Quantitative Analysis Of EKG And Blood Pressure Waveforms

Denise Erin McKaig

William & Mary - Arts & Sciences, denisemckaig@gmail.com

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Quantitative Analysis of EKG and Blood Pressure Waveforms

Denise Erin McKaig

Virginia Beach, VA

Master of Science, William & Mary, 2016
Bachelor of Science, James Madison University, 2014

A Dissertation presented to the Graduate Faculty of The College of William & Mary in Candidacy for the Degree of Doctor of Philosophy

Department of Physics

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de the requirements for the degree of

Doctor of Philosophy

Denise Erin McKaig

Approved by the Committee, January 2021

Co-Chair
John B. Delos, Adjunct Professor, Physics
College of William & Mary

Co-Chair
William E. Cooke, Professor, Physics
College of William & Mary

David Armstrong, Chancellor Professor, Physics
College of William & Mary

Dennis M. Manos, CSX Professor of Physics and Applied Science
Vice Provost for Research
College of William & Mary

Leah Shaw, Associate Professor, Mathematics
College of William & Mary
ABSTRACT

In the intensive care unit (ICU) of a hospital, patients are monitored continuously and the data on those patients provide powerful diagnostic tools for the medical community. However, the patient data creates incredibly large data sets with instruments measuring multiple signals simultaneously. This work seeks to improve monitoring techniques through analysis of large data sets from former ICU patients. By knowing the outcomes of patients in the past, can we detect patterns to diagnose future patients while also reducing the amount of recorded information? This thesis first seeks to improve methods of storing infant electrocardiograms (EKGs) by reducing the full EKG signal to only a vector of timestamps between heart beats. This work then focuses on improvements to estimating adult cardiac output (CO) from radial blood pressure waveforms. CO is estimated using nine previously proposed algorithms applied to radial blood pressure waveforms and applied to aortic waveforms estimated using three transfer functions. Results are compared with 3966 thermodilution measurements for 440 patients. Predictions based on the various algorithms are combined using linear regression and reduced linear regression methods. The method with the highest correlation coefficient was the Liljestrand method with the general transfer function waveform, with a mean squared error (MSE) of 0.50 (L/min)$^2$. The MSE when all predictors are used is 0.44 (L/min)$^2$, and the MSE after elastic net reduction is 0.49 (L/min)$^2$. The reduced model is then applied to patients that have received a blood transfusion, and it is shown that the model has potential to detect a change in a patient’s Stroke Volume leading up to the time a doctor has ordered a blood transfusion.
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Chapter 1

Introduction

The ability to share large amount of medical data and perform both physical and statistical analysis on these data has opened many avenues of research. In recent years, the use of large data set analysis has expanded the ability of medical research to identify patterns in patients that might otherwise have been overlooked [30]. The ease of data sharing internet databases has increased in part due to the transition of hospitals to computer based record keeping systems [25]. One such large database of patient records has been compiled by PhysioNet, or Research Resource for Complex Physiologic Signals, which offers freely accessible clinical and physiologic data in an effort to further biomedical research [16]. The database that this thesis largely focuses on is the MIMIC-III (Medical Information Mart for Intensive Care) database.

As a physicist, the author has utilized tools like fast Fourier transforms, wave propagation models, and even simple electric circuits to process and understand medical data such as blood pressure wave-forms and cardiac output. The bulk of chapter 1 is therefore dedicated to present all of the medical terminology necessary to understand the medical aspect of the work aggregated in this thesis. We will provide the reader with background that motivates these studies, define medical terms used in the work, and discuss the medical databases and how that information is accessed.

Chapter 2 presents data reduction techniques to process neonatal heart rates. Electr-
cardiograms (EKG) on infant hearts in this database recorded up to three separate signals at 240 Hz. The full data set can be multiple terabytes of information, but our analysis only needed what is called the QRS heartbeats, instead of the full EKG signal. Chapter 2 will discuss a selective QRS (heart beat) detector for neonates that reduces the amount of data required to perform the diagnostic functions we seek. We then present a method of combining multiple QRS detection algorithms to get a heartbeat detector that is more selective in the location time in which it labels infant heart beats.

The remaining chapters shift our studies from neonates to blood-flow in adults. Cardiac output is a measure of the volume of blood that is pumped by the heart (specifically in the ventricles) per unit time. Accurately knowing the cardiac output of an individual can provide a wealth of diagnostic information and inform medical providers of their patient’s overall health. However, the only truly accurate measure of cardiac output is to use a “scalpel and a bucket”, which is not conducive to a patient’s health. Thus the medical community continues to seek methods that can reliably predict cardiac output from other measurements that are less invasive.

Chapters 3 presents several algorithms to analyze blood pressure waveforms and estimate the volume of blood that is being pumped by the heart (the cardiac output). Some of the algorithms will model the cardiovascular system as analogous electronic circuits which allows us to use basic principles of electronics to analyze the signals. Other algorithms relate the area under a pressure versus time curve to the blood flow directly. Chapter 4 discusses the results of these methods and statistical techniques used to synthesize multiple algorithms.

Chapter 5 extends the techniques presented in chapter 3 to monitor and predict hemorrhage events. It is known that when a patient is hemorrhaging internally, an early warning is a drop in stroke volume (volume of blood pumped per heart beat). Later, the cardiac output (volume of blood pumped per minute) falls. Eventually, the blood pressure falls, but by this time the patient’s prognosis is bleak. Chapter 5 will focus on using these methods on patients that have received a blood transfusion to see if these estimations of blood
volume can be used as early indicators of patients who are hemorrhaging in the hospital intensive care units.

1.1 Medical Terminology and Background

A cardiac cycle comprises processes that occur in the heart muscle from the start of one heartbeat to the moment before the next heartbeat. Within this cycle there is a period of time when the muscle is relaxing, called diastole, and the heart is filling with blood. Blood pressure at the end of this period is at a minimum for that cardiac cycle. The systole that follows is the period when the heart is contracting to pump blood. During this part of one cardiac cycle the blood pressure reaches its maximum value. The minimum blood pressure in a cardiac cycle is therefore called the diastolic pressure, and the maximum pressure is called the systolic pressure. The flow-rate of the blood during the heart pumps can be measured with respect to the heartbeats or a unit of time. Stroke Volume (SV) is the volume of blood the heart pumps in a single heart beat. The Cardiac Output (CO) is the volume volume of blood pumped per unit time [18].

While there is more familiarity reporting only the average maximum and minimum blood pressure (BP), our work addresses the continuous measurement of time series of BP, which we call waveforms (see Figure 1.1). BP waveforms are measured using a sensor in a catheter inside a patient (similar to that shown in Figure 1.2). Since the catheter is usually placed into an artery (often the arm or the leg), the waveform is also known as peripheral blood pressure, or arterial blood pressure (ABP). We are looking at continuous waveforms. About 20% - 30% of patients in the ICU have such an arterial catheter. Aortic pressure is the pressure inside the heart. While aortic pressure is often considered to have the most useful information, catheters generally are not placed in the aorta due to the dangers that this placement would pose to a patient. Details of the dependence of the shape of the pressure wave on where it is measured in the body are shown schematically in Figure 1.3. The labelled in the top left corner as 1 image in Figure
Figure 1.1: Example of a BP waveform. The data being analyzed is continuous and collected using a catheter in an artery, as opposed to the more familiar BP readings obtained with an arm cuff and reported as discrete values.

![Blood Pressure Waveform](image)

Figure 1.2: How the catheter is placed for invasive thermodilution measurements, adapted from [6], as well as a resulting change in temperature curve.

1.3 shows the BP in the Aortic arch (near the heart) and Figure 1.4 [17] depicts the locations along the arterial tree the signals correspond to. The cusp around 0.4 s is called the dicrotic notch. This is caused by the heart valve closing, and marks the time in the
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Images 3 and 4 are the readings as seen when placed in the Abdominal aorta and 4 is for
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Figure 1.3: How blood pressure changes shape as it propagates down the arterial tree.
Adapted from [3] pg. 535.
Consider what happens to a BP waveform that originates in the heart and propagates down to the femoral artery. We wish to take measurements from the leg and reproduce the signal as it was at the heart [17].

1.2 Motivation and Goal

When doctors suspect a patient is bleeding internally, the first thing they do is check the patient’s blood pressure. However, blood pressure doesn’t drop until approximately 20% of blood has been lost [18]. As blood is lost the arteries contract and the heart rate rises to keep the pressure high. Cardiac output, however, begins to fall much sooner (Figure 1.5), meaning that if we monitor CO instead of BP we can get advance warning of internal bleeding. Another useful physiological quantity is the stroke volume, which begins to fall even sooner than CO because the heart rate will rise and the stroke volume is cardiac output divided by heart rate. The difficulty is that measuring CO (or stroke volume) accurately involves invasive procedures which can be unsafe in sick patients.

The “gold standard” for CO assessment is currently Thermodilution. A catheter with a temperature sensor at the end (blue line to the heart in Figure 1.2) is placed in the patient’s heart and goes from the right atrium to the right ventricle and out through the pulmonary
Figure 1.5: Plot of percent of normal for cardiac output and blood pressure versus percent of blood lost. While CO falls after about 10% blood loss, BP does not begin to fall until 20% blood loss. Thus, having a safe and reliable measure of changing CO is desirable. Taken from [18] pg. 274.

artery. A measured amount of saline fluid at a known temperature (significantly cooler than body temperature) is ejected through a hole into the catheter in the right atrium (1 at the end of the green line). The temperature sensor at the end of the catheter (2 at the end of the blue line) records the change in temperature, $\Delta T$, as a function of time [3, 22]. Using the volume of saline, $V_0$, the temperature of the blood $T_B$, the temperature of the saline, $T_S$, $K_1$ (constant relating specific heat and density of the saline to the specific heat and density of the blood), and the area under the change in temperature curve, one can calculate CO using equation 1.1. A dimensional analysis is shown to the right of that equation.

\[
CO = \frac{V_0 (T_B - T_S) (K_1)}{\int_{t_i}^{\infty} \Delta T dt} \quad \rightarrow \quad \text{mL} \cdot ^\circ \text{C} \rightarrow \text{volume} \frac{\text{mL} \cdot ^\circ \text{C}}{\text{volume} \cdot \text{time}}
\] (1.1)

The thermodilution equation, eq. 1.1, can be derived from the following steps. First assume the total heat of the heart–saline system remains unchanged [22]. In fact, the distance between the saline injection and the temperature measurements is kept small to
avoid additional heat from other parts of the body [3]. Thus, \( \Delta Q = 0 \), and

\[
\begin{align*}
\text{d}Q_B + \text{d}Q_S &= 0 \quad (1.2) \\
 m_B \cdot s_B \cdot \text{d}T_b &= -m_S \cdot s_S \cdot \text{d}T_s \\
 &= (1.3)
\end{align*}
\]

where \( \text{d}Q_B \) is the flow of heat from blood, \( \text{d}Q_S \) is the heat change of the saline, \( m_B \) the mass of blood, \( s_B \) is the specific heat of the blood, \( \text{d}T_b \) is the blood’s change of temperature, \( m_S \) is the mass of saline injected, \( s_S \) is the specific heat of the saline, and \( \text{d}T_s \) is the saline's change in temperature. Now, define \( M_B \), the mass flow rate of the blood: \( M_B = m_B/t \), and integrate on both sides from \( T_{S,Bi} \), initial temperatures to \( T_B \), the final temperature of the blood/saline mixture.

\[
\begin{align*}
M_B \cdot t \cdot s_B \cdot \int_{T_{Bi}}^{T_B} \text{d}T_b &= -m_S \cdot s_S \cdot \int_{T_S}^{T_B} \text{d}T_s \\
M_B \cdot t \cdot s_B \int_{T_{Bi}}^{T_B} \text{d}T_b &= m_S \cdot s_S \cdot (T_S - T_B) \quad (1.4)
\end{align*}
\]

Now, we will change the left side of the above equation to an integral with respect to time,

\[
M_B \cdot s_B \int_{t_i}^{\infty} t \cdot \frac{\text{d}T}{\text{d}t} \text{d}t = m_S \cdot s_S \cdot (T_S - T_B) \quad (1.7)
\]

In the integral, we substitute \( t \cdot \frac{\text{d}T}{\text{d}t} = \Delta T \), \( M_B = Q_B \cdot \rho_B \), volume flow rate of blood multiplying blood density, and \( m_S = V_0 \cdot \rho_S \), volume of saline multiplying saline mass density, thus

\[
Q_B \rho_B \cdot s_B \int_{t_i}^{\infty} \Delta T \text{dt} = V_0 \rho_S \cdot s_S \cdot (T_S - T_B) \quad (1.8)
\]

Then \( Q_B \), the flow rate of the blood, is the Cardiac Output.
\[ CO = \frac{V_0 \rho_S \cdot s_S \cdot (T_S - T_B)}{\rho_B \cdot s_B \int_{i}^{\infty} \Delta T \, dt} \] \textsuperscript{[22]}. \hspace{1cm} (1.9)

Letting \( K_1 = \frac{\rho_S \cdot s_S}{\rho_B \cdot s_B} \), we recover equation 1.1.

### 1.3 MIMIC-III Tutorial

The MIMIC-III database is the only freely accessible database of its kind. It contains vital signs, chart notes, medications, laboratory measurements, diagnoses, procedure data, and continuous monitoring data \[25\]. The combined data from over forty thousand patients were recorded over an eleven year period (2001 - 2012) at Beth Israel Deaconess Medical Center, and deidentified \[46\]. This makes the MIMIC-III database a valuable tool for researchers seeking patterns in large data sets.

MIMIC-III is divided into a clinical database (discrete measurements, clinician notes, laboratory results, diagnoses, prescriptions, etc.), a waveform database (continuous monitoring), and a matched subset for those clinical records and waveform records that have been patient and time-matched. For the purposes of this thesis, the matched subset was used.

Once one is granted access to the database, it is simple to query the clinical database using the Google Cloud Computing Platform, BigQuery. Using this platform one can request information on patients that meet specific criteria, such as getting all Subject IDs of patients that have received blood transfusions, including the volume of blood that the patient received, and the time that the transfusion was recorded. For an example of this particular query, see figure 1.6.
Figure 1.6: This script in Google’s Cloud Computing Platform will search all patients and output patient Subject IDs that have received blood transfusions.

Now we know how to obtain clinical information on a patient. We must also know how to extract waveform information. In order to do this, it is wise to understand PhysioNet’s PhysioBank Record Search feature, Figure 1.7. In the ‘Subject’ drop box, we select the signal we are looking for (in the case of this example, blood pressure). Next, we are searching for continuous blood pressure, so in the ‘Name’ box we type ABP (arterial blood pressure). The ‘Value’ box would be for discrete measurements, such as age. We can search
for patient files for patients of a specific age, or greater than, or less than a specific age.

![PhysioBank Record Search](image)

**Figure 1.7:** PhysioNet’s Record Search.

This will give us a list of all patient files that contain blood pressure signals in the form ‘mimic3wdb/matched/pXX/pXXNNNN/pXXNNNN-YYYY-MM-DD-hh-mm’ where 'XXNNNN' is the matching Subject ID to the clinical database. We can then match the continuous waveforms to the discrete records in the clinical database.
Chapter 2

A Selective QRS Detector for Infants

2.1 Introduction

Neonatal Intensive Care Units (NICU) provide the medical needs for infants that are born prematurely or suffering from illness. The earlier an infant's symptoms can be diagnosed the greater the likelihood the child can be treated and kept healthy. Predictive analytics of NICU data uses patterns in an infant’s heartbeat or breathing that can serve as early indicators of illness, therefore allowing doctors at the hospital to take timely action to prevent harm to the children.

