Cardiovascular Parameter Estimation using a Computational Model

by

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Bachelor of Science in Electrical Engineering
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Submitted to the Department of Electrical Engineering and Computer Science

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To my parents, Yusuf and Nighat.
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Abstract

Modern intensive care units are equipped with a wide range of patient monitoring devices, each continuously recording signals produced by the human body. Currently, these signals need to be interpreted by a clinician in order to assess the state of the patient, to formulate physiological hypotheses, and to determine treatment options. With recent technological advances, the volume of relevant patient data acquired in a clinical setting has increased. This increase in sheer volume of data available, and its lack of organization, have rendered the clinical decision-making process inefficient. In some areas, such as hemodynamic monitoring, there is enough quantitative information available to formulate computational models capable of simulating normal and abnormal human physiology. Computational models tend to synthesize information in one common framework, thereby improving data integration and organization. Through tuning, such models could be used to track patient state automatically and to relate properties of the observable data streams directly to the properties of the underlying cardiovascular system.

In our research efforts, we implemented a pulsatile cardiovascular model and attempted to match its output to simulated observable hemodynamic signals in order to estimate cardiovascular parameters. Tracking model parameters in time reveals disease progression, and hence it can be very useful for patient-monitoring purposes. As the observable signals are generally not rich enough to allow for the estimation of all the model parameters, we focused on estimating only a subset of parameters.

Our simulations indicate that observable data at intra-beat timescales can be used to estimate distending blood volume, peripheral resistance, and end-diastolic right compliance to reasonable degrees of accuracy. Furthermore, our simulation results based on a real patient hemorrhage case reveal that clinically significant parameters related to bleeding rate and peripheral resistance can be tracked reasonably well using observable patient data at inter-beat timescales.
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Chapter 1

Introduction

1.1 Motivation

Patient care for the critically ill is provided in dedicated hospital departments known as Intensive Care Units, or ICUs. Patients suffering from various conditions, such as unstable cardiovascular disease, multiple-organ failure, or severe trauma, are usually admitted to the ICU. Though the reasons behind admissions are varied, ICU patients have one thing in common - they are often in a fragile condition which requires close monitoring of the state of the patient to guide the course of treatment, or to allow for rapid intervention if the patient’s state deteriorates.

To help accomplish this, modern ICUs are equipped with a wide range of monitoring equipment, each continuously recording a series of physiological signals. These detailed measurements are supplemented with frequent laboratory tests and imaging studies from different hospital departments. The logistics involved in data collection from different departments and the high volume of data, coupled with poor data integration and organization, complicate and prolong the clinician’s task of formulating physiological hypotheses and determining treatment options. However, timely and accurate patient care is of utmost importance in an ICU setting where patients require immediate and often proactive action. Thus, the increase in sheer volume of data available, and its lack of organization, have rendered the
clinical decision-making process inefficient. Presenting all the available information without regard to relevance can often lead to oversight of important factors which can cause serious, possibly fatal, errors in an ICU setting. This phenomenon is generally known as the problem of information overload which has contributed to several historical catastrophes including the New York City blackout of 1977 [6].

In addition to the information overload problem, ICUs suffer from inaccurate alarm systems. Bedside alarms sound an alert whenever an individual measured signal exceeds or drops below some predefined value, an event that occurs quite often with no physiological basis, as for example, when excessive patient movement interferes with electrode contacts and position. Individual signals being monitored are usually correlated and interdependent. However, current representation of these signals does not incorporate these relationships, which results in too sensitive an alarm system. In fact, several studies have shown that over 80% of these single-variable alarms are false positives [7], leading to misallocated resources and desensitization to alarms.

The inability of the ICU monitoring systems to evaluate the state of the patient efficiently increases the chances of human error. Donchin et al. [8] conducted a study in which they estimated that 1.7 human errors occur per patient per day in the ICU they observed. One of the reasons for the errors was attributed to difficulties in assessing patient state, a function which is directly affected by the limitations of the current monitoring systems coupled with the information overload problem.

The problems encountered in ICU patient monitoring motivate the use of computational models. Representing a physiological system in a mathematical form aids in understanding how the various components interact with each other to influence the outputs. Computational models tend to synthesize information in one common, holistic framework thereby improving data integration and organization. Given current computational power, computational models can cycle through many iterations of hypothesis-generation and test their compatibility with experimental data. Furthermore, computers tend to be more vigilant than humans. Thus, computational models might be able to learn from clinical data and
help significantly in developing physiological hypotheses regarding a patient’s state.

The cardiovascular system is an area which has been subjected to various modeling studies (see Section 1.3). There is enough knowledge about the cardiovascular system to formulate mathematical models that describe all the inter-component relationships accurately. Such models may be useful in helping to assess patient state, and if so, they can be employed to aid in patient monitoring.

1.2 The Cardiovascular System

The human cardiovascular system is responsible for circulating blood throughout the body to perfuse the tissues with nutrients and oxygen, and remove the waste products. The system includes the heart muscle, which acts as a pump, and the blood vessels through which the blood flows (see Figure 1-1).

There are three main kinds of blood vessels: arteries, veins and capillaries. The arteries carry blood from the heart to the tissues at high pressures. As blood is transported to the rest of the body, arteries branch out into smaller vessels through which blood is transported to individual organs. Within the organs, the exchange of oxygen and nutrients takes place through the walls of thin vessels known as capillaries. The veins, which constitute the low pressure carrying component of the system, transport blood back to the heart.

The heart consists of four chambers - two atria (left and right), each of which is connected to a ventricle. The pumping action of the heart is quasi-periodic in nature, the rhythm of which is governed by electrical impulses generated by the sino-atrial node. A cardiac cycle consists of two regimes of operation: diastole and systole. During the period of diastole, the ventricles are relaxed and fill with blood, whereas in systole, the ventricles contract and eject blood into the circulation. The left ventricle pumps oxygenated blood to the rest of the body (systemic circulation). After the exchange of nutrients and oxygen, de-oxygenated blood is returned to the right ventricle which then pumps the blood through the lungs (pulmonary circulation) where gaseous exchange occurs. The newly oxygenated blood is then driven into the left ventricle from whence the cycle continues.
As the cardiovascular system maintains blood flow, a model that accurately represents this system can be used to gain insight into the hemodynamic changes occurring in patients.

1.3 Cardiovascular Models and Model-Based Reasoning

An analogy exists between computational models of cardiovascular function and electrical circuits, a parallel that has been exploited since the late 1800's. Moens and Korteweg used transmission-line theory to describe quantitatively the circulation system in 1878. Around twenty years later, Frank introduced the Windkessel model, which consisted of a simple first-order circuit to model arterial dynamics [9]. With the advent and widespread use of digital computing, a wealth of research has been directed towards the development of computational cardiovascular models that adequately represent the underlying physiology and hemodynamics. The models vary in degree of complexity, with the 'Guyton Model',...
consisting of the combined physiological insight of Dr. Guyton and his associates, being the most comprehensive [10].

The purpose behind model development is to gain insight into physiological phenomena within a closed framework. Much of the mentioned modeling work has been directed towards forward-modeling, which consists of tweaking model parameters so that the system can output realistic data that match observations. Recently, however, interest has been generated in inverse-modeling, or parameter estimation, where the system parameters are estimated on the basis of observed data. Various techniques, including gradient-based error minimization using underlying computational models, have been used to estimate cardiac function [11], and arterial parameters [11, 12, 13].

Cardiovascular parameter estimation can provide an integrated structure that can be used to assess the patient’s hemodynamic state. Knowledge of the changes in specific parameter values can help monitor patient trajectory and guide clinical interventions. Motivated by the advantages of model-based estimation and reasoning, Zhao developed a set of heuristic algorithms to estimate 7 of the 17 independent parameters in the underlying lumped parameter, 6-compartment, cardiovascular model [14]. The system evaluated the parameters by iteratively matching the model output to pseudo-patient data. This was achieved by tweaking the model parameters based on some underlying logic using artificial intelligence. The algorithms were tested on steady-state, static, simulated data and were found to perform reasonably. However, such a system cannot be used for continuous monitoring as the algorithms use certain measurements that are only intermittently available, for example, left ventricular end-diastolic pressure (LVEDP). Moreover, the steady-state assumption is not always valid in unstable patients. In order to help monitor patients continuously, the estimation algorithm has to be devoid of the steady-state assumption and it has to be limited to using what is constantly measurable in an ICU.

1.4 Hemodynamic Monitoring in an ICU

Modern day ICUs have the capability to record the following hemodynamic data:
• Electrocardiograph (ECG): ECG is a recording of the body surface potentials generated by the electrical activity of the heart. ECG recordings are important indicators of the state of the heart and are extensively used for diagnosis of cardiac conduction abnormalities (arrhythmias), ischemia, infarction, hypertrophy, etc. Moreover, ECG monitors record heart rate (HR) and rhythm which are important factors in judging the stability of all patients.

• Systemic Arterial Blood Pressure (ABP): ABP is monitored invasively using an arterial line inserted into an accessible artery. The preferred site of insertion is the radial artery on the wrist as it is easily accessible and simple to keep clean. Continuous ABP monitoring is essential as abnormal ABP is indicative of diseased states. In addition, continuous ABP monitoring serves as a feedback to clinical interventions such as medication. The monitoring system records ABP waveforms and also computes derivable quantities such as systolic, diastolic, and mean pressures.

• Central Venous Pressure (CVP): CVP waveforms are monitored by inserting a venous catheter into a peripheral vein and by advancing the catheter through the subclavian vein and the superior vena cava. CVP is an important determinant of right ventricular function as it correlates with the filling pressure of the right heart.

• Pulmonary Artery Pressure (PAP): The introduction of PAP monitoring has been one of the most popular and important advances in patient monitoring [15]. Although recently PAP recordings have become subjected to increased scrutiny, it is not uncommon to have patients inserted with a Swan-Ganz catheter to record PAP waveforms. The catheter is inserted into a peripheral vein, and it is pushed past the right atrium and ventricle until it enters the pulmonary artery. The tip of the catheter is fitted with a balloon, which, when inflated, obstructs flow and gives a measure of left ventricular filling pressure.

• Cardiac output (CO) is an important hemodynamic parameter which can be measured intermittently in an ICU. CO is a measure of the blood volume pumped by the heart
per minute and hence it is an important indicator of cardiac function. CO is usually measured by the thermodilution technique in which a patient is administered a bolus of cold liquid. The ensuing temperature changes, measured by a thermistor attached to a catheter, are then plotted over time forming what is known as the thermodilution curve. A measure of CO is obtained by exploiting its inverse relationship to the area under the thermodilution curve.

1.5 Thesis Goals and Outline

In this thesis, we explore model-based quantitative methods for estimating selected cardiovascular parameters over time. Tracking the time evolution of these parameters would not only aid in determining patient state, but it may also help in identifying the onset of complications, thereby increasing the quality and effectiveness of patient care. The data used for estimation is limited to what can be monitored continuously in an ICU. This includes waveforms and other derivable quantities of ECG, ABP, CVP, and PAP. The challenge lies in using a small number of observable signals to perform parameter estimation based on an underlying high-detail model. To overcome this difficulty, we focus on estimating only a subset of parameters.

In chapters 2 and 3, we detail the computational cardiovascular model used for our investigation and we describe its implementation in Simulink.

In chapter 4, we use synthetic waveform data to estimate cardiovascular parameters using a non-linear least squares optimization technique along with subset selection - an algorithm that identifies a subset of parameters that can be estimated robustly.

In chapter 5, we explore a real hemorrhage case. We attempt to track the bleeding rate and the rate of change of peripheral resistance using beat-to-beat averaged data. Accurate knowledge of the value of these two parameters is critical in treating any hemorrhage case.

