uses the example of brain injury in premature infants to motivate the need for a tool like HemDAT and to demonstrate its functionality. However, HemDAT is a general tool that analyzes blood pressure and cerebral blood flow and can be used in multiple other situations requiring analysis of these hemodynamic signals.
  - Visual output: HemDAT outputs convenient visualizations of changes in signals, which make signal analysis easier.
  - Flexible: HemDAT provides flexibility in all of its computations. Users provide values for relevant parameters when performing various analyses.
  - Portable: HemDAT is portable and has been successfully tested on Windows and Linux operating systems.
  - Usability: HemDAT does not rely on expert knowledge or programming skills of the user. The graphical interface eliminates the need for programming skills to use software packages such as Matlab.
- Provides a discussion of previous work in the field: We have included in this document a detailed discussion of the techniques that have been used to approach the problem of assessing baroreflex and cerebral autoregulatory systems.

6.3 Future Work

This section briefly describes possible future work that can contribute to making HemDAT a more comprehensive and a more usable clinical research tool.

- Inclusion of other signals: Currently, HemDAT analyzes only blood pressure and cerebral blood flow signals. However, multiple other physiological signals, such as the amount of oxygen and carbon dioxide in blood, affect baroreflex and autoregulatory systems. These physiological signals can provide valuable information about the patient. They can also prove useful in better assessing physiological systems.
- On Line Analysis: Currently, HemDAT requires previously collected and preprocessed data. It would be useful if HemDAT could collect data for several minutes and produce results with

a delay of 5-10 minutes. Clinicians could use such a tool at patients' bedsides to observe short term changes in various systems in response to a stimulus.

- Output that can be used with other tools: Currently, HemDAT outputs only graphs as convenient visualizations of results of the performed analyses. However, if, in addition to graphs, HemDAT produces output in a format that can be used by other tools for further analysis, then HemDAT could be used in conjunction with other tools.

- Programming possibility: HemDAT provides an analysis tool for clinical researchers who may not have programming knowledge needed to use the available commercial software to analyze physiological signals. However, a tool that completely eliminates programming can provide only limited functionality. HemDAT would benefit from providing a programming option that allows users to define new features and analysis techniques and to specify how an analysis should be carried out.

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