Research in this area is done by collecting all electronic signals from monitors in a NICU, collecting in a relational database clinical information such as type and time of recognized illness, and then seeking correlations between phenomena in electronic signals and illnesses. The data set may be large. Electrocardiograms (EKGs) are collected as three signals, each at 240 Hz. Collection of all these signals for 45 beds for 10 years comes to 13 TB of data, approximately 8 TB of which are taken up by the EKG data. However, the detailed shape of the EKG in each heartbeat is usually not needed. For example, Sepsis events\(^1\) can be predicted by observing fluctuations in the rhythm of the heart [40]. For

\(^1\)Sepsis is a life-threatening event caused when the body is combating an infection. Chemicals released in the blood to stave off an infection inadvertently trigger a cascade of reactions throughout the body. Without treatment sepsis can damage internal tissues, lead to organ failure, and death.
this purpose, only the time of each beat and the interbeat intervals are needed.

There are three EKG leads attached to each infant in the University of Virginia (UVa) NICU, and therefore three EKGs are monitored per infant. The leads are on the upper right of the chest, the upper left of the chest, and above the left hip. The first EKG records the voltage between the right and left side of the chest, the second records the voltage across the right chest and left hip, and the third records the voltage across the left chest and the left hip. Each EKG gives different values for voltage, but we are only looking for the time between successive heartbeats, so we analyze the shape of the curve as opposed to the values of the voltage readings.

Five algorithms were researched and compared to determine which techniques are best for processing NICU data. It was necessary to compare different algorithms because they were originally created for processing adult EKGs. Infant hearts differ from adult hearts and not just in the obvious ways, such as size and CO, but in subtle features too, such as the heart rate. This means infant EKGs require different analysis tools which we are adapting from methods used on adult EKGs.

In this chapter, we develop an algorithm for labelling R-times on infant EKGs. R-times are defined as the locations on the time axis of the peaks of the R-waves of an EKG. This chapter will start with the algorithms studied to identify the time of each heartbeat, then move to algorithm comparison, and finally, EKG noise measurement.

### 2.2 Basics of EKG

Before presenting our analysis we will review the features of a heart beat that is recorded under continuous monitoring. An electrocardiogram, or EKG, measures the electrical potential across the heart through electrodes placed on opposite sides of the chest. The EKG of an “ideal” heart beat and its features are shown in Figure 2.1.

A heartbeat is not a single contraction and relaxation, it is a multistep process driving blood through the different chambers of the heart, all dictated by chemical oscillations in
the heart. In each heartbeat, an EKG displays a signal that is divided into five constituent waves; P,Q,R,S, and T waves. Each individual wave is produced as blood flows from one chamber of the heart to the next. The flow of the waves and corresponding physical locations are depicted in Figure 2.2. The P wave forms in the atrium when sodium channels open, neutralizing the polarized atrium, prior to the atrial contraction. The Q wave corresponds to depolarization intraventricular septum. The large R wave comes from the further depolarization of the rest of the ventricles. The S wave represents the remainder of the ventricles becoming depolarized. The QRS complex is the result of sodium ions depolarizing the ventricle prior to contraction. The T wave is then when the sodium channels close and potassium channels open to repolarize the ventricles [18]. The chemical oscillator process has then completed one cycle, and the sodium channels reopen to create the next P wave. The key feature of the heart beat of interest to us is the QRS complex. It is the combination of the Q, R, and S waves because the time between R peaks (RR interval) defines the time between heart beats.
Figure 2.2: Diagrammatic representation of the PQRST wave through one heart beat. The blue and red shades depict the location of blood throughout the beat. Shaded yellow regions represent components of the heart that are being depolarized through the beat. The S wave depolarization is highlighted in orange to distinguish it from the R waves depolarization of the ventricle. Heart diagram adapted from [45].

If EKG signals always looked like the idealized signal in Figure 2.1, it would be easy to define the time of each beat: just pick out the highest, sharpest maxima. Of course the reality is that the signals are noisy, and the shapes can be greatly distorted but many factors. Breathing rates and other biological factors contribute to noisy EKG signals. Physicist are well-suited to the task of signal analysis and this is why we are contributing to the biomedical field. Our goals are to construct tools that can process raw EKG data from the neonatal infants and pull out the QRS complex. We will show that the construction of consistently reliable algorithms is a challenging endeavor; see Figure 2.3.
2.3 Noise Measures

This section will define the noise measures we used when processing the EKG signals. The three noise measures we tested were kurtosis, crest factor, and the ratio of in-band to out-of-band spectral power. Each baby had three separate EKG being read simultaneously. The EKG that has the clearest signal (the least amount of noise) is used to collect R vectors. An R vector is a $1 \times n$ array, where the $i$th element of the R vector corresponds to the timestamp of the peak of the $i$th R wave in the EKG.
2.3.1 Kurtosis

The kurtosis of a signal is a measure of the heaviness of the tails of a signal, and the peakedness of a signal [61]. It is way to measure how Gaussian a signal appears, as random, uncorrelated signals are more Gaussian than correlated signals [34]. Kurtosis is defined by the expectation value in Equation 2.1, where $\mu$ is the mean of the signal, $\sigma$ is the standard deviation of the signal, and $M$ is the number of samples. A perfect Gaussian signal will have a kurtosis equal to three (the proof is below), muscle artifact and baseline wander have a kurtosis of five, Gaussian noise has a kurtosis close to three, and a clean EKG will have a kurtosis of greater than five [10]. See Figure 2.3 for an example of kurtosis measurements on simultaneous leads.

$$K \equiv E \left[ \left( \frac{x - \mu}{\sigma} \right)^4 \right] \quad (2.1)$$

Proof that a Gaussian distribution has Kurtosis = 3.

For a normal distribution, the probability density function is

$$\text{pdf}(x) = \frac{1}{\sqrt{2\pi} \sigma} e^{-\frac{1}{2} \left( \frac{x - \mu}{\sigma} \right)^2} \quad (2.2)$$

Thus, the expectation value in equation 2.1 is defined by the integral

$$K = \int_{-\infty}^{\infty} \left( \frac{x - \mu}{\sigma} \right)^4 \frac{1}{\sqrt{2\pi} \sigma} e^{-\frac{1}{2} \left( \frac{x - \mu}{\sigma} \right)^2} \, dx \quad (2.3)$$

let $y = \frac{x - \mu}{\sigma}$, and $dy = \frac{dx}{\sigma}$

$$K = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} y^4 e^{-\frac{1}{2} y^2} \, dy \quad (2.4)$$

$$K = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} y^4 e^{-\frac{1}{2} y^2} \, dy \quad (2.5)$$

Integrating by parts with $u = y^3$, $du = 3y^2 \, dy$, $dv = ye^{-\frac{1}{2} y^2} \, dy$, $v = -e^{-\frac{1}{2} y^2}$

$$\frac{1}{\sqrt{2\pi}} \left[ -y^3 e^{-\frac{1}{2} y^2} \right]_{-\infty}^{\infty} + 3 \int_{-\infty}^{\infty} \frac{1}{\sqrt{2\pi}} y^2 e^{-\frac{1}{2} y^2} \, dy \quad (2.6)$$

$$\frac{1}{\sqrt{2\pi}} \left[ -y^3 e^{-\frac{1}{2} y^2} \right]_{-\infty}^{\infty} + 3 \int_{-\infty}^{\infty} \frac{1}{\sqrt{2\pi}} y^2 e^{-\frac{1}{2} y^2} \, dy \quad (2.7)$$
In the limits as \( y \) approaches infinity and negative infinity, the first term goes to zero, and we are left with the second term. We substitute \( x \) back in for \( y \), and get

\[
3 \int_{-\infty}^{\infty} \left( \frac{x - \mu}{\sigma} \right)^2 \frac{1}{\sqrt{2\pi\sigma}} e^{-\frac{1}{2} \left( \frac{x - \mu}{\sigma} \right)^2} dx
\]

In terms of expectation values, this is the equivalent of

\[
3 \cdot E \left[ \left( \frac{x - \mu}{\sigma} \right)^2 \right] = 3 \cdot \frac{E[(x - \mu)^2]}{E[\sigma^2]} = 3 \cdot \frac{\sigma^2}{E[\sigma^2]} = 3
\]

(2.9)

It is not uncommon to see excess kurtosis used for analysis, defined as \( K - 3 \). Thus, a perfect gaussian has a \( K_{\text{excess}} = 0 \); positive values are associated with more peaked signals, and negative values associated with flatter signals [61].

### 2.3.2 Crest Factor

The crest factor is the ratio of the peak of a signal to the RMS of the signal [10]. The crest factor of three different EKG signals can be seen in Figures 2.3.

\[
C = \frac{|EKG|_{\text{maximum}}}{EKG_{\text{RMS}}}
\]

(2.10)

### 2.3.3 In Band to Out of Band Spectral Power Ratio

Another method for measuring noise that was examined was the ratio of in-band to out-of-band spectral power. The in-band frequencies for EKG signals were 5 to 40 Hz [10].

First, the Fourier Transform of each of the EKG leads was taken using Matlab’s FFT program. This is a discrete Fourier Transform.

\[
FFT(EKG) = \sum_{j=1}^{n} EKG(j) \cdot W_n^{(j-1)(k-1)},
\]

(2.11)

where \( W_n = e^{\frac{(-2\pi i)}{n}} \).

(2.12)
Then the transformed signal is normalized, and the spectral power for the frequencies between 5 and 40 Hz are summed, and compared to the sum of the spectral power for frequencies outside of that band. The ratio of in band to out of band spectral power is then defined to be,

\[ R = \frac{\sum_{f=5}^{40} \tilde{EKG}_f}{\sum_{f=0}^{5} \tilde{EKG}_f + \sum_{f=40}^{130} \tilde{EKG}_f} \]  \hspace{1cm} (2.13)

with $\tilde{EKG}$ symbolizing the EKG that has been transformed into frequency space. The lead with the highest in band ratio is taken as the cleanest EKG lead. See Figure 2.3 for an example of the in-band ratio values.

### 2.3.4 Testing Noise Measures

In order to use the noise measure that would most accurately detect the cleanest lead, the data sorting algorithm was used. The sorting algorithm, discussed later, puts NANs in places where there is algorithm disagreement. In theory, noisier signals will have less beat agreement, and therefore more NANs. The data sorting algorithm was run on all three EKG leads for all 100 random samples and it counted the number of NANs in each R vector.

Then all three noise methods were used to pick the cleanest lead for the 100 samples. The noise measure that chose the lead with the least number of NANs the most was considered the most accurate noise measure. This was the in-band to out-of-band ratio noise measure, which picked the correct lead 98 times out of the 100 random samples.

Once all the times of all the R peaks were pulled out of the EKGs, there was a reduction of 95.6% in storage space. That is, the EKG signals required 8.16 TB of storage space while the R peak times by themselves only require 0.36 TB of data. This reduction makes it much more feasible to do analysis, as it requires less time to load and is easier to transport and share with collaborators.
2.4 Algorithms

Multiple algorithms exist for processing adult EKG signals [66, 44, 8, 9]. However, infant hearts are different from adults as they beat more often and usually weaker. Therefore new analysis techniques must be adopted in order to process infant EKGs:

Five EKG algorithms were selected as candidates for processing infant EKGs, (1) Length transformation [66], (2) Haar Wavelet [8], (3) Pan–Tompkins [44], (4) Modified Pan–Tompkins [9], (5) for comparison to the algorithm written by the author of this dissertation.

We will discuss the details of each algorithm, then compare their effectiveness at capturing the QRS signal in infants.

2.4.1 Length-Transformation

This algorithm relies on the fact that the curve length of the EKG is longest during the QRS complex [66]. The Length-Transformation algorithm applies a low-pass filter to reduce noise in the EKG, then moves on to a length transform and then finishes with a decision rule. The decision rule looks at the transformed signal and identifies when the beats occurred in the source signal.

Low-pass filters can be made by smoothing a signal with the following convolution: if $\mathbf{x}(t)$ is the original signal, and $\mathbf{y}(t)$ is the smoothed signal, we may take

$$y(t) = \int_{0}^{t_{\text{max}}} b(t')\mathbf{x}(t - t') \, dt'$$

(2.14)

$b(t')$ could be a constant, or a Gaussian, or any other smoothing function. A more sophisticated filter could be made by convolutions on both $x$ and $y$.

$$\int_{0}^{t_{\text{max}}} a(t')y(t - t') \, dt' = \int_{0}^{t_{\text{max}}} b(t')x(t - t') \, dt'$$

(2.15)

This is more transparent in Fourier space; if $X(z)$, $Y(z)$, $A(z)$, and $B(z)$ are respectively
Fourier transforms of \( x(t) \), \( y(t) \), \( a(t) \), and \( b(t) \), then Equation 2.15 is equivalent to

\[
A(z) \ Y(z) = B(z) \ X(z) \quad (2.16)
\]

or

\[
Y(z) = \begin{bmatrix} B(z) \\ A(z) \end{bmatrix} X(z) \quad (2.17)
\]

\[ \equiv H(z) \ X(z). \quad (2.18) \]

Experience has shown that good low-pass filters can be obtained by choosing rational functions for \( H(z) \). The discrete form of Equation 2.15 is

\[
y(n) = \sum_{k=0}^{M} b_k x(n - k) + \sum_{k=1}^{N} a_k y(n - k), \quad (2.19)
\]

where \( n \) is the discrete index of the vectors \( x \) and \( y \), and when \( (n-k) < 1 \) then \( y(n-k) \equiv 0 \).

For the Length-Transformation, a recommended low-pass filter is [66]

\[
H(z) = \frac{(1 - z^{-5})^2}{(1 - z^{-1})^2}. \quad (2.20)
\]

\( H(z) \) is of the form

\[
H(z) = \frac{\sum_{k=0}^{M} b_k z^{-k}}{1 - \sum_{k=1}^{N} a_k z^{-k}} \Rightarrow \frac{B(z)}{A(z)}, \quad (2.21)
\]

where \( A(z) \) and \( B(z) \) are polynomials, and are used to determine the coefficients, \( a_k \), and \( b_k \) [42]. Specifically, for the case of the \( H(z) \) above,

\[
A(z) = (1 - z^{-5})^2 = (1 - 2z^{-5} + z^{-10}) \quad (2.22)
\]

and

\[
B(z) = (1 - z^{-1})^2 = (1 - 2z^{-1} + z^{-2}) \quad (2.23)
\]

so in this case, \( a_k \) has zero values except for \( k = 0 \), \( k = 5 \) and \( k = 10 \), and \( b_k \) is nonzero only for \( k = 0 \), \( k = 1 \) and \( k = 2 \). We are then able to build up the filtered signal using
Equation 2.19 [42],

\[ y(1) = b_1 x(1) \]  (2.24)
\[ y(2) = b_1 x(2) + b_2 x(1) - a_2 y(1). \]  (2.25)

This completes the low-pass filter.

Now, we describe the length-transformation. The length of a continuous differentiable curve over time interval \((T - w)\) to \(T\) is

\[ L(T, w) \equiv \int_{(T-w)}^{w} \sqrt{1 + \left(\frac{dy}{dt}\right)^2} \, dt, \]  (2.26)

where \(w\) is the width of the interval. In discrete form this becomes

\[ L = \sum_{k=i-w}^{i-1} \sqrt{1 + \left(\frac{y_{k+1} - y_k}{t_{k+1} - t_k}\right)^2} \, (t_{k+1} - t_k). \]  (2.27)

This equation can be adapted to the EKG vector that is being analyzed by moving \(\Delta t\) into the square root. Thus, the equation becomes

\[ QRS_{\text{length}}(i) = \sum_{k=i-w}^{i} \sqrt{\Delta t^2 + (\Delta EKG_k)^2}. \]  (2.28)

Now a new vector can be constructed whose \(i\)th index’s value is related to the time step of the EKG (inverse of the sampling rate) as well as the EKG vector values that occur for the indices \(i - w\) to \(i\). Note that \(QRS_{\text{length}}(i) \equiv 0\) for \(i < w\). For fixed \(w\), the longest of these lengths correspond to the QRS complexes. A diagram showing their relationship is in figure 2.4. The peak of the R wave is in the range where the length transform increases the most. Figure 2.4 shows the results of the length transformation on the EKG.