In chapter 6, we provide concluding remarks and direction for future research efforts.
Chapter 2

The Computational Hemodynamic Model

A strong analogy exists between electric circuits and fluid systems. Computational models of the cardiovascular system are therefore conveniently represented in the form of their circuit analogs. The vessels can be thought of as capacitors with compliances \( C, \frac{mL}{mmHg} \) that store blood volume \((Q, mL)\), connected to resistors \((R, \frac{mmHg}{mL} \text{ or PRU})\) which account for the fluid resistance faced by blood flow. The ventricles can be modeled as capacitors with time varying compliances. During diastole, ventricular compliance is high which allows the ventricles to store blood volume, thus mimicking the act of being filled. During systole, however, ventricular compliance decreases, thus increasing pressure, which leads to the emptying of the chamber. A periodic compliance function which varies between the diastolic and systolic compliance values can therefore be used to model the pumping action of the heart. Using this circuit analogy, blood volume maps to charge, blood flow rate \((\dot{q}, mL/s)\) to current, and pressure \((P, mmHg)\) to voltage. In this chapter, we describe the cardiovascular model used and we detail its implementation.
2.1 Simplifying Assumptions

It would be practically impossible to construct a model with a manageable level of complexity, that accounts for all the nuances of cardiovascular function. A great simplifying assumption in this regard is that the cardiovascular system can be represented by a lumped parameter model. Dispersed networks, such as that of the arteries and arterioles, can therefore be modeled using single circuit elements. Lumping the parameters together reduces the ability of the model to represent distributed behavior, such as pulse reflections, however, such level of detail is currently not the focus of our investigation.

Another simplifying assumption is that the circuit elements are linear. For the capacitors, this assumption is reasonable over the range of pressures for which the elastic fibers of the vessels are stressed, leading to an approximately linear volume-pressure relationship. Beyond this range, collagen fibers become stressed and add an element of non-linearity. The systemic arteries, however, exhibit non-linear compliance over all pressure ranges due to the presence of multiple tensions. Moreover, the pulmonary arterial resistance is notably non-linear in behavior as well [16]. However, for the sake of simplicity, these elements can be considered as linear without compromising appreciably the ability of the model to represent the cardiovascular system for the purposes of our investigation.

2.2 CVSIM

The Cardiovascular Simulator, or CVSIM, was originally developed by Davis as an aid in teaching cardiovascular physiology [4]. Figure 2-1 shows the model in its circuit representation. CVSIM comprises six compartments which model the left and right ventricles ($l, r$), the systemic arteries and veins ($a, v$), and the pulmonary arteries and veins ($pa, pv$). The atria are excluded from the model because they play no significant hemodynamic role during normal heart rates. During increased heart rates, as may be the case in disease conditions, atrial contraction may contribute significantly to stroke volume. However, the effects of the atria can be accounted for by modifying the right ventricular parameters [4].
The ventricles are modeled by time-varying compliances connected to inflow and outflow resistances \((R_{i(r)}i, R_{i(r)}o)\) that represent resistance encountered by blood flow as it enters and exits the ventricles. The time-varying compliance is completely characterized by the beat period \((T)\), and by its minimum (end-systolic \((es)\)) and maximum (end-diastolic \((ed)\)) values (see Section 2.3.3). The rest of the compartments are each modeled by a linear capacitor coupled with a linear resistor. The resistances for the systemic and pulmonary veins are lumped with the right and left ventricular inflow resistances respectively. Each capacitor acts as a storage for blood volume as determined by the characteristic relationship:

\[
Q_i = C_i \cdot (P_i - P_i^{ref})
\]  

(2.1)

where the subscript \(i\) refers to any of the six compartments. \(Q_i\) is referred to as the stressed
compartment volume. To represent the volume of the compartment at zero-pressure, each compartment has another volume parameter, $Q_0^r$, associated with it. The reference pressure, $P_{r}^{ref}$, is ground for the systemic circulation and intrathoracic pressure ($P_{th}$) for the rest of the compartments as they reside inside the thorax. Although $P_{th}$ is known to vary with respiration, it can be modeled reasonably well as a constant equal to its average value. The diodes constitute the only non-linear elements of the model and act as cardiac valves that ensure uni-directional blood flow through the ventricles.

We chose to use the CVSIM model because of its reasonable level of complexity and its remarkable ability to model normal cardiovascular dynamics. Moreover, it was also previously used successfully to model some steady-state disease conditions, thus demonstrating its ability to model abnormal conditions as well [4, 14].

2.3 The Model Implementation

2.3.1 The Platform

We developed the model in Simulink $^1$ which is a strong tool for implementing dynamic systems. Simulink allows for a good degree of abstraction by providing building blocks with built-in functions and routines. The model becomes easily extendible which is advantageous for simulating various disease conditions. Another advantage of this platform is the fact that it is automatically interfaced with Matlab which makes the analysis and presentation of data very convenient.

2.3.2 Nominal Parameter Values

The nominal parameter values were determined by Davis for a 70-kg individual [4]. We use his values which are summarized in Table 2.1.

$^1$Version 5.0 (R13) dated 20-Jun-2002
Table 2.1: Nominal parameter values for the CVSIM model.

<table>
<thead>
<tr>
<th>Compartment</th>
<th>$C, \frac{mL}{mmHg}$</th>
<th>$Q^0, mL$</th>
<th>$R, \frac{mmHg}{mL/s}$ (PRU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>left ventricle (l)</td>
<td>0.4 - 10</td>
<td>15</td>
<td>0.006 ($R_{lo}$ - left ventricular outflow resistance)</td>
</tr>
<tr>
<td>systemic arteries (a)</td>
<td>1.6</td>
<td>715</td>
<td>1.0</td>
</tr>
<tr>
<td>systemic veins (v)</td>
<td>100.0</td>
<td>2500</td>
<td>0.01 ($R_{vi}$ - right ventricular inflow resistance)</td>
</tr>
<tr>
<td>right ventricle (r)</td>
<td>1.2 - 10</td>
<td>15</td>
<td>0.003 ($R_{ro}$ - right ventricular outflow resistance)</td>
</tr>
<tr>
<td>pulmonary arteries (pa)</td>
<td>4.3</td>
<td>90</td>
<td>0.08</td>
</tr>
<tr>
<td>pulmonary veins (pv)</td>
<td>8.4</td>
<td>490</td>
<td>0.01 ($R_{ui}$ - left ventricular inflow resistance)</td>
</tr>
</tbody>
</table>

System parameters:

- $T = \frac{5}{6} s$
- $P_{th} = -4 \text{ mmHg}$
- $Q_{total} = 5000 \text{ mL}$

2.3.3 The Time-Varying Compliance Function

The compliances of the ventricles are based on the ventricular model of Suga and Sagawa [17, 18]. The time evolution of the compliance function is given below, as outlined by Mukkamala [16], in the form of its inverse, called elastance ($E$).

$$E_{i,r}(t) = \begin{cases} \frac{1}{2} \left( \frac{1}{C_{i,r}} - \frac{1}{C_{i,r}^0} \right) \cdot (1 - \cos(\frac{\pi(t-t_i)}{T_s})) + \frac{1}{C_{i,r}^0} & t_i \leq t < t_i + T_s \\ \frac{1}{2} \left( \frac{1}{C_{i,r}} - \frac{1}{C_{i,r}^0} \right) \cdot (1 + \cos(\frac{2\pi(t-(t_i+T_s))}{T_s})) + \frac{1}{C_{i,r}^0} & t_i + T_s \leq t < t_i + T_s + T_{ir} \\ \frac{1}{C_{i,r}^0} & t_i + T_s + T_{ir} \leq t < t_i+1 \end{cases}$$  \hspace{1cm} (2.2)

where the subscript $i$ refers to the $i^{th}$ cardiac cycle. $T_s$ and $T_{ir}$ refer to the systolic time period and the time for isovolumetric relaxation, respectively. These two parameters are related in the following manner:

$$T_s = 0.3\sqrt{T}$$  \hspace{1cm} (2.3)

$$T_{ir} = \frac{T_s}{2} = 0.3\sqrt{T}$$  \hspace{1cm} (2.4)

The time period for diastole, $T_d$, can therefore be calculated as follows:

$$T_d = T - T_s - T_{ir} = T - 0.45\sqrt{T}$$  \hspace{1cm} (2.5)
Figure 2-2a shows the compliance function over one cardiac cycle.

2.3.4 The Model Dynamics

Applying Kirchoff's Current Law (KCL) to the circuit topology of the model, the following set of equations is obtained:

\[
\begin{align*}
\frac{dP_l}{dt} &= \frac{\dot{q}_l - \dot{q}_o - (P_l - P_{th}) \cdot dC_l(t)/dt}{C_l(t)} \quad (2.6) \\
\frac{dP_a}{dt} &= \frac{\dot{q}_o - \dot{q}_a}{C_a} \quad (2.7) \\
\frac{dP_v}{dt} &= \frac{\dot{q}_a - \dot{q}_ri}{C_v} \quad (2.8) \\
\frac{dP_r}{dt} &= \frac{\dot{q}_ri - \dot{q}_ro - (P_r - P_{th}) \cdot dC_r(t)/dt}{C_r(t)} \quad (2.9) \\
\frac{dP_{pa}}{dt} &= \frac{\dot{q}_ro - \dot{q}_pa}{C_{pa}} \quad (2.10) \\
\frac{dP_{pc}}{dt} &= \frac{\dot{q}_pa - \dot{q}_l}{C_{pc}} \quad (2.11)
\end{align*}
\]
The compartmental flow rates are obtained through the application of Ohm’s Law:

\[
\dot{q}_{ti} = \begin{cases} 
\frac{P_{pu} - P_i}{R_{ti}} & \text{if } P_{pu} > P_i \\
0 & \text{otherwise}
\end{cases} \quad (2.12)
\]

\[
\dot{q}_{t_o} = \begin{cases} 
\frac{P_t - P_o}{R_{t_o}} & \text{if } P_t > P_o \\
0 & \text{otherwise}
\end{cases} \quad (2.13)
\]

\[
\dot{q}_{ia} = \frac{P_a - P_v}{R_a} \quad (2.14)
\]

\[
\dot{q}_{ri} = \begin{cases} 
\frac{P_r - P_i}{R_{ri}} & \text{if } P_r > P_i \\
0 & \text{otherwise}
\end{cases} \quad (2.15)
\]

\[
\dot{q}_{ro} = \begin{cases} 
\frac{P_r - P_o}{R_{ro}} & \text{if } P_r > P_o \\
0 & \text{otherwise}
\end{cases} \quad (2.16)
\]

\[
\dot{q}_{pa} = \frac{P_{pa} - P_{pu}}{R_{pu}} \quad (2.17)
\]

Equations 2.6 - 2.11 give the time derivatives of the compartmental pressures, which act as state variables. The system of equations can be solved by discretizing the problem. Given an initial set of pressures, the corresponding flow rates are calculated which are used to determine the local gradient information for the pressures. The pressure gradients are then integrated over time to obtain the compartmental pressures at the next time step. Once the new set of pressures is obtained, the cycle continues and the system is evolved iteratively in time. The integration routine used is the standard, fourth-order Runge-Kutta method with a fixed step-size of 0.005 s [19]. The fixed step-size is on the order of the smallest time-constant of the system and it is smaller than 0.006 s, which was identified as the maximum allowable step-size by Davis [4]. The details of the model implementation outlined here, including the choice of state variables, are similar to previous realizations of CVSIM [4, 16].
2.3.5 Initial Conditions

The initial conditions for the state variables are obtained by employing the method used by Davis [4]. A set of linear equations, formulated on the basis of conservation of volume (charge), are solved to obtain the end-diastolic pressures which are used as initial conditions for the start of a cardiac cycle.

\[
C_i^{cd}(P_i^{cd} - P_{th}) - C_t^{es}(P_t^{es} - P_{th}) = C_r^{cd}(P_r^{cd} - P_{th}) - C_r^{es}(P_r^{es} - P_{th}) \tag{2.18}
\]

\[
= T_i \frac{P_i^{cd} - P_a}{R_t} \tag{2.19}
\]

\[
= T_r \frac{P_a - P_v}{R_a} \tag{2.20}
\]

\[
= T_d \frac{P_a - P_r^{cd}}{R_{rd}} \tag{2.21}
\]

\[
= T_s \frac{P_v^{es} - P_{pm}}{R_{pa}} \tag{2.22}
\]

\[
= T_p \frac{P_{pa} - P_{pv}}{R_{pv}} \tag{2.23}
\]

\[
= T_d \frac{P_{pv} - P_i^{cd}}{R_{li}} \tag{2.24}
\]

\[
Q_{total} - Q_{total}^p = C_i^{cd}(P_i^{cd} - P_{th}) + C_a P_a \tag{2.25}
\]

\[
+ C_r P_v + C_r^{cd}(P_r^{cd} - P_{th}) \n
+ C_p(P_{pa} - P_{th}) + C_pv(P_{pv} - P_{th})
\]

Equations 2.18 - 2.25 are independent and can be solved to obtain the six initial, compartmental pressures. Equation 2.18 equates the left and right ventricular stroke volume (volume of blood pumped out by the left and right ventricles during one cycle). Equations 2.19 - 2.24 equate the stroke volume to the average volume of blood that passes through each of the remaining compartments. Equation 2.25 applies the conservation of volume (charge) phenomenon to equate the total distending blood volume to the sum of the stressed volumes of each compartment.
2.3.6 Conservation of Volume

The CVSIM model described is a closed system with no external sources or sinks of charge: the amount of charge in the model is completely defined by the initial conditions and must remain constant throughout the simulation. However, when the model was implemented with the state variables as described by Equations 2.6 - 2.11, volume conservation was not observed (see Figure 2-3).