Finally, a decision rule is implemented. A decision rule takes the transformed signal and decides where the beats are in the signal. The length transform uses thresholding to find the beats because where the signal is increasing past a threshold is where the beats
Figure 2.4: (Top) Length Transform Decision Rule bounds in relation to the EKG. (Left) Length transformed EKG. (Right) Example EKG with threshold applied. The vertical black dashed lines are a 250 ms window centered on the time where the signal crossed the threshold (red horizontal line).

occur. The threshold is the mean value of the length transformed signal for the first 10 seconds. Next, find where the length transform exceeds the threshold. From this point, we build a window of 250 ms around the point where the length transformed signal exceeds the threshold, 125 ms before the point and 125 ms after. The minimum and maximum value in that window are recorded. Figure 2.4 illustrates this.

So an overview of this algorithm is as follows: The EKG is sent through a low pass filter to eliminate high frequency noise. For adults, the ideal frequency cutoff is 5 Hz. Then that filtered EKG goes through the length transform described above, and the decision rule finds the maxima, and the preceding minima. Then within those bounds (see Figure
2.4), the maximum of the original EKG is found, and that is recorded as the R peak.

### 2.4.2 Haar Wavelet

The next method uses a continuous wavelet transform (CWT) to obtain the R peaks of the EKG. First, in order to clean the signal, the signal is transformed to the frequency domain using a Fast Fourier Transform (FFT), see equation 2.11. Then, the areas of the Fourier Transformed signal that correspond to frequencies of power line interference, between 58 and 62 Hz, are eliminated before an inverse Fourier Transform is done to bring the signal back to the time domain. See results of the Fourier Transform filtering in Figure 2.5

![Original and Cleaned EKG](image)

**Figure 2.5:** Cleaning the signal using a Fourier Transform before using a Haar wavelet to transform the signal. The original signal is represented by red dots and the cleaned signal is the blue line.

Next, this method finds the coefficients of the Haar wavelet, $d_{s,t}$, such that for an EKG signal, $EKG(u)$,

$$
d_{s,t} = \int_{-\infty}^{\infty} du \cdot \overline{\psi}_{s,t}(u) \cdot EKG(u)
$$

$$
(2.29)
$$
with

\[ \psi_{s,t}(u) \equiv \psi_s(u - t) = |s|^{-p} \cdot \psi \left( \frac{u - t}{s} \right) \]  

(2.30)

where \( \psi(t) \) is called the mother wavelet, \( s \) scales \( \psi(t) \), and \( p > 0 \) \([28, 32]\). Here we are using the Haar Wavelet, which has the form

\[
\psi(t) = \begin{cases} 
1 & 0 \leq t < \frac{1}{2}, \\
-1 & \frac{1}{2} \leq t < 1, \\
0 & \text{otherwise}
\end{cases}
\]  

(2.31)

and plotted in Figure 2.6.

**Figure 2.6**: The Haar Mother Wavelet is a square wave because of our goal to capture the QRS complex. The R wave peak and S wave trough will be picked up by this wavelet.

This algorithm transforms the EKG five times using the scaling factor \( 2^p \) for \( p = 1, 2, 3, 4, 5 \). Note here that in Equation 2.30, \( s = 2 \). The five separate sets of coefficients are then squared and normalized and averaged over 80 ms of source EKG signal. The resulting averaged coefficients share peaks with the QRS complexes \([8, 7]\). See Figure 2.7 to see the peaks. The averaged wavelet transform is then broken into 80 ms segments that are created around the maxima of the transform. These segments are our candidates for a QRS complex. In order to distinguish between QRS complexes and peaks arising from noise, the segments are compared to each other. Segments that are highly correlated
to 50% or more of the other segments are then considered to be QRS complexes. High correlation is defined by a correlation coefficient above 0.01 [8, 7]. The R-times are then labelled as the locations of the maxima of these highly-correlated segments. The code that applies this Wavelet method to EKGs was written and made available to us by Matthew Clark [7].

![EKG and Average Wavelet Transform](image)

**Figure 2.7:** Averaged Haar Wavelet coefficients (red) and the EKG signal (blue).

### 2.4.3 Pan-Tompkins Algorithm

Pan-Tompkins is a popular choice for adult EKG analysis due to the fact that it is so effective at reducing noise in EKG signals. The algorithm takes advantage of the extreme slope of the R wave in comparison to the rest of the signal [44]. The Pan-Tompkins algorithm consists of linear digital filtering, nonlinear transformation, and decision rule algorithms. The linear digital filtering does a bandpass filter, then a derivative on that filtered signal, and a moving window integrator. The nonlinear transformation is the squaring of the derivative of the signal. The decision rule is then an adaptive thresholding algorithm [44]. The code used to implement this method was made available on Matlab and was written by Hooman Sedgehamiz [51, 52].
The bandpass filter is effective because it eliminates the high frequency noise of the muscle artifact (the noise in the signal generated by processes occurring in the muscles and separate from the heart). This is usually very high frequency noise (around 10,000 Hz). It also eliminates the 60 Hz power line frequency, and baseline drift (between 0.15 and 0.3 Hz). The best passband for the QRS complex is 5-15 Hz. Pan and Tompkins designed a real-time calculator, so they needed a filter that would run quickly. The transfer function has a polynomial denominator, and therefore cannot be defined at that polynomial’s zeros. This makes a band pass filter difficult to design, so a combined low pass and high pass filter is utilized instead [44]. The low-pass filter uses the following transfer function, [44].

\[ H(z) = \frac{(1 - z^{-6})^2}{(1 - z^{-1})^2} \]  

(2.32)

and the high-pass filter was obtained by subtracting the output of a different low-pass filter from an all-pass filter. The high-pass filter uses the following transfer function, suggested by Pan and Tompkins [44]:

\[ H(z) = \frac{(-1 + 32z^{-16} + z^{-32})}{(1 - z^{-1})} \]  

(2.33)

The cutoff frequency for the high-pass filter is 5 Hz and that for the low-pass filter is 11 Hz. Figure 2.8 shows the results from the original EKG, low and high pass filters, the differentiation, and the squaring of the differentiated signal respectively.

It is important to take the derivative of the signal, because this algorithm relies on the fact that the R wave has such a large slope. The derivative is squared because it is possible for the EKG to record the features upside down, meaning that the slope of the R wave may appear very largely negative rather than positive. The derivative function used is as follows:

\[ H(z) = \frac{1}{8T}(-z^{-2} - 2z^{-1} + 2z^{1} + z^{2}) \]  

(2.34)

The next step in the Pan-Tompkins algorithm is to integrate the differentiated signal.
Figure 2.8: The Original Signal that will be used throughout this section to illustrate concepts explained. Low-pass filtered signal. Observe that the rapid changes have been eliminated, leaving a significantly smoother curve. High-pass filtered signal. Observe that the baseline wander of the EKG has been eliminated. The derivative of the filtered signal, Pan and Tompkins suggest a moving window integrator with a window of 150 ms. Results of the moving window integrator can be seen in Figure 2.9.
Figure 2.9: Note that the integrated signal is not a single integration over the entire time domain of the signal. Instead it is composed of 150 ms domains of integration on the differentiated signal.

Next comes the adaptive thresholding. The thresholding is done on both the filtered signal and the moving window integrated signal, and R peaks are only recorded if the calculations on both signals are in agreement that there is an R peak. The thresholds for both signals are based on estimates of the signal and noise peaks, and the overall signal peak as in equations 2.36 to 2.38, taken from Pan and Tompkins’s paper [44].

\[
S_{\text{peak}} = 0.125 \cdot OS_{\text{peak}} + 0.875 \cdot S_{\text{peak}} \\
N_{\text{peak}} = 0.125 \cdot ON_{\text{peak}} + 0.875 \cdot N_{\text{peak}} \\
Threshold_1 = N_{\text{peak}} + 0.25 \cdot (S_{\text{peak}} - N_{\text{peak}}) \\
Threshold_2 = 0.5 \cdot Threshold_1
\]  

(2.35)  
(2.36)  
(2.37)  
(2.38)

where \( S_{\text{peak}} \) is the current estimate of the signal peak, \( OS_{\text{peak}} \) is the maximum being analyzed, \( N_{\text{peak}} \) is the current estimate of the noise peak, \( ON_{\text{peak}} \) is the maximum being analyzed, \( Threshold_1 \) is the first threshold, and \( Threshold_2 \) is used if an R peak is not found within a chosen time interval [44]. The initial signal threshold is taken to be one
third of the maximum of the signal in the first two seconds, and the initial noise threshold is taken to be one half of the mean of the signal in the first two seconds.

Next, a vector is formed that is all the local maxima of the signal. Now that we have the local maxima of the signal and initial threshold tests, we are able to determine if each local maximum is an R peak, or a noise peak. Starting at the first entry in the maxima vector, and moving through each entry one by one, the maximum currently being analyzed is labelled as an R peak if it is greater than $Threshold_1$. If that is the case, then the vector entry being analyzed is considered $OS_{peak}$, and $S_{peak}$ is updated accordingly. If the maximum being analyzed is less than $Threshold_1$ then that maximum is considered $ON_{peak}$, and the $N_{peak}$ gets updated accordingly. Then $Threshold_1$ is updated and the analysis moves to the next maximum in the vector. If an R peak is not detected within a certain time interval then there is a back search with a lower threshold, $Threshold_2$. Examples of the thresholding can be found in Figure 2.10 and Figure 2.11 which were created using Matlab code adapted from [51, 52].

2.4.4 Pan-Tompkins Variant from Physionet

This next algorithm is a variant on the Pan-Tompkins’s algorithm, and the Matlab code we use was downloaded from Physionet, made available under GNU general public license [9]. The difference is the thresholding [19]. Rather than using an adaptive threshold, this method uses a constant threshold of one fifth of the integrated signal’s maximum peak over the entirety of the integrated signal [9]. The new thresholding can be seen in Figure 2.12.

2.4.5 Writing a New Algorithm

When writing a new algorithm, patterns from all four previously studied algorithms were observed. The final algorithm uses the Pan-Tompkins method for filtering and transformation because according to research and observations after running tests on random samples, this is the best method when analyzing noisy data.
Figure 2.10: Pan-Tompkin integrated signal thresholding. The dashed red line is the moving signal peak estimate, the dashed green line is the threshold, and the dashed black line is the noise threshold. The black points are the maxima of the signal after the signal crosses the threshold line. Adapted using [51, 52]

Like the previous method, the new method differs from Pan-Tompkins in the thresholding. Unlike Pan-Tompkins method which uses an adaptive thresholding to find the R peaks, the new algorithm uses the integrated signal and finds the peaks and the corresponding minima to the peaks. See Figure 2.13 for details.

The peaks of the integrated signal correspond to the end of the QRS complex, and the minima prior to these peaks correspond to the beginning of the QRS complex. This is a different decision rule than used in any previously studied algorithm. From here the algorithm uses these boundaries as locations to search for R waves, which are labelled as the maximum of the EKG in the search range.
Figure 2.11: Pan-Tompkin EKG signal thresholding. The dashed red line is the moving signal peak estimate, the dashed green line is the threshold, and the dashed black line is the noise threshold. The black points represent the maxima of the signal between when the signal crosses the threshold line. Adapted using [51, 52]

2.5 Algorithm Comparison

Next, the best three algorithms from the five were chosen. In order to do that 100 random 30 minute samples were collected from the data, and all five algorithms were run on the samples. This means that for each random sample, five R vectors were analyzed, and two algorithms were compared at a time.

In order to compare the algorithms, Matlab used the two R vectors created by the algorithms being compared. Algorithm beats were considered to be simultaneous if they were recorded within 150 ms of each other [34]. If an algorithm’s R vector has a beat recorded, and there is no corresponding beat within 150 ms in the second algorithm’s R vector, then the program records that beat as a discrepancy. Then, all the discrepancies were labelled and visually inspected to determine which algorithms were most reliable. See Figure 2.14 for a visual representation of what would be seen if a beat was added or
dropped, respectively. The three best algorithms were Pan-Tompkins’, and the Physionet variant, and my variant.

2.5.1 A More Selective Algorithm

Added beats are harder to detect than missing heart beats in predictive analysis. Therefore, the focus was moved to create more selective algorithm by requiring beat agreement between multiple algorithms.

In order to do this, a program was created that compared the three R vectors from the best algorithms. A visual representation of this can be seen in Table 2.1, in the columns labelled Algorithm 1, Algorithm 2, and Algorithm 3. The left hand side is the beat number in the sample, and recorded numbers in the vectors are the indices of the EKG that each algorithm marked as an R peak (recall that EKGs are sampled at 240 Hz). Beats that are within 150 ms of each other, or 36 samples, are lined up next to each other. When an

Figure 2.12: Physionet’s rpeakdetect.m signal thresholding. The red line is the filtered EKG signal, the blue line is the integrated signal. The black points represent when the signal crosses the threshold line. The r peaks are then labelled as the maximum of the EKG in each search area (between two consecutive black dots). Adapted from [9].
Figure 2.13: EKG with integrated signal overlaid. It can be seen that the peaks of the integrated signal correspond to the end of the QRS complex, and the minima prior to these peaks correspond to the beginning of the QRS complex.

algorithm missed a beat, as in beat number 509, a NAN was put as a placeholder.

Notice that the algorithms consistently differ by a time shift from each other. This analysis only needs the time between beats, not the actual time when a beat happens, therefore R vectors can be shifted on the time axis and the shift is irrelevant to our analysis.

For an example of this, we turn to beats number 496 and 497. The third algorithm is consistently 2 indices lower than algorithms one and two. The Matlab program sorting beats keeps track of this shift, and if it ever is observed by the program to have a sharp increase compared to the average shift, a NAN is put in place. To obtain the final R vector, rows with more than one NAN, as in beat number 510, are deleted as there must be agreement with at least two algorithms.

This program is useful because it can be easily edited and expanded to other R-Peak detectors. One can substitute any three methods of obtaining R vectors into it, and still obtain a more selective R-Peak vector. In total, four terabytes of EKGs were put through
Figure 2.14: Recall our focus is to capture the time of R wave peaks. The red dots and black crosses mark the timestamps that two different algorithms placed the R peak at. In processing the signals our algorithms can sometimes add beats that are not real (left graph) or miss beats and not include them in future analysis (right graph).
<table>
<thead>
<tr>
<th>Deleted?</th>
<th>Beat Number</th>
<th>Algorithm 1</th>
<th>Algorithm 2</th>
<th>Algorithm 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-Time</td>
<td>496</td>
<td>42933</td>
<td>42933</td>
<td>42931</td>
</tr>
<tr>
<td>R-Time</td>
<td>497</td>
<td>43015</td>
<td>43015</td>
<td>43013</td>
</tr>
<tr>
<td>R-Time</td>
<td>498</td>
<td>43097</td>
<td>43097</td>
<td>43096</td>
</tr>
<tr>
<td>R-Time</td>
<td>499</td>
<td>43180</td>
<td>43180</td>
<td>43178</td>
</tr>
<tr>
<td>R-Time</td>
<td>500</td>
<td>43262</td>
<td>43262</td>
<td>43260</td>
</tr>
<tr>
<td>R-Time</td>
<td>501</td>
<td>43344</td>
<td>43344</td>
<td>43342</td>
</tr>
<tr>
<td>R-Time</td>
<td>502</td>
<td>43426</td>
<td>43426</td>
<td>43424</td>
</tr>
<tr>
<td>R-Time</td>
<td>503</td>
<td>43507</td>
<td>43507</td>
<td>43505</td>
</tr>
<tr>
<td>R-Time</td>
<td>504</td>
<td>43588</td>
<td>43588</td>
<td>43586</td>
</tr>
<tr>
<td>R-Time</td>
<td>505</td>
<td>43669</td>
<td>43669</td>
<td>43667</td>
</tr>
<tr>
<td>R-Time</td>
<td>506</td>
<td>43750</td>
<td>43750</td>
<td>43748</td>
</tr>
<tr>
<td>R-Time</td>
<td>507</td>
<td>43832</td>
<td>43832</td>
<td>43830</td>
</tr>
<tr>
<td>R-Time</td>
<td>508</td>
<td>43914</td>
<td>43914</td>
<td>43912</td>
</tr>
<tr>
<td>R-Time</td>
<td>509</td>
<td>43996</td>
<td><strong>NAN</strong></td>
<td>43996</td>
</tr>
<tr>
<td>Delete</td>
<td>510</td>
<td><strong>NAN</strong></td>
<td><strong>NAN</strong></td>
<td>44007</td>
</tr>
<tr>
<td>R-Time</td>
<td>511</td>
<td>44078</td>
<td>44078</td>
<td>44076</td>
</tr>
<tr>
<td>R-Time</td>
<td>512</td>
<td>44160</td>
<td>44160</td>
<td>44157</td>
</tr>
<tr>
<td>R-Time</td>
<td>513</td>
<td>44241</td>
<td>44241</td>
<td>44239</td>
</tr>
<tr>
<td>R-Time</td>
<td>514</td>
<td>44324</td>
<td>44324</td>
<td>44322</td>
</tr>
</tbody>
</table>

Table 2.1: Results of the data sorting algorithm. Times for each algorithm are in time indices, each index is 4.166 ms apart.
Chapter 3

Algorithms for Estimating Cardiac Output

In this chapter we will present several methods to process human blood pressure waveforms to measure the bloodflow from the heart (i.e. the cardiac output). Measuring CO directly is medically invasive where in contrast, blood pressure is standard diagnostic tool that is recorded for all patients. Our algorithms seek to convert BP data into measures of CO, since the pressure of the blood and its flow from the heart must be connected. There is no formula that provides a one-to-one correspondence between BP and CO, therefore every algorithm here will use some underlying assumptions as we attempt to bridge the BP to CO. Further compounding the task is that the BP is typically measured in either femoral or radial arteries (the arm or leg), so we will utilize transfer functions to “shift” the BP waves to how they are near the heart.

The algorithms and models they use to connect BP and CO are presented in this chapter. The results of these methods are given in Chapter 4.
3.1 Long Time Interval Analysis

Blood pressure (BP) waveforms can be analyzed over long time intervals to simulate what blood pressure would occur if the heart suddenly stopped beating after a single contraction. This gives an exponential decay that has a time constant which can be used to monitor changes in the volume of blood that the heart pumps with each beat. These changes may give early warning signs of excessive bleeding.

This algorithm takes advantage of the theory that if the human heart suddenly stopped beating, then the BP would decay exponentially with a decay time $\tau$ [41]. This decay time is proportional to the volume of blood the heart has pumped (SV) [41]. However, this decay time is not simple to extract as it is covered by the patient’s next heart beat (see figure 3.1). This algorithm will use subtle changes that occur over many cardiac cycles in order to give an average $\tau$ over a long time interval (on the order of a few minutes). This will allow the measurement of changes in SV without the dangers to a patient that are involved in measuring SV directly.

![Exponential Decay Problems](image)

**Figure 3.1:** The potential exponential decay in blood pressure is obscured by the next heart beat.
3.1.1 Long Time Interval Algorithm

This algorithm has several components. First, a cardiac impulse train is constructed using the pulse pressures of the waveform. This impulse train is a single column matrix that is the same length as the BP data column matrix. It is mostly zeros, except at the point that corresponds to the beginning of a cardiac cycle, where the matrix value is the magnitude of the pulse pressure for the upcoming cardiac cycle. Figure 3.2 is a depiction of this impulse train construction [41].

![Construction of Pulse Pressure Train](image)

**Figure 3.2**: A pulse pressure (PP) train marked by the timestamps of diastole pressure (green stars). Red stars are systolic pressures. PP is the difference between systole and diastole pressure for every beat (marked by the vertical lines).

Next, a relationship is established between the previous \( m \) BP data points, and the current BP point through the following equation (see Figure 3.3),

\[
BP(n) = \sum_{k=1}^{m} a_k BP(n - k) + \sum_{k=1}^{m} b_k PP(n - k). \tag{3.1}
\]

As the algorithm moves down the BP waveform, for each BP point, we get one new
Figure 3.3: The top figure shows several beats and the boxed region is zoom in on and displayed in the bottom graph. Claim: There is a linear relationship between the previous $m$ points ($m = 10$ in this case) enclosed in the black box, the pressure pulse, and the next point, indicated by the red arrow.

The equation and one new unknown, $b_k$. However, we preselect a number ($m = 10$) of $b_k$s (as well as that many $a_k$s), and we continue step by step through the whole signal. Since there are many more equations than unknowns generated, a linear least squares fit to the measured BP is used to calculate values for these coefficients. This presumes a linear relationship between blood pressure now and blood pressure several points earlier together with recent pulse pressure.

Then, the relationship between each impulse and the arterial blood pressure (ABP) wave is characterized by estimating an impulse response function, $h(n)$. The functional
form, \( h(n) \) represents the ABP as a response to an idealized impulse (Dirac delta function \( \delta \)) at the beginning of each contraction. The equation used to generate \( h(n) \) is given below, and an example of an impulse response function is found in figure 3.4 [41].

\[
h(n) = \sum_{k=1}^{m} a_k h(n - k) + \sum_{k=1}^{m} b_k \delta(n - k)
\]  

(3.2)

As can be seen in Figure 3.4, the impulse response function is comprised of a primary pulse along with a reflection, and then an exponential decay. The reflection of the primary pulse represents the reflection of the BP wave off of the iliac artery bifurcation. The algorithm takes the logarithm of the impulse response function (Figure 3.5). To obtain \( \tau \), the logarithm of the impulse response is fitted linearly, starting one second after the peak value to capture only the exponential decay (instead of noise immediately after the peak), and the slope of that fit is the decay constant that will be used to estimate SV. SV is
inversely proportional to the decay time of the blood pressure [41],

$$SV \propto \frac{ABP}{\tau \ast HR}$$  (3.3)

where HR is the heart rate of the patient. SV is calculated as only a proportionality. In order to calculate the actual SV the algorithm must be trained with an initial SV reading. For the purposes of this research, training is not necessary because predictive monitoring is only interested in changes in SV, and we can eliminate the proportionality by normalizing the data.

**Figure 3.5**: Approximately 1 second after a peak, only the exponential decaying signal remains which we can fit with a linear equations.

### 3.1.2 Data and Results

Data obtained from the University of Virginia was used to test this algorithm on several waveforms. The data were in the form of a BP waveform with a time stamp of when a doctor ordered a blood transfusion for a patient. The ordering of a blood transfusion is
known as an event. The algorithm was run on the waveforms in 6 minute segments. Then the proportional SV as well as CO, HR, and $\overline{BP}$, and the decay constant are plotted. The results for one event is shown in Figure 3.6. This figure shows the results of one patient leading up to a hemorrhage event. A patient is said to have experienced a hemorrhage event if they required three or more blood transfusions in less than a 24 hour period. In Figure 3.6 zero seconds on the horizontal axis marks the time of the first blood transfusion. We then calculate average BP (purple), $\tau$ (orange), CO (yellow), HR (green), and SV (blue) every 10 minutes for one hour before and one hour after the first blood transfusion. Average BP is defined as the mean of the BP waveform data in the interval, and HR is calculated by counting the number of heart beats in the 10 minute interval.

![Example from Hemorrhage Event](image)

**Figure 3.6:** Example of data from a hemorrhage event, plotting stroke volume, cardiac output, the decay constant, and average blood pressure vs. time for one hour leading up to and an hour after a doctor ordered a transfusion on the patient.

This algorithm has been tested extensively and has a flaw that looking over such long periods means that there is a high probability that the signals that have large sections of noise, and the changes in SV that are noticed may be due to the sections of noise rather
than clinical deterioration of a patient. Examples of this effect can be seen in Figure 3.7.

![Figure 3.7](image)

**Figure 3.7:** (a) Blood pressure sample hand-selected to demonstrate a low noise signal. The stroke volume is relatively stable. (b) A high noise BP signal contributes to large fluctuations in the measured stroke volume.

In both figures we see the BP waveform (blue) and SV (orange), before the first blood transfusion of a hemorrhage event. Figure 3.7 (a) we see that when the BP is clean and has few noise spikes, then the SV stays mostly constant. However, when we look at a noisy BP in figure 3.7 (b), we see that the SV spikes with noise peaks due to the average BP shifting past physiologically possible values. It becomes desirable to remove these large sections of noise. However, eliminating large sections of noisy data is impractical as this algorithm relies on six continuous minutes of uninterrupted data.

One way to combat this challenge is to shift focus onto measures of SV so that can be done on a beat-by-beat basis, so even small sections of data can be analyzed effectively. Therefore, it is desirable to use algorithms that work on a beat by beat basis, and to test these methods on a large data set. The rest of this chapter’s methods were tested using Physionet’s MIMIC III database [16, 25, 46].
3.2 Physionet Patients and Data

The cardiac output data comes from the online public database, Physionet’s MIMIC III [16, 25, 46]. Matlab code is adapted that was written by Sun and is available on Physionet for download [56, 24]. Blood pressure waveforms of 440 patients are analyzed. There are 3966 total CO thermodilution measurements spread among the 440 patients. Statistics associated with the Cardiac Output measurements and information about the patients is shown in Table 3.1.

<table>
<thead>
<tr>
<th>Statistic</th>
<th>CO (L/min)</th>
<th>Age (years)</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>5.1</td>
<td>68.9</td>
<td>9</td>
</tr>
<tr>
<td>Median</td>
<td>4.8</td>
<td>70</td>
<td>7</td>
</tr>
<tr>
<td>Max</td>
<td>17.3</td>
<td>89</td>
<td>51</td>
</tr>
<tr>
<td>Min</td>
<td>1.6</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Std. Dev.</td>
<td>1.6</td>
<td>11.8</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 3.1: Statistics of CO, Patients’ ages, and number of thermodilution measurements per patient.

It can be seen that not all patients have an equal number of measures. There are two ways to think about the significance of each measurement. Often one considers measurements from each patient to be independent, and if there are several measurements from a single patient, then one should put a fractional weight on each measurement so that each patient is weighted equally. However it is not unreasonable to put more weight on those patients who (for whatever reason) need more measurements. One way to do this is to weight each measurement equally. That is what we have done.

Thermodilution is widely considered the best available measure of cardiac output, but this complex and invasive procedure is not carried out without good reason. Accordingly, the patients in this study suffered from a variety of severe illnesses, including heart failure, hemorrhage or posthemorrhagic anemia, hyperlipidemia, atherosclerosis and heart valve disorders. We seek a general purpose algorithm that can be used under a wide range of conditions, so we include all CO measurements in the MIMIC III database regardless of underlying pathologies.
3.3 Methods

Nine of the algorithms for CO that we use have been previously proposed, and one is adapted for our purposes. In this dissertation we apply each algorithm to the peripheral blood pressure wave, and combine them with four ways of estimating the transfer function that relates the measured peripheral blood pressure to aortic blood pressure. These steps make for a total of 46 algorithms tested. The results of each of these algorithms are used as predictors in a linear regression model. Of the nine previously proposed algorithms, four are based on circuit models of circulation and four use the area under the BP curve [56]. We utilized the Matlab code that has been made available on Physionet for signal quality analysis and estimations [56, 55]. These nine methods were also examined by Sun et al., but they did not give values of correlation coefficients values for each, and they did not combine them by multivariate regression [55]. We also examined one other method proposed by Zhang et al [64]. This approach needs five minutes of continuous artifact-free data, and we found it to be less useful for the data available to us.

3.4 Preprocessing

Ten minute segments of blood pressure waveforms are analyzed per measurement, centered around the time of the thermodilution measurement. Prior to the algorithms being performed on a blood pressure waveform, the signal is cleaned, and noisy or nonphysiologic beats are removed.

The signal is cleaned using a Savitsky-Golay filter to eliminate noise. A Savitsky-Golay Filter creates smoothed values for the blood pressure by fitting a kth order polynomial to a subset of m points (m must be odd [43]), and the current point, j, being smoothed is centered in the interval $j - \frac{m-1}{2}$ to $j + \frac{m-1}{2}$. The resulting smoothing function ends is a convolution of the original BP with predetermined convolution coefficients, $A_i$. The $A_i$ coefficients are given by the interval size (m) and order of the polynomial fit selected for
the smoothing. $A_i$ is independent of the signal, and

$$BP_{smoothed}(j) = \sum_{i=-m/2}^{m/2} C_i \cdot BP_{i+j}.$$  \hfill (3.4)

In order to understand where this convolution came from, consider a point $(j)$ in BP signal vector, $BP_j$, with associated time stamp, $t_j$, and smoothing window $m = 5$. We define a coordinate change on $t_{j-m/2}$ to $t_{j-m/2}$,

$$z_i = \frac{t_i - t_j}{\Delta t}, \quad \Delta t = t_{i+1} - t_i \forall i$$  \hfill (3.5)

For ease of the derivation we now have a “time” vector, $\vec{z}$, that goes from -2 to 2 in integer steps of 1 \(^1\). The polynomial fit is then,

$$BP_{smoothed}(i) = \sum_{n=0}^{k} a_n \cdot z_i^n$$  \hfill (3.6)

where the least squared error is minimized. Now, in order get the coefficients, $a_n$, define $S$ as the time matrix, and $A$ as the coefficient matrix, as

$$S = \begin{bmatrix} 1 & z_1 & z_1^2 & \ldots & z_1^k \\ 1 & z_2 & z_2^2 & \ldots & z_2^k \\ 1 & z_3 & z_3^2 & \ldots & z_3^k \\ 1 & z_4 & z_4^2 & \ldots & z_4^k \\ 1 & z_5 & z_5^2 & \ldots & z_5^k \end{bmatrix} = \begin{bmatrix} 1 & -2 & 4 & \ldots & z_1^k \\ 1 & -1 & 1 & \ldots & z_2^k \\ 1 & 0 & 0 & \ldots & z_3^k \\ 1 & 1 & 1 & \ldots & z_4^k \\ 1 & 2 & 4 & \ldots & z_5^k \end{bmatrix}$$  \hfill (3.7)

\(^1\Delta t \) must be the same value for all of $t$ for an SG-filter to be valid.
\[ \mathbf{A} = \begin{bmatrix} a_0 \\ a_1 \\ a_2 \\ \vdots \\ a_k \end{bmatrix} \]  

(3.8)

\[ \mathbf{BP}_{j-2:j+2} = \begin{bmatrix} BP_{j-2} \\ BP_{j-1} \\ BP_j \\ BP_{j+1} \\ BP_{j+2} \end{bmatrix}. \]  

(3.9)

We define an error, which is equal to

\[ \text{error} = e = \mathbf{BP}(j - 2 : j + 2) - \mathbf{BP}_{\text{smooth}}(j - 2 : j + 2) \]  

(3.10)

\[ e = \mathbf{BP}(j - 2 : j + 2) - \mathbf{SA}. \]  

(3.11)

It is then possible to use minimization techniques to solve for the coefficient matrix, \( \mathbf{A} \) in terms of the values of the \( \mathbf{BP} \) matrix,

\[ \mathbf{A} = (\mathbf{S}^T \mathbf{S})^{-1} \mathbf{BP} \]  

(3.12)

\[ \mathbf{BP}_{\text{smooth}}(j - 2 : j + 2) = \mathbf{SA} = \mathbf{S}(\mathbf{S}^T \mathbf{S})^{-1} \mathbf{BP}(j - 2 : j + 2). \]  

(3.13)

Now, if we let \( \mathbf{C} = \mathbf{S}(\mathbf{S}^T \mathbf{S})^{-1} \) (note that the coefficients are independent of the signal), the convolution then becomes

\[ \mathbf{BP}_{\text{smooth}}(j) = \frac{1}{N} \sum_{i=-2}^{2} C_i \cdot BP_{i+j}, \]  

(3.14)

where \( N \) is a normalization coefficient. For the case of this study, a \( k = 3 \) order polynomial was used, and the window size was \( m = 9 \). The convolution coefficients for a third degree
polynomial with window length 9 are

<table>
<thead>
<tr>
<th>N</th>
<th>C_{-4}</th>
<th>C_{-3}</th>
<th>C_{-2}</th>
<th>C_{-1}</th>
<th>C_0</th>
<th>C_1</th>
<th>C_2</th>
<th>C_3</th>
<th>C_4</th>
</tr>
</thead>
<tbody>
<tr>
<td>231</td>
<td>-21</td>
<td>14</td>
<td>39</td>
<td>54</td>
<td>59</td>
<td>54</td>
<td>39</td>
<td>14</td>
<td>-21</td>
</tr>
</tbody>
</table>

**Table 3.2:** Convolution coefficients for a Savitsky-Golay filter for a polynomial of order 3 and window length 9.

An example of a SG Filtered BP can be seen in Figure 3.8. Once the high frequency noise is removed from the waveform, the jSQI algorithm from Physionet [56, 55, 35, 24] is used. This algorithm uses nine features to determine whether a beat is normal or abnormal. The thresholds for what defines a normal beat can be seen in Table 3.3 [35, 53]. If any of these features are flagged as abnormal then the beat is eliminated from the analysis. If less than 80% of the beats in a ten minute segment remain then the signal is considered unreliable and the measurement is not used in further analysis. The same preprocessing was used by Sun et al. [55].