Deviations in volume were being caused by numerical errors associated with the time-varying derivative terms \( \left( \frac{dC(t)}{dt}, \frac{dC_r(t)}{dt} \right) \), see Equations 2.6 and 2.9). Figure 2-2b shows a plot of the derivatives of the compliance functions for one cardiac cycle. The derivatives are not well behaved in that they vary dramatically over short periods of time when transitions occur from systole to isovolumetric contraction, and from isovolumetric contraction to diastole. The abrupt changes in the ventricular compliance derivatives lead to numerical integration errors when computing ventricular pressures. Moreover, the magnitudes of the ventricular compliance derivatives are relatively large which further magnify the numerical errors. A simple fix to this problem is a change of ventricular state variables to volume, instead of pressure, which removes the dependency on the ventricular compliance derivatives. Equations 2.26 - 2.27 represent the revised state equations for the ventricles.

\[
\begin{align*}
\frac{dQ_l}{dt} &= \dot{q}_l - \dot{q}_o \\
\frac{dQ_r}{dt} &= \dot{q}_r - \dot{q}_ro
\end{align*}
\]  

(2.26)  

(2.27)

Figure 2-4 shows a time-series plot of the deviation in expected and calculated total blood volume after the change of ventricular state variables. Barring insignificant numerical errors, the change of state variables leads to volume conservation.
Figure 2-3: Difference between expected total blood volume ($Q_{Total}$) and calculated total blood volume ($\hat{Q}_{Total}$), with left and right ventricular pressure (voltage) as state variables.

Figure 2-4: Difference between expected total blood volume ($Q_{Total}$) and calculated total blood volume ($\hat{Q}_{Total}$), with left and right ventricular volume (charge) as state variables.
Table 2.2: Comparison between model outputs and reported norms for compartmental pressures, stroke volume and cardiac output.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reported norm</th>
<th>Simulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressures (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P_t$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>125</td>
<td>113</td>
</tr>
<tr>
<td>Diastolic</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>$P_a$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>120</td>
<td>112</td>
</tr>
<tr>
<td>Diastolic</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>$P_v$ (average)</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>$P_r$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>Diastolic</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>$P_{po}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Diastolic</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>$P_{po}$ (average)</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Volume (mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke volume</td>
<td>77</td>
<td>74</td>
</tr>
<tr>
<td>Cardiac output ($L_{min}$)</td>
<td>5.0</td>
<td>5.3</td>
</tr>
</tbody>
</table>

2.3.7 Model Validation

The ability of the CVSIM model to reasonably represent the underlying physiology can be gauged from a comparison of the model outputs, at different time scales, to what is generally observed in humans.

**Beat-to-Beat comparisons**

Table 2.2 shows a comparison of steady-state cardiac output, and beat-to-beat pressure values and stroke volume. The norms listed are for a 70-kg adult as reported by Milnor in Mountcastle's *Physiology* [20, 21].

**Pulsatile Waveforms**

The validation of the intra-beat dynamics is made by plotting the pressure waveforms for all the compartments. Figure 2-5 shows the plots for all the compartmental pressures for a single
Figure 2-5: Pulsatile pressure waveforms for a single beat.

On average, the pressure waveforms look similar to the actual catheterized data. The pressure magnitudes and time-constants involved seem reasonable, thus validating the choice of parameter values used. However, expected differences, such as the absence of reflected waves due to the lumping of parameters, are visible.

2.3.8 Interstitial Fluid Compartment

Body fluid is divided into two distinct categories: intracellular and extracellular fluid. As the name suggests, intracellular fluid consists of the volume within the cells which forms approximately $\frac{2}{3}$ of the total body fluid. Extracellular fluid is further divided into interstitial fluid and blood plasma. The division is such that in steady state, $\frac{11}{14}$ of the extracellular volume resides in the interstitial space, whereas the rest is blood plasma. Figure 2-6 shows the distribution of fluid volume for an average 70-kg adult.
Figure 2-6: Volume distribution for an average 70-kg adult. Approximately 60% of body mass is fluid. This percentage can vary depending on age, sex, and obesity [2].

The fluid in plasma constantly interacts with the interstitial space through the capillary pores, however, the CVSIM model does not represent this communication. In steady-state, the absence of the interstitial compartment does not significantly inhibit the ability of the model to represent the underlying physiology, as no net exchange of volume takes place between the two compartments. However, during disease conditions, such as hemorrhage, or during clinical interventions, such as administration of fluid boluses, the role of the interstitial compartment becomes significant. In this section, we describe the addition of the interstitial fluid compartment \((\text{int})\), and we detail the derivation of the nominal parameter values associated with the compartment. ²

**Model Addition**

The interstitial fluid compartment is represented by an additional resistor and capacitor \((R_{\text{int}}, C_{\text{int}})\), connected between the systemic arteries and veins (see Figure 2-7). The ca-

²Note: The interstitial compartment is used only in Chapter 5, when matching simulated data to actual patient data.
pacitor models the volume storage ability of the interstitial fluid space, whereas the resistor models the resistance faced by the fluid when diffusing between the two compartments.

The nominal value for $C_{int}$ can be determined using the following logic, which analyzes the fluid dynamics before and after the administration of a fluid bolus 3 (saline, for example):

- In steady-state, $P_v = P_{int}$, as no net exchange of volume takes place. Consider an initial (i) steady-state where $P_{int}^i = P_v^i = P$.

- After intra-venous administration of a fluid bolus $\Delta V$, a new steady-state will be reached where $\frac{11}{14}$ of the bolus volume will diffuse into the interstitial space, whereas $\frac{3}{14}$ will remain in the circulatory system. Since the veins form the largest blood reservoirs of the circulatory system (storing $64\%$ of the volume [2]), $64\%$ of the fraction of the bolus volume remaining in the intra-vascular space will reside in the veins once the new steady-state has been reached. As compartmental pressure can be expressed as a ratio of volume to compliance (see Equation 2.1), the following set of equations is obtained when equating the final (f) steady-state pressures $P_{int}^f$ and $P_v^f$:

$$P_{int}^f = P_v^f$$

$$P + \frac{11}{14} \cdot \Delta V \cdot \frac{1}{C_{int}} = P + \frac{3}{14} \cdot \Delta V \cdot 64\% \cdot \frac{1}{C_v}$$

$$C_{int} = \frac{11}{14} \cdot \frac{14}{3} \cdot \frac{100}{64} \cdot C_v$$

Using the nominal value $C_v = 100 \frac{mL}{mmHg}$, $C_{int} \approx 573 \frac{mL}{mmHg}$.

We use the same analysis, which considers the dynamics after the administration of a fluid bolus, to determine the value of $R_{int}$. The nominal $R_{int}$ value can be resolved using the time-constant involved in the transfer of fluid volume between the interstitial space and the circulatory system. Based on an extensive literature review, Heldt determined that the time-constant for diffusion to and from the interstitial space is the same, with a nominal

3We assume the administration of isotonic fluids which redistribute between the intravascular and interstitial spaces only [22].
Figure 2-7: Addition of the interstitial compartment between the systemic arteries and veins.

value $\tau_{\text{int}} = (4.6 \pm 0.4)$ min [5].

In the circuit representation of the model, the topology is such that the venous charge decay (post-administration of a fluid bolus) does not follow a simple RC time-constant. Therefore, it is not trivial to determine an analytical formula for the time-constant which can be used to pinpoint the exact $R_{\text{int}}$ value. To overcome this problem, we assume that on a beat-to-beat averaged basis during the transient, the charge flowing in from the arterial side ($Q_{\text{incoming}}$) is offset by the charge flowing into the right ventricle ($Q_{\text{outgoing}}'$, see Figure 2-7). With this assumption, the added venous charge redistributes itself between $C_v$ and $C_{\text{int}}$, which are connected in series through $R_{\text{int}}$. This configuration leads to the following approximate value for $R_{\text{int}}$:

$$\tau_{\text{int}} = 276s$$

$$R_{\text{int}} \cdot \frac{C_vC_{\text{int}}}{C_v + C_{\text{int}}} = 276s$$

$$R_{\text{int}} \approx 3.2\text{PRU}$$

Next, we carried out several simulations of fluid bolus administration in which $R_{\text{int}}$ was varied around its approximate value of 3.2 PRU. Based on simulation results, $R_{\text{int}} = 2.3$ PRU yielded a venous charge decay time-constant of approximately 4.5 mins. Hence, a nominal value of 2.3 PRU was assigned to $R_{\text{int}}$. Figure 2-8 shows the plot of simulated venous volume vs time which captures the dynamics induced by a fluid bolus administration. Figure 2-9 shows a plot of the difference between $Q_{\text{incoming}}^{\text{av}}$ and $Q_{\text{outgoing}}^{\text{av}}$. We observe that
Figure 2-8: Beat-to-beat averaged venous charge ($Q_{av}^{mv}$) vs time. Sub-figure (a) shows the plot of $Q_{av}^{mv}$ vs time before and after the administration of a fluid bolus. Sub-figure (b) shows the plot of $ln(Q_{av}^{mv})$ vs time, and its best straight line fit, after the administration of a fluid bolus. The time-constant for the charge decay is the reciprocal of the slope of the best straight line fit: $\tau_{int} \approx 4.5$ min.

this difference is indeed small compared to the venous charge decay. Thus, the assumption we made in approximating a value for $R_{int}$ is verified to be reasonable.

The addition of the interstitial fluid compartment adds another state variable to the model. See Appendix A for the details of the new model equations.

### 2.3.9 Concluding Remarks

Though the CVSIM model does not capture the fine details of cardiovascular function, it is a reasonable model to start investigating the use of parameter estimation as an aid in patient monitoring. Since the average behavior of the model is similar to the underlying physiology, there is credibility in the use of the system. However, various additions to the model have been proposed, including the use of inductors to model the inertial effects of blood [11]. Moreover, the systemic circulation has also been modeled as a distributed set of parallel compartments, as opposed to a single compartment, in order to include the
individual effects of prominent arteries and veins [5]. Nevertheless, there is a clear trade-off between model complexity and ability to represent minute details. The CVSIM model strikes a healthy balance by providing a system which is of manageable complexity, and reasonable in its ability to represent the cardiovascular system.

Figure 2-9: $Q_{\text{incoming}} - Q_{\text{outgoing}}$ after the administration of a fluid bolus.
Chapter 3

The Cardiovascular Control System

The cardiovascular system forms the lifeline for cell survival as it transports oxygen and nutrients. Entrusted with such a mammoth responsibility, cardiovascular function maintains homeostasis by adapting dynamically to meet the current needs of the body and to counteract hemodynamic perturbations. For example, in the absence of a control system, the commonplace act of regaining the head-up posture from a supine state causes the blood pressure at the level of the heart to drop to such a degree that one might faint. In the presence of cardiovascular control, however, changes in posture are activities that we perform seemingly effortlessly without even noticing the stress that we impose upon the cardiovascular system.

In order to accomplish its task, the cardiovascular system exerts control at both local and global levels. Local control includes the modulation of vascular resistance by tissue beds to maintain adequate blood flow in a specific region. Global control, on the other hand, involves the regulation of hemodynamic variables to maintain overall pressure. The reflex mechanisms involved in employing control span many time scales, from the fast neurally-mediated (seconds to minutes) to the slower hormonally-mediated (days) [2].