![Original BP and SG Filtered BP](image)

**Figure 3.8:** Original BP (black) and SG Filtered BP (red). This shows how the filter smooths high frequency noise.
### Table 3.3: Summary of abnormality criteria used to eliminate beats. Adapted from [53].

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
<th>Abnormality Thresholds</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_S$</td>
<td>Systolic BP</td>
<td>$P_S &gt; 300$ mmHg</td>
</tr>
<tr>
<td>$P_D$</td>
<td>Diastolic BP</td>
<td>$P_D &lt; 20$ mmHg</td>
</tr>
<tr>
<td>$P$</td>
<td>Mean BP</td>
<td>$P &lt; 30$ mmHg or $P &gt; 200$ mmHg</td>
</tr>
<tr>
<td>$HR$</td>
<td>HR</td>
<td>$HR &lt; 20$ BPM or $HR &gt; 200$ BPM</td>
</tr>
<tr>
<td>$PP$</td>
<td>Pulse Pressure</td>
<td>$PP &lt; 20$ mmHg</td>
</tr>
<tr>
<td>$w$</td>
<td>mean of negatives slopes</td>
<td>$w &lt; \frac{40}{100}$ mmHg/ms</td>
</tr>
</tbody>
</table>

| Change in $P_S$ | $|P_S(b) - P_S(b-1)| > 20$ mmHg |
| Change in $P_D$ | $|P_D(b) - P_D(b-1)| > 20$ mmHg |
| Change in $HR$  | $|HR(b) - HR(b-1)| > \frac{5}{s}$ |

### 3.5 Circuit Models

Blood flowing through the body is analogous to current in an electrical circuit. Physicists, ever the lazy bunch, are always looking to exploit hard problems by relating them to other systems that are well understood. So we shall model human blood circulation in a variety of ways with electric circuits. In this case, cardiac output (or stroke volume) is represented by electric current. The blood pressure correlates to electric potential. Arterial compliance measures the elasticity of the arteries; it is the gain in the amount of blood stored in an artery per unit pressure rise in that artery. The greater the elasticity, the larger range of volume of blood that the artery can contain, i.e. the arteries swell or shrink to house the blood flowing through. For these reasons the arterial compliance is represented by electric capacitance. Finally the resistance of the blood vessels to the flowing blood will be modeled by resistors. In this way, human circulation is modeled as an electric circuit. In Section 3.5 we will describe six different circuit models that were used in our blood pressure waveform analysis.

<table>
<thead>
<tr>
<th>Physiology</th>
<th>Electric Analog</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Output</td>
<td>Current</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Voltage</td>
</tr>
<tr>
<td>Arterial Compliance</td>
<td>Capacitance</td>
</tr>
<tr>
<td>Blood Vessel Resistance</td>
<td>Resistance</td>
</tr>
</tbody>
</table>
3.5.1 Mean Arterial Pressure

Our first model will be the simplest, an RC circuit (Figure 3.9), where we apply Ohm’s law to determine the blood pressure,

\[ I = \frac{V}{R} \]  

(3.15)

Because current is analogous to blood flow and voltage to pressure, Ohm’s Law becomes

\[ CO = \frac{P}{R} = k_1P \]  

(3.16)

with \( P \) standing for mean arterial pressure. Here the resistance is presumed to be constant.

3.5.2 Pulse Pressure

This method is based on an RC circuit and Kirchoff’s Loop Law [11]. The charge on a capacitor is equal to capacitance times the voltage drop, \( V_1 - V_2 \),

\[ Q = C(V_1 - V_2). \]  

(3.17)

Because charge, \( Q \), is analogous to volume of blood and voltage to pressure we have

\[ \text{Volume of blood per beat} = k(P_1 - P_2) \]  

(3.18)
and

\[ CO = k_2(P_1 - P_2) \times HR \] (3.19)

with \( HR \) equal to heart rate and \( k_2 \) is a proportionality constant.

### 3.5.3 Liljestrand and Zander

This method starts from the same setup as the pulse pressure method, Equation 3.17, but adds an additional step by assuming that the capacitance of the arteries decreases with increasing stretch of the arteries, resulting in capacitance being inversely proportional to the average pressure [37],

\[ CO = \frac{k_3(P_1 - P_2)}{(P_1 + P_2)} \times HR \] (3.20)

This method has been found to be reliable in another study done by Koenig et al. [31].

### 3.5.4 AC Power

This algorithm is based on the idea that average power (PWR) in an AC Circuit is related to the root-mean-square of both current and voltage [26, 54],

\[ PWR_{Avg} = I_{RMS}^2 R = \frac{V_{RMS}^2}{R} \] (3.21)

\[ I_{RMS} = \frac{V_{RMS}}{R} \] (3.22)

\[ CO = k_4 P_{RMS}. \] (3.23)

Cardiac output in this model is proportional to the root-mean-squared pressure (\( k_4 \) is another proportionality constant).

### 3.5.5 RC Decay

The total current is any expansion of the arteries and the flow through the capillaries added together,

\[ I_{total}(t) = I_C + I_R. \] (3.24)
Using Ohm’s Law to substitute in equivalent expressions for current in both cases, we have

\[ I_{total}(t) = C \frac{dP}{dt} + \frac{P(t)}{R}. \]  
(3.25)

We can solve this differential equation during diastole, when the current is zero, \( I_{total} = 0 \),

\[ C \frac{dV}{dt} + \frac{V(t)}{R} = 0 \]  
(3.26)

with the solution

\[ V(t) = V_0 e^{-\frac{t}{RC}}. \]  
(3.27)

Let \( RC = \tau \), the RC time constant. Ohm’s Law dictates Equation 3.15. Since \( \tau = RC \),

\[ I = \frac{VC}{\tau}. \]  
(3.28)

Assuming that the arterial and vascular compliance, \( C \), is nearly constant, we have

\[ I = k_5 \frac{V}{\tau} \]  
(3.29)

\[ CO = k_5 \frac{P}{\tau}, \]  
(3.30)

where \( k_5 \) is a proportionality constant. To calculate \( \tau \), one assumes that the systolic and diastolic pressures (\( P_S \) and \( P_D \)) are two points on the exponential decay at times \( t_S \) and \( t_D \) [55], so

\[ \frac{P_D}{P_S} = e^{-\frac{(t_D-t_S)}{\tau}} \]  
(3.31)

\[ \tau = \frac{(t_D - t_S)}{\log(P_D/P_S)}. \]  
(3.32)

Using this decay time together with the average pressure for each beat, Equation 3.30 gives the cardiac output.
3.5.6 Wesseling Four-Element Model

A new method we studied is a modification of a three-element model proposed by Wesseling et al. [59]. A diagram of the three element model can be seen in Figure 3.10. This model factors in the aortic impedance along with the capacitance of the aorta and arterial tree.

![Three Element Model Diagram](image)

**Figure 3.10:** Three Element model. Wesseling’s three element model adds an extra impedance to represent internal resistance in the aortic artery.

In addition, both the impedance and the capacitance are functions of pressure, changing within each beat. These quantities are related to the change of aortic area with pressure, for which a formula was given by Langewouters et al. [33]. This formula has parameters that depend on the patient’s age and gender. This three-element model is widely believed to be accurate, at least if the aortic pressure is known. However, in the measurements of Wesseling et al. [59], the aortic pressure was not always available, so they used measurements of radial pressure instead, the three element circuit was also analyzed by Godje et al. [14], but only the capacitance was treated as being nonlinear. In his Master’s thesis [56], Sun reports that the three-element method gave poor results, and it was not discussed in the related published article [55]. We also found that it gave poor results.

We give here a four-element model, as a hoped-for improvement of the three-element model. A problem with the three-element model is that when we compute the flows using the peripheral pressure \( P(t) \), during part of each heartbeat we find that the peripheral pressure \( P(t) \) is greater than \( P_0(t) \). So the computed flow through the aorta is negative.
This can also be seen in Fig. 3 of Ref. [59]. Negative blood flow should not happen in the aorta. Therefore we add a rectifier (diode) representing the aortic valve and preventing any backflow from aorta to ventricle.

Figure 3.11 shows this model. The current through the impedance $Z$ is the sum of the current into the capacitor and that through the resistor,

\[ I_Z(t) = I_+(t) = \left[ \frac{d}{dt} \left( C(P(t)) \cdot P(t) \right) + \frac{P(t)}{R} \right]_+ \]  \hspace{1cm} (3.33)

but only when that quantity is positive. By definition $I_+(t) = 0$ when the bracket < 0.

Over many beats the total blood volume through the impedor must equal the total volume through the resistor,

\[ \int I_{Z+}dt = \int \frac{P(t)}{R} dt \]  \hspace{1cm} (3.34)

\[ \int \frac{P(t)}{R} dt = \int \left[ \frac{d}{dt} \left( C(t) \cdot P(t) \right) + \frac{P(t)}{R} \right]_+ dt \]  \hspace{1cm} (3.35)

\[ \int \left( \left[ R \cdot \frac{d}{dt} \left( C(t) \cdot P(t) \right) + P(t) \right]_+ - P(t) \right) dt \to 0. \]  \hspace{1cm} (3.36)

We chose to integrate this over an integer number of heartbeats, corresponding to one respiratory cycle. The respiratory cycle is identified by local minima in the cycle of diastolic pressures (Fig. 3.12). We used the formula for capacitance given in Ref. [59], and assumed that the peripheral resistance is constant over a respiratory cycle. That resistance was
then calculated by making the positive integrated current through the impedor equal the integrated current through the peripheral resistor. From this approach we get an estimate of cardiac output without an estimate of $P_0(t)$, so we do not apply a transfer function to these results. This method differs from all the others in that it provides a way to estimate a patient’s systemic vascular resistance.

This method is the most elaborate and sophisticated of the methods we tested. Sadly, we show later that it gave the poorest results of any single method. However, perhaps because it is quite distinct from all the other methods, it (barely) survives the elastic net reduction.

![Figure 3.12: Red indicates the minima of the diastolic pressures. This indicates the start of a new breath.](image)

**Figure 3.12**: Red indicates the minima of the diastolic pressures. This indicates the start of a new breath.

### 3.6 Area Under the Curve

Switching away from circuits, we can instead use fluid dynamics principles to calculate the blood flow. As more blood is squeezed into the finite space of the arteries the pressure will
correspondingly increase\(^2\). Three methods are presented here that are based on the theory that the area under the pressure curve, Figure 3.13 is proportional to the volume of blood pumped [58]. Calculating the area of blood pressure over time curves yields information on the cardiac output.

\[\text{Figure 3.13: The area under the BP curve can be related to the blood volume, as can the decay time of the fitted exponential decay.}\]

### 3.6.1 Systolic Area

This theory comes from a restricted Navier-Stokes equation [27],

\[
-\frac{\partial P}{\partial x} = \rho \frac{du}{dt}
\]  \hspace{1cm} (3.37)

where \(P\) is the blood pressure, \(\rho\) is the blood density, and \(u\) is the blood velocity. In simpler terms, this is Newton’s second law. The pressure gradient is analogous to force, blood density is analogous to mass, and the derivative of blood velocity is like an acceleration.

\(^2\)In the conclusion we suggest improvements on these methods as arterial expansion is assumed to be negligible in these area-curve models.
Now we can relate the pressure gradient to the time derivative of pressure. If the pressure wave passes a detector without much change of shape, it can be described by the function $P(x - vt)$, so
\[
-\frac{\partial P}{\partial x} = \frac{1}{v} \frac{\partial P}{\partial t}
\]  
(3.38)
\[
\frac{\partial P}{\partial t} = \rho v \frac{du}{dt}.
\]  
(3.39)

We integrate twice with respect to time during the contraction of the heart, from $T_0$ to $T_s$ where $T_0$ is the time at diastole and $T_s$ is the time at which the aortic valve closes. If the aortic BP were measured, then the time in systole would be identified by the dicrotic notch. Since (in this study) only peripheral BPs are measured, we take the time in systole to be $0.3\sqrt{\text{cycle time in seconds}}$, about one third of the square root of the beat period [55]. This empirical formula was proposed by H.C. Bazett, and used also by Sun et al. [55, 2].

Thus we can integrate to yield
\[
\int_{T_0}^{T_s} P(t) dt = \rho v \int_{T_0}^{T_s} u(t) dt.
\]  
(3.40)

The integral of blood velocity with respect to time is blood volume. Therefore, the systolic area (SA) integral over the time that the heart is contracting is proportional to the volume of blood pumped,
\[
CO = k_0 SA.
\]  
(3.41)

### 3.6.2 Corrected Systolic Area

Wesseling et al., through empirical analysis of clinical research, found that arterial impedance is related to heart rate. That empirical analysis suggested a correction to the systolic area curves by introducing Ohm’s law [60].

The total volume of blood pumped by the heart during one contraction is the integral
of the blood flow during ventricular ejection,

\[
\text{Volume} = \int_{\text{ejection}} \text{Flow} \cdot dt. \tag{3.42}
\]

Using Ohm’s Law and the biological analogies discussed above,

\[
\text{Volume} = \int_{\text{ejection}} \left( \frac{P(t)}{R} \right) dt = \frac{1}{R} \cdot \text{SA}. \tag{3.43}
\]

The impedance, \( R \), is related to the heart rate and can be estimated using the following general relationship, where \( R \) has units of impedance, \( \left[ \frac{\text{mmHg} \cdot \text{sec}}{\text{cm}^3} \right] \) [60]:

\[
R = \frac{20 \left[ \frac{\text{mmHg}}{\text{cm}^3} \right]}{HR[\text{Hz}] + x(P)[\text{Hz}]} \tag{3.44}
\]

Then, after plotting \( x \) vs. \( P \), the relationship between \( x \) and \( P \) was estimated to be

\[
x = 163[\text{Hz}] - 0.48 \left[ \frac{\text{Hz}}{\text{mmHg}} \right] \cdot P, \tag{3.45}
\]

thus,

\[
R = \frac{20}{HR + 163 - 0.48 \cdot P}. \tag{3.46}
\]

Finally,

\[
CO = k_8(163 + HR - 0.48 \overline{P}) \cdot \text{SA} \cdot HR \tag{3.47}
\]

### 3.7 Herd Method

This method was created using clinical testing and observation of dogs [20], and predicts (or models) \( CO \) as

\[
CO = k_9(\overline{P} - P_D)HR \tag{3.48}
\]
3.8 Transfer Functions

Many of these methods are thought to be most accurate if aortic blood pressure is used instead of the BP measurements that are recorded “far” away from the heart (in the leg or arm). Accordingly, several methods have been proposed to estimate aortic pressure from peripheral BP by transferring the peripheral measurements back to the heart. These involve a linear transfer function in frequency space. Consider the heart beat as a wave generator, at every junction in the circulatory system, some of that wave is transmitted and some is reflected. We will investigate several transfer functions that approach this task with slightly different assumptions about how the wave propagates through the circulatory system.

3.8.1 General Transfer Function

\[ \tilde{P}_{\text{peripheral}}(\omega) = \tilde{T}(\omega) \tilde{P}_{\text{aortic}}(\omega) \]  (3.49)

The peripheral blood pressure is transformed into the frequency domain using a Fourier transform. Then the transformed pressure is divided by the transfer function \( T(\omega) \), and an inverse Fourier transform is used to get back to the time domain.