In order to faithfully track patient state continuously, we are interested in modeling the short-term cardiovascular control to clinical interventions and to changes in the degree of a disease condition. In this chapter, we describe the arterial baroreflex, which is a principal component of short-term neurally-mediated control, and we outline its implementation.
Furthermore, we qualitatively validate the baroreflex function by simulating certain disease conditions.

3.1 Arterial Baroreflex

The arterial baroreflex is a negative feedback system that aims to maintain ABP around a particular set-point. The afferent leg of the system includes pressure sensors, known as baroreceptors, located in the aortic arch and the carotid sinuses. These receptors sense ABP and transmit this information via afferent fibers to the brain where the deviation in ABP from the set-point is mapped to sympathetic (α and β) and parasympathetic activity. Increased α-sympathetic action leads to increased peripheral resistance and decreased zero-pressure venous volume, while increased β-sympathetic action causes an increase in cardiac contractility and heart rate. Parasympathetic action affects the heart rate in a manner opposite to β-sympathetic action; an increase in parasympathetic activity reduces the heart rate instead of increasing it. Figure 3-1 presents a block diagram of the arterial baroreflex system.

Our representation of the arterial baroreflex is based on Davis’s extension of deBoer’s work [4, 23] with certain changes in implementation that are described in the next section.

3.2 Implementation

Previous implementations of the baroreflex mechanism adopted relatively coarse time-steps for the control system as compared to the rest of the cardiovascular model [4, 16]. It was deemed computationally inefficient for the reflex system to react to every sample of ABP, as pulsatile ABP is bandlimited at frequencies below ten times the mean heart rate, while the frequency response of the cardiovascular regulatory mechanism is bandlimited at frequencies less than the mean heart rate [16]. Thus, in Davis’s model of the baroreflex, pulsatile ABP was averaged over 0.5 s and then sampled at 0.5 s [4]. This implementation, however, leads to aliasing as the frequency content above 1 Hz is not sufficiently filtered by the 0.5 s running
Figure 3-1: Block diagram of the arterial baroreflex system. $P_{ap}^{sp}$ is the set-point pressure that the system is aiming to maintain.

average filter. A subsequent implementation by Mukammala [16] averaged the pulsatile ABP over 0.25 s and then sampled it at 0.0625 s, thus reducing the aliasing effects. In order to completely remove the effects of aliasing, we decided to implement the control system in continuous-time.

### 3.2.1 Preprocessing and Error Calculation

Since the cardiovascular regulatory mechanism responds to low-frequency fluctuations of ABP from a set-point, the pulsatile ABP signal is first low-pass filtered to remove the strong frequency content at, and above, the mean heart rate. Next, the low-pass filtered ABP signal ($P_{ap}^{lp}(t)$) is subtracted from the set-point to produce the error signal ($e(t)$), which

---

1In principle, the low-pass filter should not be required as the physiological control system response itself is bandlimited at frequencies below the mean heart rate. However, as shown in Section 3.2.2, the response of the estimated control system does not sufficiently attenuate the strong, high-frequency content present in the ABP waveform.
then is passed-on to a non-linear mapping block that represents the baroreflex saturation characteristic [24]. As the autonomic nervous system exhibits a limiting behavior in action, the following mapping is applied to $e(t)$ [23]:

$$e_{sat}(t) = 18 \arctan \left( \frac{e(t)}{18} \right)$$  \hspace{1cm} (3.1)

This mapping restricts the input to the effector mechanism to approximately ±28 mmHg. Figure 3-2 illustrates the preprocessing mechanism.

### 3.2.2 Effector Mechanism

#### Control Filters

The effector mechanisms are modeled as a linear combination of two LTI filters which represent the sympathetic ($\alpha$ and $\beta$) and the parasympathetic limbs of the autonomic nervous system. The filters are defined by their unit-area impulse responses, $s(t)$ (sympathetic) and $p(t)$ (parasympathetic). Figure 3-3 illustrates $s(t)$ and $p(t)$ along with their Fourier transforms.

The filters were implemented using Simulink’s continuous-time blockset which allows for the representation of rational transfer functions and continuous-time delays. The transfer
functions for the control filters are given as follows:

\[
S(s) = \frac{1}{350s^2}e^{-30s} - \frac{2}{75s^2}e^{-5s} + \frac{1}{42s^2}e^{-2s} \\
P(s) = \frac{-200}{3s^2}e^{-\frac{s}{10}} + \frac{50}{s^2}e^{-\frac{s}{10}} + \frac{50}{3s^2}e^{-s}
\]  

(3.2)  
(3.3)

**Autonomic Mediation**

Autonomic mediation is executed by convolving \( e_{sat}(t) \) with a linear combination of \( s(t) \) and \( p(t) \) to obtain \( \Delta X(t) \), which is the control system contribution to each effector variable \( X(t) \).
Figure 3-4: Diagrammatic representation of the effector mechanism depicting autonomic mediation.

(see Figure 3-4). $G^s_X$ and $G^p_X$ represent the scalings of the unit area impulse responses $s(t)$ and $p(t)$ respectively, where $X$ denotes the effector variable (see Table 3.1 for a summary of the control system parameters). The output of the control filters is then added to the nominal value of the effector variable, $X^0$, in order to yield the value of the variable at the current time-step.

The effector limbs corresponding to heart rate, zero-pressure venous volume, and peripheral resistance, are all updated every simulation time step. Ventricular contractility, on the other hand, is updated every beat since the contractility variables are used to define the compliance function (see Section 2.3.3), and hence must remain constant for the entire beat. The onset time for the start of a cardiac-cycle, which begins with ventricular contraction, is determined through an Integral Pulse Frequency Modulation (IPFM) model. The IPFM model integrates heart rate over time until the integral reaches a threshold, after which ventricular contraction starts. The integral is then reset to zero and the process repeats itself (see Heldt [5] for a more detailed description of the IPFM model).

**Stability Issues**

When the control system was implemented using Simulink’s continuous-time blockset, the parasympathetic implementation turned out to be unstable. Figure 3-5 shows the open-loop step responses of the implemented filters.

In order to obtain a stable implementation of the parasympathetic filter, Padé approximations were used to convert continuous-time delays to rational transfer functions. The
Table 3.1: Nominal parameter values for the arterial baroreflex model. The values are taken from Davis’s implementation [4].

<table>
<thead>
<tr>
<th>Reflex limb</th>
<th>$G^s$</th>
<th>$G^p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR-interval</td>
<td>$\frac{m_s}{\text{mmHg}}$</td>
<td>9</td>
</tr>
<tr>
<td>Left ventricular contractility</td>
<td>$\frac{m_b}{\text{mmHg}^2}$</td>
<td>0.007</td>
</tr>
<tr>
<td>Right ventricular contractility</td>
<td>$\frac{m_L}{\text{mmHg}^2}$</td>
<td>0.021</td>
</tr>
<tr>
<td>Peripheral resistance</td>
<td>$\frac{PRU}{\text{mmHg}}$</td>
<td>-0.011</td>
</tr>
<tr>
<td>Zero-pressure venous volume</td>
<td>$\frac{mL}{\text{mmHg}}$</td>
<td>26.5</td>
</tr>
</tbody>
</table>

$P_a^{sp} = 94 \text{ mmHg}$

The first-order Padé approximation is given as follows:

$$e^{sx} \approx \frac{1 - sx/2}{1 + sx/2}$$  \hspace{1cm} (3.4)

Using this approximation, the parasympathetic transfer function can be approximated as follows:

$$P(s) = \frac{-200}{3s^2} e^{-7s/20} + \frac{50}{s^2} e^{-5s/20} + \frac{50}{3s^2} e^{-s}$$

$$\approx \frac{-200}{3s^2} \cdot \frac{1 + 7s/20}{1 - 7s/20} + \frac{50}{s^2} \cdot \frac{1 + 6s/20}{1 - 6s/20} + \frac{50}{3s^2} \cdot \frac{1 + s/2}{1 - s/2}$$

$$\approx \frac{1}{0.0525s^3 + 0.43s^2 + 1.15s + 1}$$  \hspace{1cm} (3.5)

Figure 3-6a shows the desired parasympathetic impulse response overlaid on the one obtained with the first-order Padé approximation. We observe that while the approximation captures the peak action time, it fails to accurately model the magnitude, initial delay, and the end-response time. In order to correct some of these inadequacies, the response was localized in time by expanding in frequency to obtain what is labeled as the 'tweaked' response. However, only minor improvements were observed. Clearly, the first-order Padé
approximation is not sufficient. Therefore, higher order approximations were used to model better the parasympathetic response. Figure 3-6b shows the impulse response obtained with the fifth-order Padé approximation. This higher order approximation maintains the integrity of the magnitude and response times, and thus is better able to model the desired response. Figure 3-7 shows a comparison of the open-loop step response of the desired parasympathetic filter, and its first- and fifth-order Padé approximations. The fifth-order Padé approximation is seen to be a viable one as it closely follows the desired response.

**Parasympathetic Response Simplification**

Since the parasympathetic impulse response lasts for only a fraction of a heart beat, we tried replacing it with two simplifying approximations: a simple gain, and a pure delay followed by a gain. The closed-loop performances using the simplifications and the fifth-order Padé approximation were compared for two simulated disease conditions: hemorrhage, and left MI (see Section 3.3). Figure 3-8 shows the closed-loop output of the parasympathetic block when using different approximations for the filter. We observe that there is no visible difference amongst the block outputs, indicating that the parasympathetic filter can be represented by
3.3 Qualitative Validation

The control system was validated qualitatively by observing its response to certain disease conditions.

3.3.1 Hemorrhage

A case of hemorrhage was simulated for 30 mins with a blood loss rate of $1 \frac{L}{m}$. The blood leakage was created by adding a branch to the arterial side of the model which provided a path for blood to exit the system at a constant rate. Figure 3-9 illustrates how the various pressures change versus time and how the control system responds. The bleeding causes the pressures to fall thereby activating the control system, which increases the heart rate, peripheral resistance and ventricular contractility, and decreases zero-pressure venous volume. All the mentioned actions executed by the control system serve to increase ABP, hence the control system responds as expected.
3.3.2 Left Myocardial Infarction (MI)

A left myocardial infarction was simulated by disconnecting the left end-systolic compliance \( C_{es} \) from the control system. This compliance was then explicitly changed from its nominal value of 0.4 to 1.8 \( \frac{mL}{mmHg} \) according to a ramp function over the period of a minute. Figure 3-10 shows the plots of the various pressures along with the control system response. Increasing \( C_{es} \) decreases the contractility of the left ventricle which causes ABP to drop. Consequently, the control system increases heart rate, peripheral resistance and right ventricular contractility, and decreases the zero-pressure venous volume. Once \( C_{es} \) reaches the value of 1.8 \( \frac{mL}{mmHg} \) and remains constant, the control system output levels off, indicating how the short-term control system eventually adapts to a disease condition.
Figure 3-8: Parasympathetic block output during hemorrhage and left MI simulations using different approximations for the parasympathetic filter.

3.4 Concluding Remarks

The arterial baroreflex adds an element of reality to the model by implementing short-term cardiovascular control. This addition enhances the model's ability to represent sudden physiological changes more accurately. With the implementation and qualitative validation of the control system, the model construction is complete and we now turn our focus to parameter estimation.
(a) Pressure waveforms versus time.

(b) Effector variables versus time.

Figure 3-9: Hemorrhage simulation.

(a) Pressure waveforms versus time.

(b) Effector variables versus time.

Figure 3-10: Left MI simulation.
Chapter 4

Parameter Estimation using Waveform Data

The previous chapters were focused on the topic of forward-modeling: we outlined and described the implementation of a pulsatile cardiovascular model that is capable of simulating both normal and abnormal physiology. In this chapter, we tackle the problem of inverse-modeling or parameter estimation using waveform data.

Given observable patient data in the form of ABP, CVP, and PAP signals, we would like to estimate the underlying parameters of the model in an effort to track patient state. The observable signals, however, are generally not rich enough to allow for the estimation of all the parameters. This leads to an ill-conditioned estimation problem. To overcome the ill-conditioning, we employ subset selection that improves the conditioning of the problem by reducing the dimensionality of the estimation problem. Such a scheme was successfully adopted by Heldt [5] to estimate cardiovascular parameters during transient responses to head-up tilt, using a more complex underlying computational model.

First, we give a general outline of a non-linear least squares optimization technique. Next, we illustrate the problem of ill-conditioning, and subsequently we describe the subset selection solution to improve the conditioning of the problem. Finally, we describe the set-up of the estimation experiments we performed using both steady-state and transient data, and
we present their results.

4.1 Non-linear Least Squares and Subset Selection

4.1.1 Non-linear Least Squares Optimization

In the context of parameter estimation, the non-linear least squares optimization method iteratively arrives at the best estimates for the parameters of an underlying system by minimizing the error between the model output and the observation. Let $r(\theta) = \mathbf{y}(\theta) - \mathbf{y}$ denote a measure of residual error where $\mathbf{y}(\theta) \in \mathbb{R}^n$ corresponds to the model output, which is a function of the parameter vector $\theta \in \mathbb{R}^m$, and where $\mathbf{y} \in \mathbb{R}^n$ refers to the observation (or data) vector. The cost function we try to minimize is a weighted sum of squares of residual errors and is given as follows:

$$\Phi(\theta) = \frac{1}{2}(r^TQr)$$

(4.1)

where $Q \in \mathbb{R}^{nxn}$ is a matrix of weights, usually diagonal, that weighs the individual error components$^1$.

The second-order Taylor series expansion $\Psi(\theta)$ of $\Phi(\theta)$ gives a good approximation of the cost function for small perturbations of $\Delta \theta = \theta_1 - \theta_0$ around the initial estimate $\theta_0$. $\Psi(\theta)$ is given as follows:

$$\Psi(\theta) = \Phi(\theta_0) + \left[\frac{\partial \Phi}{\partial \theta}\right]_{\theta_0} \Delta \theta + \frac{1}{2} \Delta \theta^T \left[\frac{\partial^2 \Phi}{\partial \theta^2}\right]_{\theta_0} \Delta \theta$$

(4.2)

where $[\partial \Phi / \partial \theta]_{\theta_0}$ and $[\partial^2 \Phi / \partial \theta^2]_{\theta_0}$ denote the first- and second-order derivatives evaluated at the current best estimate $\theta_0$, respectively. To minimize $\Psi(\theta)$, we equate its gradient to zero:

$$\frac{\partial}{\partial \theta} \Psi(\theta) = \left[\frac{\partial \Phi}{\partial \theta}\right]_{\theta_0} + \left[\frac{\partial^2 \Phi}{\partial \theta^2}\right]_{\theta_0} \Delta \theta = 0$$

$^1$For the purposes of our analyses, we consider $Q$ to be diagonal.
To find the stationary point $\theta_1$, the previous equation can be rearranged as follows:

$$\left[ \frac{\partial^2 \Phi}{\partial \theta^2} \right]_{\theta_0} (\theta_1 - \theta_0) = -\left[ \frac{\partial \Phi}{\partial \theta} \right]_{\theta_0}$$

(4.3)

If the inverse of the second-order derivative matrix exists, $\theta_1$ is given by:

$$\theta_1 = \theta_0 - \left[ \frac{\partial^2 \Phi}{\partial \theta^2} \right]_{\theta_0}^{-1} \cdot \left[ \frac{\partial \Phi}{\partial \theta} \right]_{\theta_0}$$

(4.4)

If the matrix of second-order derivatives is positive definite, $\Phi(\theta_1) < \Phi(\theta_0)$, making $\theta_1$ a valid estimate which assumes the role of $\theta_0$ in the next iteration [25]. The iterations continue until some exit criteria are satisfied, which usually include setting thresholds on the cost function value, and on the distance between two consecutive parameter estimates.

For the cost function defined by Equation 4.1, the matrix of first-order derivatives is given as:

$$\left[ \frac{\partial \Phi}{\partial \theta} \right] = J^T Q r(\theta) \text{ where } J_{ij} = \frac{\partial r_i(\theta)}{\partial \theta_j} = \frac{\partial y_i(\theta)}{\partial \theta_j}$$

(4.5)

$J \in \mathbb{R}^{mxm}$ is the Jacobian matrix of the error vector with respect to the parameter vector. The elements of the second-order derivative matrix of the cost function, known as the Hessian matrix $H \in \mathbb{R}^{mxm}$, are given by:

$$H_{ij} = \frac{\partial^2 \Phi}{\partial \theta_i \partial \theta_j} = (J^T Q J)_{ij} + \sum_{l=1}^{n} \sum_{p=1}^{n} Q_{lp} \cdot r_p \cdot \frac{\partial^2 r_l}{\partial \theta_i \partial \theta_j}$$

In the presence of small residuals, the Gauss-Newton approximation to the Hessian states that the terms containing the residuals can be ignored, thus giving the following approximation:

$$H_{ij} = \frac{\partial^2 \Phi}{\partial \theta_i \partial \theta_j} \approx (J^T Q J)_{ij}$$

Substituting the expressions for the cost function derivatives in Equation 4.3, we obtain
the following equation for the parameter estimate updates:

\[
J^T Q J \cdot (\theta_{i+1} - \theta_i) = -J^T Q \cdot r
\]  

(4.6)

The Gauss-Newton approximation reduces the non-linear least squares optimization problem to a series of linear least squares equations which are solved iteratively.

Let \( R \) represent the Hessian matrix or its Gauss-Newton approximation. To illustrate the problem of ill-conditioning, we follow the reasoning presented by Heldt [5], based on the arguments of Burth and co-workers [26]. If the matrix \( R \) is rank-deficient, then it is singular with at least one of its eigenvalues at zero, and its column space does not span the entire \( \mathbb{R}^m \) space. Consequently, the parameter update vector can be arbitrarily varied in the direction of \( \theta \), which belongs to the null-space of \( R \), without affecting the error criterion:

\[
R \cdot (\theta_{i+1} - \theta_i + \theta) = R \cdot (\theta_{i+1} - \theta_i) + R \cdot \theta = R \cdot (\theta_{i+1} - \theta_i) = -J^T r
\]

Thus, if \( R \) is singular, then the model parameters are not uniquely determinable from the available observation data; such an estimation problem is said to be an ill-conditioned one.

Typically though, \( R \) is not exactly singular, but nearly so, with its largest singular value much greater than its smallest. Nearness to singularity is measured by the condition number, \( \kappa(R) \), which, for real and symmetric matrices, is given by the ratio of the largest to the smallest eigenvalues.

To overcome the problem of ill-conditioning, we turn to the subset selection algorithm that determines which parameters should be discarded from the estimation formulation in order to improve the conditioning of the system.

4.1.2 Subset Selection

Subset selection aims to identify the parameter axes that lie closest to the ill-conditioned directions of the Hessian matrix [26]. As the error criterion varies very slowly in the direction of ill-conditioned parameter axes, the corresponding parameters are fixed at prior values while
the estimation process is carried out with a reduced-order formulation. Though fixing the ill-conditioned parameters introduces some bias into the estimates, the effect of the bias is offset by the improved reliability with which the rest of the parameters are estimated.

The number of well-conditioned parameters is determined from the structure of the Hessian eigenspectrum. If the Hessian eigenspectrum contains \( \rho \) large eigenvalues and \( m - \rho \) small ones, then this indicates that the Hessian has a numerical rank of \( \rho \), and that only the corresponding \( \rho \) parameters should be included in the estimation formulation. The reduced-order estimation problem involves the use of reduced dimension Jacobian and Hessian matrices, indicated by \( J_\rho \) and \( H_\rho \) respectively. \( J_\rho \) contains \( \rho \) columns of the original Jacobian matrix that are strongly independent, which results in a small condition number for the corresponding \( H_\rho \).

The following procedure, based on the work of Vélez-Reyez [27] and as described in Burth and co-workers [26], outlines the algorithm for subset selection:

1. Using an initial parameter vector estimate \( \hat{\theta}_0 \), calculate the eigendecomposition of \( H(\theta_0) : H = V \Lambda V^T \), such that the eigenvalues in \( \Lambda \) are in descending order.
2. Determine \( \rho \) such that the first \( \rho \) eigenvalues of \( H \) are much larger than the remaining \( m - \rho \) ones.
3. Partition \( V = [V_\rho \ V_{m-\rho}] \).
4. Determine a permutation matrix \( P \) by constructing a \( QR \) decomposition with column-pivoting for \( V_\rho^T \) i.e. determine \( P \) such that:

\[
V_\rho^T \cdot P = Q \cdot R
\]

where \( Q \) is an orthogonal matrix and the first \( \rho \) columns of \( R \) form an upper triangular matrix.
5. Use \( P \) to re-order the parameter vector \( \theta \) according to \( \bar{\theta} = P^T \theta \).

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6. Partition $\tilde{\theta} = [\tilde{\theta}_\rho^T \tilde{\theta}_{m-\rho}^T]^T$, where $\tilde{\theta}_\rho^T$ contains the first $\rho$ elements of $\tilde{\theta}$. Fix $\tilde{\theta}_{m-\rho}$ at prior estimate $\tilde{\theta}_{m-\rho}$.

7. Compute $\hat{\theta}$ by solving the reduced-order problem $\hat{\theta} = \arg\min_{\theta} \Phi(\theta)$ subject to $\theta_{m-\rho} = \tilde{\theta}_{m-\rho}$.

4.1.3 Jacobian Calculation and Scaling

Although methods exist to compute the Jacobian matrix analytically, the large number of parameters and output variables warrant the use of a finite-difference approximation. We used a two-sided finite difference method with a step-size of 4% of the nominal parameter values. Equation 4.7 illustrates the finite-difference approximation:

$$J(\theta) = \frac{\delta \hat{y}(\theta)}{\delta \theta} = \frac{\hat{y}(\theta + \Delta \theta) - \hat{y}(\theta - \Delta \theta)}{2 \Delta \theta} \quad (4.7)$$

As the input parameter values span several orders of magnitude and have different units of measurement, the columns of the Jacobian need to be normalized. Normalizing the columns would lead to meaningful comparisons between the column norms, which represent the strengths with which perturbations in parameters affect the entire observable output. Moreover, the Jacobian rows also need to be normalized as they too span several orders of magnitude. The observable output consists of single-cycle waveforms of ABP, CVP, and PAP signals which vary greatly in magnitude, not only amongst each other, but also within a signal itself during a cardiac cycle. In order to prevent the residual errors in any one output variable from dominating, which can cause a loss of information contained in the rest of the residuals, the rows of the Jacobian need to be normalized. Furthermore, the subset selection algorithm is not scaling-invariant [28], hence meaningful scalings of the Jacobian can be used to improve the curvature of the error-criterion surface and therefore help in identifying the well-conditioned parameters.

We applied two different kinds of scalings to the Jacobian. The first scheme, which we shall refer to as nominal scaling, scaled the columns of the Jacobian by the nominal parameter
values, and scaled the rows by some characteristic output values, which in our case, were the nominal output values. Such a scaling leads the columns of the Jacobian to contain percentage changes in observable output as a response to percentage changes in parameter values. The second scheme, which we shall refer to as range scaling, scaled the columns by the dynamic ranges of the parameters instead of the nominal values \(^2\). Subsequently, the rows were scaled so that they would have a norm of unity. Scaling the columns using the ranges of the parameters gives a sense of how the parameters affect normalized output when they are perturbed as a percentage of their dynamic ranges.

In the context of solving the non-linear least squares problem, row scaling leads to the weighting of residuals which is handled by the \(Q\) matrix in Equation 4.1. Column scaling, however, needs to be explicitly added which modifies the parameter update equation (see Equation 4.6) to the following:

\[
MJ^TQJM\hat{p} = -MJ^Tqr
\]  

(4.8)

where \(M \in \mathbb{R}^{m \times m}\) is a diagonal matrix of column scalings and \(\hat{p} = M^{-1} \cdot (\theta_{i+1} - \theta_i)\). The above equation is obtained by replacing each occurrence of \(J\) in Equation 4.6 with its column scaled version \(JM\). Equation 4.8 can be re-written as follows:

\[
(\sqrt{QJM})^T \cdot (\sqrt{QJM}) \cdot \hat{p} = -(\sqrt{QJM})^T \cdot \tilde{r}
\]

(4.9)

where \(\tilde{r} = \sqrt{Qr}\). The Gauss-Newton approximation of the Hessian using the scaled version of the Jacobian is therefore given as:

\[
H \approx (\sqrt{QJM})^T \cdot (\sqrt{QJM})
\]

(4.10)

\(^2\)See Appendix B for a list of all the independent parameters of the model and their range of values.
Table 4.1: Parameters identified as being well-conditioned by the subset selection algorithm.