The amplitude and phase of the transfer function were measured by Karamanoglu et al. using 14 patients with sensors in the aorta and a peripheral artery [29]. The transfer functions found by Karamanoglu et al. depend on the location of the pressure sensing catheter. There were transfer functions proposed for the brachial artery and the radial artery, and both transfer functions were used on this data set. The results can be seen in Figures 3.14 and 3.15, and the transfer function itself is obtained using

\[ TF = Amp \cdot e^{i \text{phase}} \]  (3.50)

An example of a resulting aortic blood pressure waveform from the brachial transfer function can be seen in Figure 3.16. After the estimate of the aortic blood pressure was obtained, the nine previously discussed methods were applied to the estimated waveform.
3.8.2 K-Point Moving Average

This alternate transfer method assumes that each point of the aortic blood pressure is the average of the K radial points that came immediately prior. K is related to the sampling frequency of the radial blood pressure such that approximately a quarter of a second is averaged. This method has been shown to give accurate peak systolic pressure when compared to peak pressures measured in the aorta [62, 63]; we have

$$P_{aortic}(J) = \frac{1}{K} \sum_{i=J-K}^{J} P_{radial}(i).$$

(3.51)

An example of a resulting aortic blood pressure waveform from the moving average transfer function can be seen in Figure 3.17.
3.8.3 Adaptive Transfer Function

This method presumes that during diastole, the aortic blood pressure falls exponentially with time. It also assumes that peripheral blood pressure is related to aortic blood pressure through a time delay, \( T \), and a reflection coefficient, \( \Gamma \) [13], so

\[
P_{\text{aortic}}(t) = \frac{1}{1 + \Gamma} P_{\text{peripheral}}(t + T) + \frac{\Gamma}{1 + \Gamma} P_{\text{peripheral}}(t - T). \quad (3.52)
\]

\( T \) is assumed to be between between 0 and 150 ms, and \( \Gamma \) between 0 and 1. Aortic waveforms are computed for each combination of \( T \) and \( \Gamma \) with \( T \) going by increments of 5 ms and \( \Gamma \) increasing by increments of 0.05. Each waveform is then log transformed and the ends of the diastolic interval are fitted with linear regression. The \( T \) and \( \Gamma \) that give the minimum fitting error are selected as the time delay, \( T \) and reflection coefficient, \( \Gamma \) [13].

An example of a resulting aortic blood pressure waveform from the adaptive transfer
Figure 3.16: Estimated Aortic blood pressure waveform obtained using the brachial transfer function.

function can be seen in Figure 3.18.

3.9 Proportionality Constants

Each of the nine algorithms were applied to the peripheral blood pressure wave and to the three estimates of aortic waves from the three transfer functions.

For each of the 37 algorithms, there is a coefficient $k_i$ relating the estimate from the formula to the measured value. Actually this coefficient is different for each patient. We obtain it by comparing the average measured value for each patient with the average calculated value for that patient:

$$k_{i,p} = \frac{\frac{1}{N_p} \sum_{m=1}^{N_p} CO_{meas}(m,p)}{\frac{1}{N_p} \sum_{m=1}^{N_p} CO_{est_i}(m,p)}$$

(3.53)

Here $i$ labels the algorithm (1...37), $p$ labels the patient, $m$ labels the measurement for
Figure 3.17: Estimated Aortic blood pressure waveform obtained using the moving average transfer function.

that patient and $N_p$ is the number of measurements for patient $p$.

3.10 Linear Regression

We use linear regression to combine the results from these methods. For each algorithm we select the peripheral waveform or a transfer function, whichever gives the largest $R^2$ value.

$$CO_{meas} = b \cdot CO_{est}$$ (3.54)

where $CO_{meas}$ is the vector of 3966 thermodilution measurements, and $CO_{est}$ is an 11x3966 matrix listing the values estimated by each of the ten best algorithms together with a column of ones, multiplying $b_0$, the intercept. This computation was done with 90/10 training and test sets, using Matlab. The final values of coefficients are obtained by averaging the results of the ten test sets.
Figure 3.18: Estimated Aortic blood pressure waveform obtained using the adaptive transfer function.

In Section 4.1, we show in Table 4.3 that some coefficients come out negative, and with large standard deviations. This is indicative of highly correlated variables, so it suggests the possibility of reducing the number of measures.

3.11 Elastic Net

In order to drop redundant predictors from the model, the Elastic Net method is used. This method penalizes coefficients by minimizing square error plus the sum of squares and/or absolute values of the coefficients, equation 3.55,

$$\min_b \left[ \frac{1}{2N} \sum_{i=1}^{N} (CO_{meas_i} - CO_{est_i})^2 + \lambda \sum_{j=1}^{P} \left( \alpha \|b_j\| + \left(1 - \frac{\alpha}{2}\right)b_j^2 \right) \right]$$  \hspace{1cm} (3.55)

We took $\alpha = \frac{1}{2}$. This method is performed with a tenfold cross validation. This means that the data are divided into ten random groups, and the calculations are done on all ten groups separately. The final results are the average of these ten sets.
Figure 3.19: The MSE plotted against $\lambda$ values for the iterations of the Elastic Net regularization. The blue dashed line corresponds to the minimum error plus one standard deviation of the error, and the green dashed line corresponds to the iteration of $\lambda$ that has the lowest error. The black dashed line corresponds to the iteration of $\lambda$ that we use, when MSE has flattened, and the model has been simplified.

The minimization in Eq. 3.55 is done using a range of $\lambda$ from nearly 0 to nearly 3. Note that when $\lambda = 0$ we are back to minimizing the squared error, and therefore is just ordinary least squares again. Figure 3.19 shows that values of $\lambda$ closer to 0 (ordinary least squares) gives the lowest mean squared error (MSE). However, because no coefficients are penalized, this is the most complicated model. Therefore, we take the iteration of the elastic net where the MSE in Figure 3.19 starts to flatten out. This will provide a simple model while still giving low error.
3.12 Changes in CO

We are primarily interested in using these methods for continuous monitoring, and we are more concerned about changes in CO rather than the current values. Therefore for each patient we examine two successive CO measurements, and calculate the percent change,

\[
\text{%Change} = \frac{CO_i - CO_{i+1}}{CO_i} \cdot 100\%.
\]  \hspace{1cm} (3.56)

We put these changes into three categories: decrease by more than 25\%, increase by more than 25\% and smaller increases or decreases. We compared the changes predicted by linear regression with changes in successive measurements, and calculated the percent of cases for which the two agree.

The percent agreement was calculated for the best methods and can be seen in Section 4.1, Table 4.6.
Chapter 4

Results

Cardiac output is an important measure of health, but the best methods for measuring it are difficult, time-consuming, and highly invasive. It would be good to have methods which, albeit less accurate, could be used continuously in an ICU to give early warning of substantial changes in CO. For this reason, we have tested 46 algorithms that seek to obtain CO from peripheral BP waveforms.

4.1 Results

The ten algorithms are summarized in Table 4.1. Matlab code that applies these methods to blood pressure waveforms has been made available by JX Sun on Physionet [56, 55, 54]. This code was adapted for this work. All were applied to the peripheral blood pressure waveform. Nine to the transferred waves, in total of 46 algorithms tested. The results of these evaluations were compared to 3966 CO thermodilution measurements from 440 patients in the MIMIC III database on Physionet. Table 4.2 gives the coefficient of determination \( R^2 \) between the measured and computed values of CO. The magnitude of the errors are larger when the measured CO is larger, but the relative errors are more nearly independent of the magnitude of CO. Table 4.2 shows the value of the median
absolute error in percent for the best method in the row, equation 4.1

\[ mAE = \text{median} \left[ 100\% \cdot \frac{|CO_{\text{meas}_i} - CO_{\text{est}_i}|}{CO_{\text{meas}_i}} \right], \quad (4.1) \]

where \( i \) labels the individual measurement, \( CO_{\text{meas}_i} \) is the thermodilution measurement, and \( CO_{\text{est}_i} \) is the estimated CO from the algorithm.

The best single algorithm is the Liljestrand method used together with the brachial transfer function; it has a correlation coefficient of 0.90 and a median absolute error (mAE) of 8.43\%. Four of the algorithms give their best results using the untransformed peripheral BP waveform, and four are best using the brachial transfer function. The mean pressure algorithm gives marginally better results (in the next decimal place) using the radial rather than the brachial transfer function (best results marked in bold red in Table 4.2). The

<table>
<thead>
<tr>
<th>Method</th>
<th>Equation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liljestrand</td>
<td>( k\frac{P_s - P_d}{T_s + T_d} \cdot HR )</td>
<td>Circuits</td>
</tr>
<tr>
<td>AC Power</td>
<td>( k\sigma(P(t)) )</td>
<td>Circuits</td>
</tr>
<tr>
<td>Pulse Pressure</td>
<td>( k(P_s - P_d) \cdot HR )</td>
<td>Circuits</td>
</tr>
<tr>
<td>Herd</td>
<td>( k(\bar{P} - P_d) \cdot HR )</td>
<td>Circuits</td>
</tr>
<tr>
<td>Corrected Impedance</td>
<td>( k(163 + HR - 0.48\bar{P})SA \cdot HR )</td>
<td>Area</td>
</tr>
<tr>
<td>Systolic Area</td>
<td>( kSA \cdot HR )</td>
<td>Area</td>
</tr>
<tr>
<td>Mean Pressure</td>
<td>( k\bar{P} )</td>
<td>Circuits</td>
</tr>
<tr>
<td>Corrected Area</td>
<td>( k(1 + \frac{T_d}{T_s}) \cdot SA \cdot HR )</td>
<td>Area</td>
</tr>
<tr>
<td>Two Point Decay</td>
<td>( k\frac{\bar{P}}{\tau_1} )</td>
<td>Circuits</td>
</tr>
<tr>
<td>4 Element</td>
<td>equation 3.36</td>
<td>Circuits</td>
</tr>
</tbody>
</table>

Table 4.1: A summary of the ten methods being applied to the four different waveforms for a total of 46 algorithms.

correlation coefficients for all 46 of these algorithms can be seen in Table 4.2.

Selecting for each algorithm the peripheral or transferred wave that gives the largest
Table 4.2: $R^2$ for all algorithms applied to the Peripheral BP wave and ‘aortic’ waves calculated from the three transfer functions. The red indicates the best waveform method per algorithm, and the blue indicates all methods with $R^2$ higher than 0.65. Peripheral is the original peripheral waveform from Physionet, Radial TF and Brachial TF are the waveforms that have been transformed using the Radial transfer function and the Brachial transfer function respectively, MA is the K-Point Moving Average waveform, Adaptive is the waveform that has been transformed using the adaptive transfer function, and mAE is the Median Absolute Error in % (Equation 4.1).

$R^2$, linear regression then minimizes the mean square error:

$$MSE = \frac{1}{N} \sum_{m=1}^{N} (C_{meas} - C_{est})^2 \quad (4.2)$$

where $N$ is the total number of measurements and $i$ is the individual measurement. The Elastic Net method reduces the complexity of formulas with a small reduction in accuracy. The values for the coefficients for full linear regression and for elastic net reduction are given in Tables 4.3 and 4.4. The MSE when all predictors are used is 0.44 (L/min)$^2$, and the MSE after elastic net reduction is 0.49 (L/min)$^2$; the corresponding Median Absolute Errors are 0.51 (%) and 0.54 (%) respectively. Median Absolute Error (mAE) in percent (%) and MSE are shown for several cases in Table 4.5. The last column in this table indicates the relative improvement in mAE and MSE between the full linear regression and the original Liljestrand method with no transfer function (the best method available prior to
the present work). The mAE and MSE reductions are over 9% and 18% respectively. Consistent with that, the correlation coefficient is increased from 0.90 to 0.91.

<table>
<thead>
<tr>
<th>Combined</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lil (BTF)</td>
<td>0.5280 ± 0.0267</td>
</tr>
<tr>
<td>AC (BTF)</td>
<td>1.2871 ± 0.0363</td>
</tr>
<tr>
<td>PP (BTF)</td>
<td>0.1066 ± 0.0965</td>
</tr>
<tr>
<td>Herd (Per)</td>
<td>0.0776 ± 0.00172</td>
</tr>
<tr>
<td>CI (Per)</td>
<td>1.5454 ± 0.0920</td>
</tr>
<tr>
<td>SA (Per)</td>
<td>−1.0441 ± 0.3882</td>
</tr>
<tr>
<td>$\mathcal{P}$ (RTF)</td>
<td>0.2857 ± 0.0106</td>
</tr>
<tr>
<td>SA-Corr (Per)</td>
<td>−0.5593 ± 0.3578</td>
</tr>
<tr>
<td>RC (BTF)</td>
<td>−1.2204 ± 0.1118</td>
</tr>
<tr>
<td>4 Ele.</td>
<td>−0.0054 ± 0.0089</td>
</tr>
<tr>
<td>$b_0$</td>
<td>−0.0058 ± 0.0135</td>
</tr>
<tr>
<td>Slope</td>
<td>0.9998 ± 0.003</td>
</tr>
<tr>
<td>Intercept</td>
<td>$9.88 \cdot 10^{-4}$ ± 0.0144</td>
</tr>
<tr>
<td>MSE</td>
<td>0.44 (L/min)$^2$</td>
</tr>
</tbody>
</table>

Table 4.3: Table of coefficients for each predictor in the linear regression model along with the standard deviation. The parentheses reported in column one correspond to the waveform that was used. BTF stands for the waveform created using the Brachial Transfer Function, RTF is the waveform created using the Radial Transfer Function, and Per means the original peripheral waveform. The negative values for some of the coefficients indicate high correlation among measures. Therefore, variable reduction was used.
Table 4.4: Coefficients after the Elastic Net method reduced redundant predictors, and the waveform that was used for those predictors. BTF stands for the waveform created using the Brachial Transfer Function, RTF is the waveform created using the Radial Transfer Function, and Per means the original peripheral waveform.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Combined</th>
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<tbody>
<tr>
<td>Lil (BTF)</td>
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<tr>
<td>AC (BTF)</td>
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<tr>
<td>PP (RTF)</td>
<td>0</td>
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<tr>
<td>Herd (Per)</td>
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<td>CI (Per)</td>
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<tr>
<td>SA (Per)</td>
<td>0</td>
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<tr>
<td>$P$(RTF)</td>
<td>0.1027</td>
</tr>
<tr>
<td>SA-Corr (Per)</td>
<td>0</td>
</tr>
<tr>
<td>RC Decay (Per)</td>
<td>0</td>
</tr>
<tr>
<td>4 Ele.</td>
<td>0.0142</td>
</tr>
<tr>
<td>$b_0$</td>
<td>0</td>
</tr>
<tr>
<td>$\rho$</td>
<td>0.902</td>
</tr>
<tr>
<td>MSE</td>
<td>0.49 $(L/min)^2$</td>
</tr>
</tbody>
</table>

Table 4.4: Coefficients after the Elastic Net method reduced redundant predictors, and the waveform that was used for those predictors. BTF stands for the waveform created using the Brachial Transfer Function, RTF is the waveform created using the Radial Transfer Function, and Per means the original peripheral waveform.
Table 4.5: Table Showing Median Absolute Error (mAE) (%), Mean Squared Error (MSE) for several methods. Also shows the percentage by which Linear Regression improves the results of Lil(per), the best previously available method.

<table>
<thead>
<tr>
<th></th>
<th>Lil, per</th>
<th>Lil, TF</th>
<th>Elastic Net</th>
<th>Full LR</th>
<th>Improvement</th>
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</thead>
<tbody>
<tr>
<td>mAE, %</td>
<td>8.78</td>
<td>8.43</td>
<td>8.65</td>
<td>7.99</td>
<td>9%</td>
</tr>
<tr>
<td>MSE</td>
<td>0.542</td>
<td>0.495</td>
<td>0.488</td>
<td>0.441</td>
<td>18.70%</td>
</tr>
</tbody>
</table>

Figure 4.1 shows heatmaps of results for the Peripheral Liljestrand method, the Brachial Transfer Function Liljestrand method, the Peripheral Corrected Impedance Method, as well as the Elastic Net and Full Linear Regression. It is difficult to see in these plots the distribution on either side of the $y = x$ line. Figure 4.3a shows the normalized probability density for percent error,

$$100\% \cdot \left( \frac{|CO_{calc} - CO_{meas}|}{CO_{meas}} \right)$$

for original Liljestrand with no transfer function (Lil), Elastic Net (EN), and full Linear Regression (LR). One can see that the full linear regression method gives fewer large errors (above 18%) and is more likely than the other two methods to give errors less than 10%. There is little difference in the probability densities for Lil and EN.