<table>
<thead>
<tr>
<th>Parameter no.</th>
<th>Nominal Scaling</th>
<th>Range Scaling</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Distending blood volume (DBV)</td>
<td>Right end-diastolic compliance ($C_{r}^{ed}$)</td>
</tr>
<tr>
<td>2</td>
<td>Peripheral Resistance ($R_a$)</td>
<td>Peripheral Resistance ($R_a$)</td>
</tr>
<tr>
<td>3</td>
<td>Right end-diastolic compliance ($C_{r}^{ed}$)</td>
<td>Distending blood volume (DBV)</td>
</tr>
</tbody>
</table>

4.1.4 Application of the Subset Selection Algorithm

We applied the subset selection algorithm to the problem of estimating cardiovascular parameters using single-cycle waveforms of ABP, CVP, and PAP signals. Figure 4-1 shows a plot of the eigenvalue spectrum of the Hessian approximation under the two different scaling schemes applied. The Hessian approximation has three strong eigenvalues under both scalings, indicating the existence of three well-conditioned or "active" parameters. Table 4.1 lists the parameters identified as being well-conditioned under the two scaling schemes. Although the sequence of the active parameters is different, both scalings lead to the selection of the same three parameters. Thus, in our application, the type of scaling did not affect the solution of the subset-selection algorithm.
4.1.5 Description of the Estimation Problem

Guided by the results of the subset selection algorithm, we attempted to estimate the well-conditioned parameters using single-cycle waveforms of ABP, CVP, and PAP signals, in both steady-state and transient conditions. We used the built-in Matlab routine, ‘lsqnonlin’, to apply the Gauss-Newton non-linear least squares optimization in an effort to recover the parameters. The rows of the Jacobian were scaled by the target output values and the columns of the Jacobian were scaled by nominal parameter values. As we are interested in judging the performance of the estimation algorithm, we must know the true values of the underlying parameters. We therefore used our computational model to produce synthetic data, which was then treated as “measurements” to which we applied the estimation algorithm.

For the estimation problem using steady-state data, we generated target data using randomized parameters. Each parameter, \( \theta_i \), was perturbed using a Gaussian distribution \( \sim N(\theta_i^0, 10\%\theta_i^0) \), where \( \theta_i^0 \) is the nominal parameter value. In an attempt to investigate the benefit of using subset selection, this target data was used in two different estimation schemes: one in which only the active parameters were estimated while the rest were fixed at their nominal values, and one in which all the parameters were estimated.

Next, we generated transient data by simulating several cases of hemorrhage that lasted for 30 minutes each. The data was generated using randomized parameters (same randomization scheme as before), and each waveform was inserted with additive noise from a Gaussian distribution \( \sim N(0, 1.7\%m_i) \), where \( m_i \) refers to the cycle-average of the waveform. For each hemorrhage case, the active parameters were estimated six times at uniform time intervals.

4.2 Results

4.2.1 Estimation using Steady-State Waveform Data

Table 4.2 summarizes the relative errors incurred in estimating the active parameters from steady-state waveform data under two different estimation formulations:
Table 4.2: Estimation error statistics for the active parameters under two schemes: estimating only the active parameters with the ill-conditioned ones fixed at their nominal values, and estimating all the model parameters.

<table>
<thead>
<tr>
<th>Active parameter</th>
<th>Estimating only the active parameters</th>
<th>Estimating all the parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>St. deviation</td>
</tr>
<tr>
<td>DBV</td>
<td>6.35%</td>
<td>4.77%</td>
</tr>
<tr>
<td>( R_a )</td>
<td>7.38%</td>
<td>5.78%</td>
</tr>
<tr>
<td>( C^{ed}_r )</td>
<td>7.07%</td>
<td>7.11%</td>
</tr>
</tbody>
</table>

- Estimating only the active parameters while the rest are fixed at their nominal values.

- Estimating all the model parameters.

We observe that reducing the dimensionality of the estimation problem improves the mean reliability of the active parameter estimates by more than 50%. Figure 4-2 illustrates the plots of the estimated versus actual well-conditioned parameters for the individual runs of the reduced dimensionality estimation experiment.

The estimation errors that occur when recovering the reduced set of parameters are mainly due to the bias introduced by fixing the values of the ill-conditioned parameters. In an attempt to reduce the error between model output and observed data, the estimation algorithm distorts the active parameter estimates in order to compensate for the fixing of the ill-conditioned parameters. As such, large deviations from nominal value in any ill-conditioned parameter, that has similar effect on model output as any one of the active parameters (or their combination), would lead to significant estimation errors.

In our estimation experiments, large deviations in venous compliance \( (C_v) \) value from its nominal value were seen to lead to significant errors in DBV estimates, indicating that these two parameters affect the model output in a similar fashion. This fact was verified mathematically by analyzing the Jacobian matrix. Recall that the columns of the Jacobian consist of \( \frac{\partial y}{\partial \theta_j} \) (see Equation 4.5), which is a measure of parametric sensitivity for a particular parameter \( \theta_j \). The columns of the Jacobian therefore indicate how the model output changes
in $\mathbb{R}^n$ space in response to changes in parameter values. If any of the columns of the Jacobian are collinear, then the corresponding parameters affect the model output in the same direction within the $\mathbb{R}^n$ space. It turns out that the columns of the Jacobian corresponding to $C_v$ and DBV ($\frac{\partial y}{\partial DBV}, \frac{\partial y}{\partial C_v}$) are almost collinear, with the angle between them being $0.99\pi$ radians. Hence, changes in these two parameter values can have an almost indistinguishable effect on the model output. In fact, a straightforward explanation exists for this observation. For a given venous pressure and DBV, a decrease in $C_v$ would decrease the venous volume and hence would increase the blood volume in the other compartments. Thus, a decrease in
Table 4.3: Estimation error statistics for the active parameters with $C_v$ and $C_{rd}$ fixed at their actual values.

<table>
<thead>
<tr>
<th>Active parameter</th>
<th>Mean</th>
<th>St. deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBV</td>
<td>1.06%</td>
<td>0.66%</td>
</tr>
<tr>
<td>$R_a$</td>
<td>3.14%</td>
<td>1.42%</td>
</tr>
<tr>
<td>$C_{rd}$</td>
<td>4.14%</td>
<td>7.11%</td>
</tr>
</tbody>
</table>

$C_v$ would lead to similar changes in model output as an increase in DBV.

Similarly, poor estimates of $R_a$ and $C_{rd}$ were correlated to large deviations in the left end-diastolic compliance ($C_{rd}$) value from its nominal value. Analysis of the Jacobian revealed that $\frac{\partial y}{\partial C_{rd}}$ almost lies in the plane spanned by $\frac{\partial y}{\partial R_a}$ and $\frac{\partial y}{\partial C_{rd}}$: the angle between $\frac{\partial y}{\partial C_{rd}}$ and its projection on the plane spanned by $\frac{\partial y}{\partial R_a}$ and $\frac{\partial y}{\partial C_{rd}}$ is $0.12\pi$ radians. Thus, deviations in $C_{rd}$ values can somewhat be compensated for by changes in the values of $R_a$ and $C_{rd}$.

To validate our analysis of major contributors of bias, we re-ran our estimation experiments with $C_v$ and $C_{rd}$ fixed at their actual values instead of their nominal ones. Table 4.3 summarizes the estimation errors incurred under this scheme. We observe that the mean estimation error for DBV was reduced by more than 80%, whereas the mean errors for the other two parameters were reduced by more than 40% each. These results confirm our analysis that uncertainties in the values of $C_v$ and $C_{rd}$ can lead to significant errors in estimating the active parameters.

4.2.2 Estimation using Transient Waveform Data (Hemorrhage Data)

In tracking the active parameters through time during a transient, there is an opportunity to overcome some of the bias introduced due to the unknown values of the ill-conditioned parameters. For example, during a hemorrhage, DBV is constantly changing, hence estimating change in DBV rather than actual DBV would remove some of the bias in the estimate. Figure 4-3 illustrates the plot of estimated versus actual change in DBV for all the hemor-
Figure 4-3: Estimated vs actual change in DBV for all the simulated hemorrhage cases analyzed.

Figure 4-4a shows the plot of estimated vs actual $R_a$ for all the hemorrhage cases. As the values of $R_a$ are small, and the values of changes in $R_a$ are even smaller, the numerical errors associated with the estimates of either $R_a$, or changes in $R_a$, are large and unrepresentative of the quality of the estimates. Nevertheless, a strong correlation exists between the estimated and actual values, indicated by their almost linear relationship in the plot. In order to exploit the observed correlation in an attempt to improve the estimation, we performed a first-point calibration. As measures of cardiac output (CO) are occasionally available in the ICU, they can be used in conjunction with the mean ABP and CVP measurements to calculate $R_a$. We assume that for each hemorrhage case, the initial value of peripheral resistance, $R_a^{k,i}$, is known, where $k$ represents an individual hemorrhage case. The ratio of the initial peripheral resistance value to its estimated value is used to determine a gain factor, $g^k$, which scales

\[ g^k = \frac{R_a^{k,i}}{\hat{R}_a^{k,i}} \]

3 Recall that for each hemorrhage case, the active parameters were estimated six times at uniform time intervals.
all subsequent estimates of $R_a$ during the hemorrhage case $k$. This scaling procedure, where the gain factor is constant and calculated based on the first estimate, is known as first-point calibration. Figure 4-4b shows the estimation results for $R_a$ obtained with first-point calibration. The resulting estimation errors are small, with the mean error standing at less than 2%. However, the estimates exhibit a deviating trend from the $y = x$ line, indicating the need for re-calibration as often as possible.

For each hemorrhage simulation, the value of $C_{r}^{ed}$ remained constant and did not change during the hemorrhage, therefore, we were unable to exploit the bias removal techniques used previously for the estimates of DBV and $R_a$. Figure 4-5 illustrates the results for the $C_{r}^{ed}$ estimates. As multiple $C_{r}^{ed}$ estimates were obtained for every case, each value on the plot represents the mean value of the estimates for each case. The estimation errors for $C_{r}^{ed}$ are relatively higher compared to those of DBV and $R_a$, however, the estimates are still quite reasonable, with mean error less than 8.0%.
4.3 Concluding Remarks

In this chapter, we focused on parameter estimation using waveform data. We employed a non-linear least squares optimization technique to recover the model parameters and we used subset selection to improve the conditioning of the problem. We observed that the reduced dimensionality estimation problem improved the reliability of the estimated parameters substantially. Furthermore, the estimation algorithm showed promising results when tested on simulated steady-state and transient data.
Chapter 5

Parameter Tracking using Beat-to-Beat Averaged Data

In the previous chapter, we investigated the use of subset selection to reduce the dimensionality of the estimation problem. The reduced dimensionality problem increased the reliability of the estimated parameters and outperformed the full-fledged estimation of all the model parameters. In this chapter, we focus on another method of dimensionality reduction which results from a simplifying assumption.

Depending on the disease condition, only a selected few parameters change in time as the disease state progresses. In this case, it is not required to estimate all the parameter values; estimating only the disease-dependent, physiologically significant parameters would suffice to reveal information about patient state. If we assume prior knowledge of initial parameter values, we need to track only the physiologically significant parameters in time, and thus the dimensionality of the estimation problem is reduced.

We carry out our investigation in the context of a real patient hemorrhage case. As we are interested in tracking parameters over transients spanning long periods of time, we use beat-to-beat averaged data for estimation instead of waveform data. The averaged data sufficiently represents long-term transients, and hence it is not necessary to use the high-resolution waveform data. Though we are using a pulsatile computational model, the model
output can be averaged to represent beat-to-beat trend data.

We begin by providing a brief patient history and description of the data available. Next, we outline the estimation algorithm and highlight some issues faced during parameter estimation. Subsequently, we present the results of the algorithm and provide concluding remarks.