We applied a Two-Sample Kolmogorov-Smirnov (KS) test to better see the differences among these distributions. A KS test compares the cumulative distribution functions of two different distributions using the KS statistic,

$$D_n = \max_x |F_{exp}(x) - F_{obs}(x)|$$

(4.4)

where $F(x)$ is the distribution function for observations in the vector $x$. Thus,

$$F(x) = \frac{\text{number observations} < x}{n}$$

(4.5)

where $n$ is the total number of observations in vector $x$ [39]. Examples of $F(x)$ are plotted in Figure 4.2. The null hypothesis is that the observed probability distributions actually are different statistical realizations of the same underlying distribution. The resulting p-
values are: between LR and Lil, $p < 3 \cdot 10^{-5}$, between LR and EN, $p < 0.005$, and between EN and Lil, $p = 0.12$.

**Figure 4.1:** (a - e) Heat maps for (a) The Peripheral Liljestrand method. This was previously the best of the ten method explored, prior to this work. (b) The Brachial Transfer Function Liljestrand method, the best individual measure. (c) Peripheral Corrected Impedance. (d) Linear Regression. (e) The Elastic Net method.
Figure 4.2: Comparisons of CDFs for the Lil, LR, and EN methods. Units for each plot is liters per minute. Black: Elastic Net (EN), blue: Liljestran (LIL), and red: Linear Regression (LR)
Figures 4.3b, 4.3c, and 4.3d are Bland-Altman plots with the error distributions on the side. We can see that the errors are generally smaller when the measured CO is smaller. This is why we report percent errors.

Finally, in Table 4.6 we show the percent of measurements in which the change predicted by linear regression is consistent with the change found in successive measurements.
4.2 Error Correlation

In order to show that there is little to no correlation between features of the blood pressure waveforms and errors in estimated CO, correlation coefficients were calculated for the error correlated with features that make up the blood pressure waveform. It can be seen in Table 4.7 as well as Figure 4.4 that the features of blood pressure are not significantly correlated to the estimates of cardiac output.

<table>
<thead>
<tr>
<th></th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
<th>PP</th>
<th>MAP</th>
<th>Systolic Area</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per. MAP</td>
<td>-0.207</td>
<td>-0.404</td>
<td>0.019</td>
<td>-0.383</td>
<td>-0.089</td>
<td>0.158</td>
</tr>
<tr>
<td>Per. PP</td>
<td>-0.435</td>
<td>-0.252</td>
<td>-0.331</td>
<td>-0.340</td>
<td>-0.203</td>
<td>-0.107</td>
</tr>
<tr>
<td>Per. SA</td>
<td>-0.426</td>
<td>-0.312</td>
<td>-0.284</td>
<td>-0.429</td>
<td>-0.340</td>
<td>0.103</td>
</tr>
<tr>
<td>Per. Cor. SA</td>
<td>-0.426</td>
<td>-0.312</td>
<td>-0.284</td>
<td>-0.428</td>
<td>-0.340</td>
<td>0.102</td>
</tr>
<tr>
<td>Per. Lil</td>
<td>-0.048</td>
<td>0.057</td>
<td>-0.090</td>
<td>0.047</td>
<td>0.033</td>
<td>-0.114</td>
</tr>
<tr>
<td>Per. Herd</td>
<td>-0.402</td>
<td>-0.340</td>
<td>-0.240</td>
<td>-0.453</td>
<td>-0.235</td>
<td>-0.118</td>
</tr>
<tr>
<td>Per. CI</td>
<td>-0.346</td>
<td>-0.225</td>
<td>-0.249</td>
<td>-0.328</td>
<td>-0.301</td>
<td>0.115</td>
</tr>
<tr>
<td>Per. AC</td>
<td>-0.444</td>
<td>-0.293</td>
<td>-0.316</td>
<td>-0.393</td>
<td>-0.228</td>
<td>-0.128</td>
</tr>
<tr>
<td>Per. RC</td>
<td>-0.428</td>
<td>-0.293</td>
<td>-0.299</td>
<td>-0.385</td>
<td>-0.207</td>
<td>-0.116</td>
</tr>
<tr>
<td>Per. LP</td>
<td>0.035</td>
<td>0.231</td>
<td>-0.105</td>
<td>0.194</td>
<td>-0.090</td>
<td>0.178</td>
</tr>
<tr>
<td>Rad TF. MAP</td>
<td>-0.207</td>
<td>-0.403</td>
<td>0.019</td>
<td>-0.382</td>
<td>-0.088</td>
<td>0.156</td>
</tr>
<tr>
<td>Rad TF. PP</td>
<td>-0.452</td>
<td>-0.307</td>
<td>-0.316</td>
<td>-0.423</td>
<td>-0.315</td>
<td>0.035</td>
</tr>
<tr>
<td>Rad TF. SA</td>
<td>-0.403</td>
<td>-0.319</td>
<td>-0.254</td>
<td>-0.427</td>
<td>-0.354</td>
<td>0.202</td>
</tr>
<tr>
<td>Rad TF. Cor. SA</td>
<td>-0.403</td>
<td>-0.318</td>
<td>-0.254</td>
<td>-0.426</td>
<td>-0.355</td>
<td>0.205</td>
</tr>
<tr>
<td>Rad TF. Lil</td>
<td>-0.098</td>
<td>0.043</td>
<td>-0.137</td>
<td>-0.006</td>
<td>-0.103</td>
<td>0.039</td>
</tr>
<tr>
<td>Rad TF. Herd</td>
<td>-0.443</td>
<td>-0.341</td>
<td>-0.285</td>
<td>-0.449</td>
<td>-0.266</td>
<td>-0.047</td>
</tr>
<tr>
<td>Rad TF. CI</td>
<td>-0.324</td>
<td>-0.236</td>
<td>-0.217</td>
<td>-0.330</td>
<td>-0.318</td>
<td>0.225</td>
</tr>
</tbody>
</table>

Table 4.6: Percent of measurements that have directional change agreement.
<table>
<thead>
<tr>
<th></th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
<th>PP</th>
<th>MAP</th>
<th>Systolic Area</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rad TF. AC</td>
<td>-0.443</td>
<td>-0.316</td>
<td>-0.300</td>
<td>-0.435</td>
<td>-0.312</td>
<td>0.001</td>
</tr>
<tr>
<td>Rad TF. RC</td>
<td>-0.458</td>
<td>-0.309</td>
<td>-0.321</td>
<td>-0.429</td>
<td>-0.314</td>
<td>0.017</td>
</tr>
<tr>
<td>Rad TF. LP</td>
<td>-0.068</td>
<td>0.223</td>
<td>-0.215</td>
<td>0.168</td>
<td>-0.155</td>
<td>0.216</td>
</tr>
<tr>
<td>Brach TF. MAP</td>
<td>-0.207</td>
<td>-0.404</td>
<td>0.019</td>
<td>-0.383</td>
<td>-0.088</td>
<td>0.156</td>
</tr>
<tr>
<td>Brach TF. PP</td>
<td>-0.438</td>
<td>-0.305</td>
<td>-0.302</td>
<td>-0.412</td>
<td>-0.285</td>
<td>-0.002</td>
</tr>
<tr>
<td>Brach TF. SA</td>
<td>-0.413</td>
<td>-0.321</td>
<td>-0.264</td>
<td>-0.433</td>
<td>-0.353</td>
<td>0.166</td>
</tr>
<tr>
<td>Brach TF. Cor. SA</td>
<td>-0.413</td>
<td>-0.320</td>
<td>-0.265</td>
<td>-0.432</td>
<td>-0.354</td>
<td>0.169</td>
</tr>
<tr>
<td>Brach TF. Lil</td>
<td>-0.061</td>
<td>0.038</td>
<td>-0.092</td>
<td>0.004</td>
<td>-0.057</td>
<td>-0.004</td>
</tr>
<tr>
<td>Brach TF. Herd</td>
<td>-0.412</td>
<td>-0.358</td>
<td>-0.240</td>
<td>-0.468</td>
<td>-0.259</td>
<td>-0.060</td>
</tr>
<tr>
<td>Brach TF. CI</td>
<td>-0.337</td>
<td>-0.239</td>
<td>-0.229</td>
<td>-0.338</td>
<td>-0.318</td>
<td>0.186</td>
</tr>
<tr>
<td>Brach TF. AC</td>
<td>-0.444</td>
<td>-0.322</td>
<td>-0.298</td>
<td>-0.439</td>
<td>-0.300</td>
<td>-0.034</td>
</tr>
<tr>
<td>Brach TF. RC</td>
<td>-0.436</td>
<td>-0.322</td>
<td>-0.289</td>
<td>-0.431</td>
<td>-0.281</td>
<td>-0.020</td>
</tr>
<tr>
<td>Brach TF. LP</td>
<td>-0.013</td>
<td>0.229</td>
<td>-0.158</td>
<td>0.180</td>
<td>-0.137</td>
<td>0.232</td>
</tr>
<tr>
<td>MA. MAP</td>
<td>-0.198</td>
<td>-0.401</td>
<td>0.027</td>
<td>-0.377</td>
<td>-0.080</td>
<td>0.153</td>
</tr>
<tr>
<td>MA. PP</td>
<td>-0.393</td>
<td>-0.314</td>
<td>-0.246</td>
<td>-0.426</td>
<td>-0.332</td>
<td>0.110</td>
</tr>
<tr>
<td>MA. SA</td>
<td>-0.337</td>
<td>-0.206</td>
<td>-0.250</td>
<td>-0.288</td>
<td>-0.318</td>
<td>0.242</td>
</tr>
<tr>
<td>MA. Cor. SA</td>
<td>-0.330</td>
<td>-0.197</td>
<td>-0.247</td>
<td>-0.278</td>
<td>-0.314</td>
<td>0.237</td>
</tr>
<tr>
<td>MA. Lil</td>
<td>-0.025</td>
<td>0.035</td>
<td>-0.050</td>
<td>-0.007</td>
<td>-0.117</td>
<td>0.121</td>
</tr>
<tr>
<td>MA. Herd</td>
<td>-0.363</td>
<td>-0.331</td>
<td>-0.202</td>
<td>-0.429</td>
<td>-0.255</td>
<td>-0.012</td>
</tr>
<tr>
<td>MA. CI</td>
<td>-0.253</td>
<td>-0.117</td>
<td>-0.211</td>
<td>-0.183</td>
<td>-0.275</td>
<td>0.259</td>
</tr>
<tr>
<td>MA. AC</td>
<td>-0.413</td>
<td>-0.325</td>
<td>-0.262</td>
<td>-0.439</td>
<td>-0.312</td>
<td>0.033</td>
</tr>
<tr>
<td>MA. RC</td>
<td>-0.390</td>
<td>-0.321</td>
<td>-0.238</td>
<td>-0.430</td>
<td>-0.317</td>
<td>0.082</td>
</tr>
<tr>
<td>MA. LP</td>
<td>-0.035</td>
<td>0.189</td>
<td>-0.157</td>
<td>0.146</td>
<td>-0.163</td>
<td>0.296</td>
</tr>
<tr>
<td>Ada TF. MAP</td>
<td>-0.196</td>
<td>-0.401</td>
<td>0.030</td>
<td>-0.377</td>
<td>-0.079</td>
<td>0.152</td>
</tr>
<tr>
<td>Ada TF. PP</td>
<td>-0.328</td>
<td>-0.182</td>
<td>-0.254</td>
<td>-0.251</td>
<td>-0.166</td>
<td>-0.069</td>
</tr>
<tr>
<td>Ada TF. SA</td>
<td>-0.302</td>
<td>-0.195</td>
<td>-0.217</td>
<td>-0.264</td>
<td>-0.207</td>
<td>0.036</td>
</tr>
<tr>
<td>Ada TF. Cor. SA</td>
<td>-0.302</td>
<td>-0.195</td>
<td>-0.218</td>
<td>-0.264</td>
<td>-0.208</td>
<td>0.038</td>
</tr>
<tr>
<td>Ada TF. Lil</td>
<td>-0.073</td>
<td>0.060</td>
<td>-0.119</td>
<td>0.038</td>
<td>-0.019</td>
<td>-0.065</td>
</tr>
<tr>
<td>Ada TF. Herd</td>
<td>-0.369</td>
<td>-0.299</td>
<td>-0.228</td>
<td>-0.391</td>
<td>-0.210</td>
<td>-0.112</td>
</tr>
<tr>
<td>Ada TF. CI</td>
<td>-0.245</td>
<td>-0.136</td>
<td>-0.190</td>
<td>-0.194</td>
<td>-0.174</td>
<td>0.039</td>
</tr>
<tr>
<td>Ada TF. AC</td>
<td>-0.354</td>
<td>-0.205</td>
<td>-0.270</td>
<td>-0.281</td>
<td>-0.179</td>
<td>-0.100</td>
</tr>
<tr>
<td>Ada TF. RC</td>
<td>-0.348</td>
<td>-0.209</td>
<td>-0.260</td>
<td>-0.287</td>
<td>-0.182</td>
<td>-0.078</td>
</tr>
</tbody>
</table>
Table 4.7: Shows how correlated the errors are to the features of blood pressure

<table>
<thead>
<tr>
<th>Method</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
<th>PP</th>
<th>MAP</th>
<th>Systolic Area</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ada TF. LP</td>
<td>-0.048</td>
<td>0.207</td>
<td>-0.183</td>
<td>0.164</td>
<td>-0.108</td>
<td>0.139</td>
</tr>
<tr>
<td>LASSO</td>
<td>-0.108</td>
<td>-0.052</td>
<td>-0.089</td>
<td>-0.084</td>
<td>-0.087</td>
<td>0.048</td>
</tr>
<tr>
<td>LR</td>
<td>-0.003</td>
<td>-0.006</td>
<td>0.0004</td>
<td>-0.007</td>
<td>-0.017</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Figure 4.4: (a - d) Select results showing whether the features that are used to estimate the cardiac output are related to the error. Each figure shows the error plotted with the feature that is most highly correlated to the error. The table of full correlations can be seen in Table 4.7. (a) Average Systolic BP vs. Error in Peripheral Corrected Impedance. (b) Average Pulse Pressure vs. Error in Brachial Transfer Function Liljestrand (c) Average Heart Rate vs. Error in Linear Regression (d) Average Pulse Pressure vs. Error in Elastic Net
4.3 Discussion

Cardiac output is an important measure of health, but the best methods for measuring it are difficult, time-consuming, and highly invasive. It would be good to have methods which, albeit less accurate, could be used continuously in an ICU to give early warning of substantial changes in CO. For this reason, we have tested 46 algorithms that seek to obtain CO from peripheral BP waveforms.

It seemed reasonable to expect that calculating CO might work best when applied to measurements of aortic BP. Following that hypothesis suggests that using optimized transfer functions for estimating aortic BP from peripheral BP could improve the estimates of CO, however, that is not what we observed. The brachial transfer function gives improved CO estimation for only four of the nine algorithms. Radial transfer function gives improved estimates with only one of the algorithms. The Moving Average and the Adaptive transfer functions never give the best results in this study (Table 4.2). Further, the three-element model worked poorly, and the most elaborate and theoretically complete method - the four-element model - was worse than all the others. On the bright side, the Liljestrand method without alteration gave accurate results.

Effective graphical presentation of these results is challenging, and Fig. 4.1 needs careful examination. Dot plots tend to overemphasize the outliers, while heat maps tend to hide them.

Bland-Altman plots are a graphical way to compare two methods of measurement. They plot the difference between the two methods versus the average of the two methods. Plotting differences this way makes the magnitude of the differences more clear and shows better if there is a correlation between the magnitudes of the differences and measurements [1]. In the Bland-Altman plot, it might appear that large errors are common; however the histogram on the left side of that plot shows that they are rare. The probability density of percent errors (Fig. 4.1a) is perhaps the clearest presentation, but one cannot see much improvement in that picture. Indeed the Liljestrand-Zander method is better than we had
expected, but the full linear regression gives a 9% reduction in median absolute error.

The linear regression (LR) method combines the ten best algorithms, and leads to a median absolute error (MAE) under 8%. These results are within what is thought to be the error range of thermodilution in clinical practice [5]. Because the measures are correlated, the coefficients obtained from LR are unstable and uninterpretable. Nevertheless, results computed by the final set of coefficients are expected to be consistent and to have accuracy within the stated error [5].

The elastic net method, which minimizes the mean square error together with the number and size of the coefficients, gives a somewhat larger MSE and MAE. Frequently one selects the simplest method that gives good results, and that could be an argument in favor of the elastic net results. However, in this case, analysis of ten minutes of BP wave using the ten algorithms in the full LR method requires less than one second on a PC, so there is no point to making any compromise of accuracy for simplicity. Furthermore, a Kolmogorov-Smirnov test shows that the probability distribution of absolute errors in the EN method is not much different from that in the Lil with no transfer function.

Additionally, Mean arterial pressure (in Tables 4.2-4.4) is a commonly-used measure; its individual correlation with CO is the poorest in Table 4.2, but it contributes significantly to the full linear regression (LR) and it survives the Elastic Net reduction (EN). No further justification for its inclusion is needed. Pulse Pressure (PP) gives a better individual correlation function but contributes weakly to LR and not at all to EN. Such results cannot be anticipated a priori; one has to carry out the calculations. Combining all the measures gives the smallest Median Absolute Error and smallest Mean Square Error. There are products commercially available for obtaining CO from peripheral BP [38, 47, 26, 50, 23, 14, 15, 57]. We could not access or evaluate proprietary algorithms.
Chapter 5

Transfusions

5.1 The Patients

In order to test whether the above methods could be used to find patterns in the blood pressure waveforms of patients that have received a blood transfusion, another study was done that used the same MIMIC II data set [46, 25]. As with the above study, all patients suffered from a variety of illnesses. In total we studied 4911 blood transfusions spread among 1214 patients (522 females, 692 males). The average age of these patients as well as number of transfusions, and other patient statistics can be seen in table 5.1.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Number of Transfusions</th>
<th>Time Apart</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>20 years</td>
<td>1</td>
<td>&lt;1 hour</td>
<td>&lt;25 mL</td>
</tr>
<tr>
<td>Maximum</td>
<td>89 + years</td>
<td>48</td>
<td>73 hours</td>
<td>&gt;500 mL</td>
</tr>
<tr>
<td>Mean</td>
<td>65 years</td>
<td>4</td>
<td>5.35 hours</td>
<td>334 mL</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>16 years</td>
<td>5</td>
<td>0.37 hours</td>
<td>96 mL</td>
</tr>
</tbody>
</table>

Table 5.1: Statistics of Patients that have received a blood transfusion. It is interesting that some patients received a small volume of blood (< 25 mL), however this is what the database indicated.
5.2 Combining the Data with the Found Linear Combination

The time of interest for the analysis of the patient’s blood pressure waveforms was taken to be 24 hours before the time of transfusion and 24 hours after to allow for sufficient time to detect changes leading up to the physician’s order for blood transfusion, and see the change. The blood pressure waveforms were divided into 10 minute segments, to give 288 BP segments per patient, centered at time zero. The methods described in Chapter 3 were implemented to smooth the blood pressure data and Chapter 3’s algorithms were utilized on each segment. The algorithm results were then combined using the linear regression model detailed in Chapter 4. We briefly remind the reader of the method below. The CO was estimated using

\[
CO_{EN} = 0.7652 \cdot CO_{NLit} + 0.0014 \cdot CO_{NAC} + 0.0899 \cdot CO_{NCI} + 0.1027 \cdot CO_{NP} + 0.0142 \cdot CO_{N4\text{-}Ele}. \quad (5.1)
\]

The \( CO_f \) values for each formula, however, have been normalized by proportionality constants that depend on both patient and algorithm, \( k_{p,f} \) (as indicated by the N in each formula abbreviation). Thus, the elastic net equation is

\[
CO_{EN} = 0.7652 \cdot k_{p,Lit} CO_{Lit} + 0.0014 \cdot k_{p,AC} CO_{AC} + 0.0899 \cdot k_{p,CI} CO_{CI} + 0.1027 \cdot k_{p,\overline{p}} CO_{\overline{p}} + 0.0142 \cdot k_{p,4\text{-}Ele} CO_{4\text{-}Ele}. \quad (5.2)
\]

In order to find appropriate \( k_{p,f} \) values per patient, we define a new scaling factor, \( \kappa_{p,f} \) which is related to a formula’s non-normalized CO estimate at the time when the Liljestrand Method is at its median value (\( CO_f \)). We choose median here rather than average to reduce the effects of outliers. Here

\[
\kappa_{p,f} = 5/CO_f \quad (5.3)
\]
Then $k_{p,f}$ is related to $\kappa_{p,f}$ through the true average CO measurement, $CO_{\text{Mean}}$, and the factor of 5 from above.

$$k_{p,f} = \kappa_{p,f} \cdot \frac{CO_{\text{Mean}}}{5}$$

(5.4)

to yield a new CO estimate, $CO_{\text{EN}\kappa}$,

$$CO_{\text{EN}\kappa} = 0.7652 \cdot \kappa_{p,Lil} CO_{\text{Lil}} + 0.0014 \cdot \kappa_{p,AC} CO_{\text{AC}} + 0.0899 \cdot \kappa_{p,C1} CO_{\text{C1}} + 0.1027 \cdot \kappa_{p,T} CO_{\text{T}} + 0.0142 \cdot \kappa_{p,4-Ele} CO_{4-Ele}$$

(5.5)

which is related to the $CO_{\text{EN}}$ through $\frac{5}{CO_{\text{Mean}}}$.

$$CO_{\text{EN}\kappa} = \frac{5}{CO_{\text{Mean}}} (0.7652 \cdot k_{p,Lil} CO_{\text{Lil}} + 0.0014 \cdot k_{p,AC} CO_{\text{AC}} + 0.0899 \cdot k_{p,C1} CO_{\text{C1}} + 0.1027 \cdot k_{p,T} CO_{\text{T}} + 0.0142 \cdot k_{p,4-Ele} CO_{4-Ele})$$

(5.6)

$$CO_{\text{EN}\kappa} = \frac{5}{CO_{\text{Mean}}} CO_{\text{EN}}$$

(5.7)

Then, this factor will disappear when we look at the percent change.

$$\% \text{ Change} = \frac{CO_{\text{EN}\kappa_i} - CO_{\text{EN}\kappa_{i+1}}}{CO_{\text{EN}\kappa_i}} \cdot 100\%$$

(5.8)

Therefore, this is a valid way to normalize the data in order to combine it with the Reduced Linear regression model from Chapter 3.

### 5.3 Cleaning and Data Basis Functions

Once we obtain all of the normalized CO vectors for the patients, we first divide by the mean heart rate for each 10 minute segment in order to obtain SV rather than CO because SV falls prior to CO. We follow the methods of analysis laid out in [65], which analyzed trajectories of data from neonates leading up to a septic event. We must consider that some patients have missing data as not all patients have blood pressure waveforms 24 hours
before and after a blood transfusion was ordered. In order to account for this, we used linear interpolation to find data for time stamps that were missing in the center of the time vector, and data missing at the end points was filled in with repetition of the end point data. This method has been used before by those looking to fill in missing values in trajectories of patient data [65].

In order to smooth the data, we use B-Spline basis functions to create new curves that are linear combinations. Thus,

\[ SV_{fit,i}(t) = \sum_{j=1}^{n} c_{j,i} \phi_j(t) \] (5.9)

where \( \phi \) is the basis system for \( SV_{fit} \), and \( n \) is the number of basis functions being used, to compute \( i \)th patient curve. Assuming that \( SV_{EN\kappa} \) is the data we are fitting, then we want to minimize the sum of the squared error for each patient curve,

\[ \min \left[ \sum_{h=1}^{m} (SV_{EN\kappa,h} - SV_{fit,h})^2 \right] = \] (5.10)

\[ \min \left[ \sum_{h=1}^{m} (SV_{EN\kappa,h} - c^T \phi(t_h))^2 \right] \] (5.11)

We know this solution from ordinary least squares to be

\[ c = (\phi^T \phi)^{-1} \phi^T SV_{EN\kappa} \] (5.12)

\[ SV_{fit} = \phi(t)c \] (5.13)

We now have a way to fit the \( SV_{EN\kappa} \) data with basis functions [21]. For basis functions we chose B-splines because they are are useful for fitting nonperiodic data [48, 65]. The B-spline basis functions for this data can be seen in Figure 5.1. We use 5 basis functions at order 4. The algorithms utilized for this B-Spline analysis have been made publicly available by Ramsay et al. [48].
The benefits of the smoothing can be seen in Figure 5.2. Prior to the cleaning there is no clear sign that the SV of this patient is falling as there are large fluctuations in the data, however, after these fluctuations are smoothed there is a clear decline in the patient’s SV in the hours leading to the blood transfusion.

5.4 Clustering the Data

Next, we group the data using K-means clustering in order to show that there are group patterns, or clusters, for patients that received a blood transfusion. K-means clustering partitions a dataset into $k$ groups by alternating between assigning data points to their nearest cluster center (centroid) based on minimum sum of squared Euclidean Distances.
Figure 5.2: Using the smoothed BP curve, it is easier to see that the patient’s CO begins to fall. Even in the hours -10 to -3 when the raw data are still showing large fluctuations and it is not clear that the patient’s BP is falling.

Then updating the cluster centroid to be the mean value of the data in the cluster. The data are then reassigned using the new centroid locations, and the centroids are updated again. This continues until an iteration happens and no data are reassigned. The $k$ initial centroids are chosen at random [36]. For 2-Dimensional data, the squared Euclidean Distance ($E$) that is minimized is

$$E(m_1, \ldots, m_k) = \sum_{i=1}^{N} \sum_{j=1}^{k} ||x_i - m_j||^2$$

(5.14)

where $M$ is the number of clusters, $N$ is the number of observations in cluster $j$, $x_i$ is the $i$th observation, and $m_j$ is the cluster center of the $j$th cluster [36].
In order to cluster the data, we take each patient’s SV trajectory and divide by the maximum SV in the trajectory, and multiply by 100%. This provides us with consistency in the range of SV across all patients.

5.4.1 Number of Clusters

In order to know the optimal number of clusters we use the Calinski-Harabasz criterion. This method calculated the ratio of variance between clusters \( SS_B \) and variance within one cluster \( SS_W \) for multiple cluster divisions \( k \). Then, the \( k \) value that provided the highest number is chosen as the optimal \( k \). Here

\[
SS_B = \sum_{j=1}^{k} n_j \|m_j - m\|^2
\]

where \( n_j \) is the number of data points in cluster \( j \), and \( m \) is the mean of the data, and

\[
SS_W = \sum_{j=1}^{k} \sum_{i=1}^{N} \|x_i - m_j\|^2.
\]

Then, the Calinski-Harabasz index is defined as

\[
C = \frac{SS_B}{SS_W} \cdot \frac{O - k}{k - 1}
\]

where \( O \) is the total number of observations. The \( k \) value that gives the highest index is then considered the optimal \( k \) value [4].

For our data, the optimal number of clusters was two, therefore in the results we show the results of K-means clustering when the data is divided into two groups. However, we also divide the data into four groups because there was a second spike of the index for \( k = 4 \), see figure 5.3. This figure shows the values for the Calinski-Harabasz index for five different \( k \) values, ranging from two to 6. It can be seen that the highest index value is at two clusters, and there is a second spike at four clusters.
5.5 Results

Next, we will show results for three different clusterings of the data. First, we will show the data divided into two clusters, then four, then five. Each time we will show the centroid of the clusters. Table 5.2 shows the number of patients per cluster for clustering the patients into two, four, and five clusters.

<table>
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<th>2</th>
<th>4</th>
<th>5</th>
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<td>1357</td>
<td>2051</td>
</tr>
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<td>716</td>
<td>969</td>
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<td>323</td>
</tr>
<tr>
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<td>-</td>
<td>2450</td>
<td>390</td>
</tr>
<tr>
<td>5</td>
<td>Patients in Cluster 5</td>
<td>-</td>
<td>-</td>
<td>1171</td>
</tr>
</tbody>
</table>

Table 5.2: The number of patients in each cluster.
The vertical axis of each figure of the percentage of the maximum SV for that group. We can see that there is a decline in SV leading up to the time of the blood transfusion for all groups. This shows there are promising patterns in the analysis of BP waveforms that warrant further exploration.

![Figure 5.4: Patients that have had a blood transfusion divided into two clusters.](image)

In order to show that the drop between a patient’s SV 24 hours prior to a blood transfusion was more significant than the fluctuations between the hourly SV measurements, the average change in SV was calculated per patient using the original SV trajectory. The values on the endpoints of the trajectories that were filled in with extrapolation were not taken into account for the average fluctuations. The average hourly fluctuation per patient was then

\[
\text{Average Fluctuation} = \frac{\sum_{i=1}^{N-1} |SV_{i+1} - SV_i|}{N - 1}, \tag{5.18}
\]

where \(N\) is the number of non-extrapolated measurements. The average fluctuation was calculated per patient as well as the difference between the SV at 24 hours before the transfusion time and SV at the transfusion time,

\[
\Delta SV = |SV_{t=0} - SV_{t=-24}|. \tag{5.19}
\]

Once the average fluctuation and the change in SV was calculated per patient, a ratio
Figure 5.5: Patients that have had a blood transfusion divided into four clusters.

was calculated to compare the change in SV to the average fluctuation. The change in SV was on average 2.5 times higher than the average fluctuation per patient.
Figure 5.6: Patients that have had a blood transfusion divided into five clusters.
Chapter 6

Conclusion and Future Work

The first project of this thesis processed infant EKG signals with the goal of improving diagnostics of the infant’s health. This worked sought to reduce the large data produced by EKG monitors to just the R-times intervals of the infant’s heart beats. Algorithms that were originally created to analyze adult EKGs were modified and used to produce a new algorithm for processing the infant EKGs.

In this work we included every thermodilution measurement of CO in the MIMIC III database, weighting each measurement equally. This approach has advantages and disadvantages. Some studies might favor weighting each patient equally, thereby weighting individual measurements from those patients having multiple measurements less heavily. However, it is not unreasonable to weight those patients who need multiple measurements more heavily than those who only need one. Our methods are oriented toward creating a general-purpose algorithm, so we have included all measurements regardless of underlying pathology.

More generally, using a peripheral waveform to estimate CO can have only limited reliability. Reflections of pressure waves from arterial bifurcations affect the waveform, this method uses pressure as a measure of flow, and patient position, movement and other details can affect the signal. Nevertheless, it has been proved in other contexts [12] that continuous monitoring and prompt analysis of ICU signals is so powerful that even methods
having weak positive predictive value can give dramatic improvements to patient outcomes by providing early warnings of deterioration to physicians.

A different project might seek a collection of algorithms each of which is optimized for a selected group of patients, such as those with atherosclerosis, or those with valve disorders, or sepsis, or congestive heart failure. The utility of such a suite of specialized algorithms is not clear.

In conclusion, analysis of blood pressure waveforms using ten algorithms combined with transfer functions gives a respectable measure of cardiac output, with correlation coefficient above 0.9 and MAE less than 8%.

The B-Spline fitting and clustering methods show that there are promising patterns that can be used to detect a patient’s falling SV prior to requiring a blood transfusion. Future researchers can explore these B-Spline coefficients, and look for an average of coefficients across all patients in order to have a more general algorithm that can work for many patients without requiring future data for fitting. There can then be programmed a method that continually updates the predicted trajectories of the patient.
Bibliography