5.1 Brief Patient History

The patient is an 83 year old female who was admitted to the ICU after falling at her nursing home. She complained of pains in her left knee and hip; an x-ray revealed that she had a loose acetabular shell and possibly a loose femoral head. As the patient was on anticoagulants due to a previous aortic valve replacement, it was decided not to take any immediate surgical action, but wait for the anticoagulant effects to wear off.

During the waiting period, the patient suddenly developed pain in her lower right abdomen. Upon further examination, a 6x6 cm mass was found in the right abdomen caused by a lumbar artery bleed. The patient was then transferred to interventional radiology where the bleed was embolized. After the embolization procedure, the patient was returned to the ICU where she made a full recovery with the help of fluid resuscitation and vasoactive drugs.

5.2 Patient Data for Parameter Tracking

For purposes of parameter tracking, we consider a time-period of approximately 50 minutes pre-embolization when the patient vital statistics displayed some interesting characteristics. Figure 5-1 shows a plot of the patient heart rate and blood pressure during that period. The heart rate stays relatively constant at around 130 beats/min, indicating that the control system may have saturated, while the blood pressure goes through significant transients.

The only other relevant information available for this time-period consists of clinical intervention data regarding medication and fluid resuscitation. This information is necessary for determining the causes for the observed changes in patient state, however, it may lack
Figure 5-1: Heart rate (upper panel) and arterial blood pressure (lower panel) patient data.

time accuracy. Information regarding changes in medication and their doses is usually hand-recorded afterwards, using approximate, rounded-off time-stamps. Therefore, the times at which the changes actually occur may differ from the recorded ones. Moreover, fluid resuscitation information is only recorded on an hourly basis, hence the exact time of a fluid bolus administration is not available. Furthermore, hand-recorded information is often prone to errors and omissions. Figure 5-2 shows the time-series plot of a vasopressor drug called Levophed (the beat-to-beat averaged ABP data is also shown so that the medication data can be put into perspective). Vasopressors serve to increase blood pressure by constricting the arterioles. Levophed was the only drug whose dosage changed during this time period. The doses of the rest of the administered drugs remained constant not only within this time-period, but also in its neighborhood; hence those medications were not considered to be significant contributing factors to the patient’s physiology for this time portion. Although there are no recorded fluid boluses administered during this time-period, our in-house medical experts believe that to be a recording artifact. Expert medical opinion suggests that rises in blood pressure at around \( t = 1000 \) s, and again at around \( t = 1100 \) s, are results of
5.3 Simulating Patient Data

Given anthropometric measurements of a patient, allometric scaling can be applied to nominal parameter values to obtain a set of parameters that are more representative of a particular individual [5]. However, anthropometric measurements for this patient were not available,
hence, we used nominal values for all parameters except heart rate and distending blood volume (DBV). The patient heart rate data is available (see Figure 5-1) and is considered to be relatively constant, therefore, the heart rate parameter was fixed at 130 beats/min in our simulation. As this is a case of hemorrhage, we reduced the initial DBV until the simulator output matched the initial patient ABP data.

The model used to simulate patient data included a leak on the arterial side to model bleeding, and it had capabilities to incorporate a time-varying peripheral resistance ($R_a$). These changes add two new parameters to the model: bleeding rate and rate of change of $R_a$. To capture the dynamics displayed by blood pressure data, we modified bleeding rate and rate of change of $R_a$ following some reasonable assumptions based on the patient pathology and nurse’s notes. The changes in $R_a$ were guided by Levophed medication; whenever Levophed dose went down, we reduced $R_a$ and vice versa. The partial recoveries in blood pressure at times $t=1000$ s and $t=1100$ s were simulated by administering fluid boluses. Figure 5-3 shows a plot of simulated and actual beat-to-beat averaged blood pressure data. The simulated plot has regions marked 1-10 which correspond to the following actions taken to simulate them:

1) $0 - 500$ s: Bled @ 0.76 mL/s.

2) $500 - 700$ s: Bled @ 0.76 mL/s + $R_a$ ramped down from 1.1 to 0.8 PRU.

3) $700 - 1010$ s: Bled @ 0.76 mL/s.

4) $1010 - 1040$ s: Bled @ 0.76 mL/s + Bolus of 470 mL administered as a ramp function.

5) $1040 - 1100$ s: Bled @ 0.6 mL/s.

6) $1100 - 1120$ s: Bled @ 0.6 mL/s + Bolus of 570 mL administered as a ramp function.

7) $1120 - 1500$ s: Bled @ 0.85 mL/s + $R_a$ ramped down from 0.8 to 0.65 PRU.

\footnote{It was taken into account that the time recordings for Levophed doses may lag behind the actual times. For example, the effects of recorded dose changes at around $t=1400$ s, and again at around $t=2300$ s, seem to occur prior to the recorded times, indicating that the medication recordings may have followed the actual times at which the changes occurred. See Appendix C for an attempt to validate the assumptions made regarding changes in peripheral resistance.}

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Figure 5-3: Simulated beat-to-beat averaged ABP data (top panel) and actual patient ABP data (bottom panel).

8) 1500 – 2200s: Bled @ 0.6 mL/s.

9) 2200 – 2250s: Bled @ 0.25 mL/s + $R_a$ ramped up from 0.65 to 0.95 PRU.

10) 2250 – 3000s: Bled @ 0.25 mL/s + $R_a$ ramped up from 0.95 to 1.2 PRU.

The simulated ABP data follows the transients exhibited by the real patient data reasonably well. Next, we added noise to each simulated point using a Gaussian distribution, $\sim N(0, 2\% p_i)$, where $p_i$ refers to the $i^{th}$ point. Figure 5-4 shows a plot of the noise-corrupted simulated ABP data and the actual patient data. We observe that the noisy simulated data closely follows the real patient data, and therefore the simulated data is said to be representative of the actual. Henceforth, the simulated data will be referred to as pseudo-patient data.

Having matched the patient data, we assume knowledge of the initial patient state and
we attempt to estimate and track certain parameters of physiological interest.

5.4 Parameter Tracking

As the bleeding rate and rate of change of \( R_a \) are responsible for the pathology of the patient, we track these two parameters in time. We assume that the initial patient state is known, which includes the initial values of all the parameters and state variables \(^2\). To estimate and track the parameters in time, the pseudo-patient ABP data is divided into non-overlapping, 100s windows which are used to recover the two parameters using the Gauss-Newton non-linear least squares optimization technique. In addition to estimating the two parameters of interest, the initial conditions for all the frames, except the initial one, need to be estimated. In order to estimate the initial conditions for the current frame, we run the model for the time duration of a frame using the parameter estimates and initial conditions of the previous

\(^2\)For the start of the simulation, the initial state variables are determined by the initial parameter values using Equations 2.18 - 2.25.
frame. The end-diastolic conditions for the last beat in this simulation are then used as initial conditions for the current frame. As the fluid boluses administered are assumed to be known quantities, the volume changes are accounted for when estimating the parameters during the times of fluid resuscitation.

First, we employed this algorithm on noise-free pseudo-patient data so that any issues with the estimation formulation can be easily identified. We encountered two issues with this estimation scheme which are elaborated on next.

**Choice of Observable Data** It turns out that bleeding rate and rate of change of $R_a$ have similar effects on ABP data. In fact, the angle between the Jacobian columns corresponding to these two parameters is $0.067\pi$ radians, indicating that they are almost collinear. Thus, using only ABP data for estimation leads to a degeneracy in the system as the two parameter estimates can be distorted without affecting the error criterion. To overcome this problem, we assume that the pseudo-patient central-venous pressure (CVP) is also observable and can be used to estimate the parameters in conjunction with ABP data. Figure 5-5 illustrates the plot of the noise-free, pseudo-patient beat-to-beat averaged CVP data. Including the use of CVP for parameter recovery empowers the estimation algorithm with greater discerning ability as the two parameters tend to affect ABP and CVP differently. For example, an increase in $R_a$ near the end of the time-period causes ABP to increase, whereas CVP still decreases.

**Estimating the Initial Conditions** Under the scheme described to estimate initial conditions, the end-diastolic conditions of the last beat in the previous frame are used as initial conditions for the current frame. This method ignores the effects of the intra-beat dynamics which occur within the last beat of the previous frame. Though the intra-beat dynamics last for only a very short-period of time, ignoring their effects caused severe distortion in the parameter estimates. Moreover, as the parameter estimates for the current frame depend on the estimates of the previous frame, any error incurred propagates and builds up.

\(^3\)The simulator expects initial conditions to be end-diastolic.
Consider the frames during which fluid resuscitation takes place. Estimating a frame's initial conditions using the proposed methodology ignores the volume of fluid that is administered for the duration of a beat. Figure 5-6 illustrates this problem diagrammatically. Neglecting the volume administered within a beat leads to significant estimation errors which build up in subsequent frames. Figure 5-7a shows a portion of data that corresponds to a frame which follows the end of fluid administration. The plot also shows the reconstruction of the same data portion using exact parameter values and estimated initial conditions which neglect the volume of fluid administered during the last beat of the previous frame. We observe that there is a mismatch between the data and its reconstruction which causes the estimation algorithm to distort the parameters in an attempt to better match the pseudo-patient data.

To overcome this problem, we included ABP and CVP initial condition estimation in the non-linear least squares problem, while the initial conditions for the rest of the state-variables were estimated as described before. Estimating the initial conditions of the observable state-variables using non-linear least squares, instead of simply using previous beat values, allows
for the incorporation of intra-beat dynamics to some extent. Figure 5-7b shows the same portion of data as Figure 5-7a, along with its reconstructed version using exact parameter values and the estimated initial conditions using the updated scheme. We observe that the two plots are almost indistinguishable, indicating that the updated scheme performs better.

After updating our choice of observable output by including the use of CVP data for estimation, and after improving the method of estimating initial conditions by incorporating two of them in the non-linear least squares formulation, we employed the estimation algorithm on noise-corrupted pseudo-patient data. Next, we present the results of the estimation algorithm.

### 5.5 Results

Figure 5-8 shows the plot of the estimated parameters versus the actual ones. The algorithm does a reasonably good job in recovering and tracking the bleeding rate and rate of change of $R_a$, with mean estimation error less than 6% for either case. In fact, the error distributions are statistically indifferent from a 0 mean distribution with a significance level $\alpha = 0.05$, with a $P$-value of 0.77 for the bleeding rate error, and a $P$-value of 0.6 for the error associated
Beat-to-beat averaged ABP data

85 - 85 --
84.5 - 84.5 --
84 - 84--
83.5 - 83.5 --
83 - 83-
82.5 - 
Pseudo-patient 82.5 -
Reconstructed version using exact parameters and estimated initial conditions 82
81.5 81.5 *
Pseudo-patient
Reconstructed version using exact parameters and estimated initial conditions

(a) Estimating the initial conditions by running the simulation for the previous time-frame.
(b) Estimating ABP and CVP initial conditions through non-linear least squares.

Figure 5-7: Plot showing portion of ABP data following a fluid bolus and its reconstructed version using exact parameters and estimated initial conditions using two different schemes.

with estimating rate of change of $R_a$.

5.6 Concluding Remarks

In this chapter, we investigated the viability of tracking selected model parameters of physiological interest in time, assuming knowledge of initial values of the parameters. We used synthetic data that was representative of a real case of hemorrhage to track bleeding rate and rate of change of $R_a$. Our simulations show promising results for dynamically tracking selected parameters of interest. This can be of great value to patient monitoring as the time evolution of these parameters would reveal information about disease progression.
Estimated vs actual bleeding rate

Mean estimation error: 2.96% 
St. deviation of estimation error: 3.46%

Estimated vs actual rate of change of R.

Mean estimation error: 5.71% 
St. deviation of estimation error: 10.31%

Figure 5-8: Estimated versus actual parameters.
Chapter 6

Conclusions and Recommendations for Future Work

In this thesis, we explored model-based quantitative methods of estimating selected cardiovascular parameters over time. Tracking the time evolution of the parameters would reveal information about disease progression and hence it can be very useful for patient monitoring purposes. Our effort was divided into two parts: constructing a computational model, and using it for investigating parameter estimation techniques.

In this chapter, we summarize our efforts and results, after which we suggest directions for future work.

6.1 Summary

In Chapter 2, we outlined and detailed the implementation of a pulsatile cardiovascular model based on Davis's CVSIM model [4]. We built the model in Simulink which is a strong tool for implementing dynamic systems. The abstraction provided by the building-blocks, and the built-in functions and routines, make the extension of the model relatively simple, which is of great value in simulating various disease conditions. Furthermore, we enhanced the functionality of the CVSIM model by adding an interstitial fluid compartment. The role
of the interstitial compartment becomes significant during transients resulting from disease conditions or clinical interventions which cause volume shifts between the intravascular and interstitial spaces. Our model implementation was validated based on analysis of the intra- and inter-cycle dynamics.

In Chapter 3, we described the implementation of the arterial-baroreflex which is a principal component of short-term, neurally mediated control. Our implementation of the control system was based on Davis's extension of deBoer's work [4, 23]. The arterial-baroreflex is modeled as a set-point controller which senses the blood pressure and responds to the error signal, which is the deviation of the sensed pressure from the set-point. In order to reduce the error signal, the arterial-baroreflex controls sympathetic and parasympathetic activity, which in turn affects zero-pressure venous volume, heart rate, ventricular contractility, and peripheral resistance. Previous implementations of the arterial-baroreflex used relatively coarse time-steps for the control system as compared to the rest of the model. However, as such implementations lead to aliasing effects, we implemented the control system in continuous-time. Furthermore, as parasympathetic dynamics last for only a fraction of a heart beat, they do not significantly affect the model output, therefore, we simplified the parasympathetic block implementation to a simple gain. Our implementation of the short-term control system was qualitatively validated based on responses to simulated conditions of hemorrhage and myocardial infarction.

In Chapter 4, we turned our attention to parameter estimation. We used a non-linear least squares optimization technique to estimate cardiovascular parameters based on waveform data that is continuously available in an ICU setting. We highlighted the problem associated with an ill-conditioned Hessian matrix and subsequently we outlined the subset-selection algorithm that improves the Hessian conditioning by reducing the dimensionality of the estimation problem. The subset selection algorithm identifies a subset of parameters that can be estimated robustly, while the rest are fixed at their nominal values. Our simulations show promising results for estimating well-conditioned parameters using both steady-state and transient data.
In chapter 5, we explored the viability of tracking selected parameters of physiological interest using beat-to-beat averaged data, assuming prior knowledge of initial parameter values. Our investigation was based on a real patient hemorrhage case where we tracked the bleeding rate and rate of change of peripheral resistance. As the patient data available was not sufficient to determine the actual parameter values, we used our model to match the patient data, and then we used the simulated data for estimation so that the performance of the estimation algorithm could be judged quantitatively. The results of Chapter 5 are encouraging as we were able to track successfully the two parameters of physiological significance.

6.2 Recommendations for Future Work

In conducting our research efforts, we identified the following directions for further work:

**Parameter Estimation**  In Chapter 4, our optimization technique was constrained to use the entire single-cycle waveforms of ABP, CVP, and PAP to estimate the cardiovascular parameters. We followed a ‘*more is better*’ approach and did not analyze the structure of the Jacobian to determine if some signals, or sections thereof, are more suitable to recover certain parameters over others. Further investigation needs to be conducted on the relationship between quality of parameter estimates and the number, type, and section (eg systolic or diastolic) of signals used for estimation.

So far we have only applied the estimation algorithms on synthetic data as real patient data with a sufficient number of observable signals was not available. To validate the reliability of the algorithms, it is necessary to apply them on real data. In order to do so, we need patient data with ABP, CVP, and PAP waveform recordings. Supplementary recordings, such as cardiac output, would be helpful as they would play a role in judging the quality of some of the estimates.
Estimating the Initial Values of the Parameters  In Chapter 5, we assumed knowledge of the initial values of the parameters and we tracked two of the physiologically relevant ones using ABP and CVP signals that are continuously available in an ICU setting. In estimating the initial values of the parameters, however, we are not limited by the data streams that are available constantly - we can use all the available data, including cardiac output, left-ventricular end-diastolic pressure, imaging studies, etc. to estimate the initial values. Zhao developed a set of heuristic algorithms that used steady-state data to estimate the parameters [14]. Further investigation should focus on developing quantitative methods that use all available information to determine the initial values of the parameters in transient conditions.

Cycle-Averaged Models  Transients spanning long periods of time are sufficiently represented by trend data, which includes beat-to-beat averages. In such cases, the high-resolution waveform data is not necessary for analysis. We would expect the models that ignore the fine intra-beat dynamics and produce only cycle-averages to be more computationally efficient and relatively simple in structure as compared to the pulsatile models. Such models could be very useful in inverse-modeling studies where the simplicity in their structure can be exploited to recover the underlying parameters. Development of cycle-averaged models is a subject of ongoing research in our group. Simple cycle-averaged models consisting of a single heart chamber, which consider the time-varying ventricular elastance function to be either a step function, or a piecewise linear function, have already been developed [29, 30]. Current focus is now on extending the cycle-averaged model to include two heart chambers and a control system.

Knowledge-Based Systems  Robust algorithms that reliably estimate cardiovascular parameters using real patient data can be integrated with knowledge-based systems to aid in patient monitoring. The knowledge-based systems can be trained to interpret the physiological significance of parameter values, and using the estimates, they can help in generating hypotheses regarding patient state, track patient trajectory, and generate alarms bases on
physiologically significant events.
Appendix A

Updated CVSIM Model Equations

Figure A-1 shows the circuit analog of the updated CVSIM model with the interstitial compartment. Applying Kirchoff’s Current Law (KCL) to the circuit topology of the model, the following set of equations is obtained:

\[
\begin{align*}
\frac{dP_t}{dt} &= \frac{q_i - q_o - (P_t - P_{th}) \cdot dC_i(t)/dt}{C_i(t)} \quad \text{(A.1)} \\
\frac{dP_a}{dt} &= \frac{\dot{q}_o - \dot{q}_a}{C_a} \quad \text{(A.2)} \\
\frac{dP_v}{dt} &= \frac{\dot{q}_a - \dot{q}_{int} - \dot{q}_{ri}}{C_v} \quad \text{(A.3)} \\
\frac{dP_{int}}{dt} &= \frac{\dot{q}_{int}}{C_{int}} \quad \text{(A.4)} \\
\frac{dP_r}{dt} &= \frac{\dot{q}_r - \dot{q}_{ro} - (P_r - P_{th}) \cdot dC_r(t)/dt}{C_r(t)} \quad \text{(A.5)} \\
\frac{dP_{pa}}{dt} &= \frac{\dot{q}_{ro} - \dot{q}_{pa}}{C_{pa}} \quad \text{(A.6)} \\
\frac{dP_{pv}}{dt} &= \frac{\dot{q}_{pa} - \dot{q}_{ti}}{C_{pv}} \quad \text{(A.7)}
\end{align*}
\]
Figure A-1: Circuit analog of the updated CVSIM model.

The compartmental flow rates are obtained through the application of Ohm’s Law:

\[
\begin{align*}
\dot{q}_{ri} &= \begin{cases} 
\frac{P_{pa} - P_r}{R_{ri}} & \text{if } P_{pa} > P_r \\
0 & \text{otherwise}
\end{cases} \\
\dot{q}_{lo} &= \begin{cases} 
\frac{P_a - P_{int}}{R_{lo}} & \text{if } P_l > P_a \\
0 & \text{otherwise}
\end{cases} \\
\dot{q}_{a} &= \frac{P_a - P_v}{R_a} \\
\dot{q}_{int} &= \frac{P_v - P_{int}}{R_{int}} \\
\dot{q}_{ri} &= \begin{cases} 
\frac{P_a - P_{in}}{R_{ri}} & \text{if } P_{in} > P_r \\
0 & \text{otherwise}
\end{cases} \\
\dot{q}_{ro} &= \begin{cases} 
\frac{P_r - P_{pa}}{R_{ro}} & \text{if } P_r > P_{pa} \\
0 & \text{otherwise}
\end{cases} \\
\dot{q}_{pa} &= \frac{P_{pa} - P_{pv}}{R_{pv}}
\end{align*}
\]
The initial conditions for all the compartments except the interstitial compartment are calculated using Equations 2.18 - 2.25. As no net exchange of volume takes place between the intravascular and the interstitial spaces in steady-state, the initial interstitial compartment pressure is set equal to the initial venous pressure.
Appendix B

Independent Parameters of the CVSIM Model
Table B.1: Independent Parameters of the CVSIM Model (adapted from Heldt [5]).

<table>
<thead>
<tr>
<th>Description</th>
<th>Symbol</th>
<th>Unit</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left end-systolic elastance</td>
<td>$E_{es}^L$</td>
<td>mmHg/mL</td>
<td>2.5 ± 0.6</td>
</tr>
<tr>
<td>Left end-diastolic elastance</td>
<td>$E_{ed}^L$</td>
<td>mmHg/mL</td>
<td>0.1 ± 0.015</td>
</tr>
<tr>
<td>Right end-systolic elastance</td>
<td>$E_{es}^R$</td>
<td>mmHg/mL</td>
<td>0.83 ± 0.51</td>
</tr>
<tr>
<td>Right end-diastolic elastance</td>
<td>$E_{ed}^R$</td>
<td>mmHg/mL</td>
<td>0.1 ± 0.043</td>
</tr>
<tr>
<td>Left inflow resistance</td>
<td>$R_{il}$</td>
<td>PRU</td>
<td>0.01 ± 0.005</td>
</tr>
<tr>
<td>Left outflow resistance</td>
<td>$R_{lo}$</td>
<td>PRU</td>
<td>0.006 ± 0.0017</td>
</tr>
<tr>
<td>Right inflow resistance</td>
<td>$R_{ri}$</td>
<td>PRU</td>
<td>0.01 ± 0.005</td>
</tr>
<tr>
<td>Right outflow resistance</td>
<td>$R_{ro}$</td>
<td>PRU</td>
<td>0.003 ± 0.0015</td>
</tr>
<tr>
<td>Peripheral resistance</td>
<td>$R_a$</td>
<td>PRU</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>Pulmonary venous resistance</td>
<td>$R_{pv}$</td>
<td>PRU</td>
<td>0.08 ± 0.0457</td>
</tr>
<tr>
<td>Arterial compliance</td>
<td>$C_a$</td>
<td>mL/mmHg</td>
<td>1.6 ± 0.3</td>
</tr>
<tr>
<td>Venous compliance</td>
<td>$C_v$</td>
<td>mL/mmHg</td>
<td>100 ± 15</td>
</tr>
<tr>
<td>Pulmonary venous compliance</td>
<td>$C_{pv}$</td>
<td>mL/mmHg</td>
<td>8.4 ± 2.8</td>
</tr>
<tr>
<td>Pulmonary arterial compliance</td>
<td>$C_{pa}$</td>
<td>mL/mmHg</td>
<td>4.3 ± 1.77</td>
</tr>
<tr>
<td>Distending blood volume</td>
<td>DBV</td>
<td>mL</td>
<td>1175 ± 138</td>
</tr>
</tbody>
</table>
Appendix C

Peripheral Resistance Estimation based on Patient Data

In simulating the patient data in Chapter 5, we made certain assumptions regarding how peripheral resistance ($R_a$) changes based on the ABP patient data and based on recorded changes in doses of Levophed. In this section, we use the Windkessel model of arterial dynamics to estimate $R_a$ using the patient ABP data in an attempt to validate our assumptions a posteriori.

C.1 Assumptions on Changes in Peripheral Resistance

Figure C-1 shows a time-series plot of the patient beat-to-beat averaged ABP data and of the Levophed medication. Based on this information, we made the following assumptions regarding changes in $R_a$:

- At 500 s, we assumed $R_a$ starts to drop as it is preceded by a recorded reduction in Levophed dose, the effect of which is observed when the patient’s ABP drops soon after. We continued to reduce $R_a$ till 700 s when ABP stopped to drop as rapidly as before.

- As the patient’s ABP drops rapidly starting at 1120s, with a subsequent recorded
Beat-to-beat averaged patient ABP data

Figure C-1: Beat-to-beat averaged patient ABP data (top panel) and Levophed medication (bottom panel).

reduction in Levophed dose, we hypothesized a further drop in $R_a$ starting at 1120s and ending at 1500s. The discrepancy between the time ABP starts to drop and the recorded time at which the Levophed dose changes can be attributed to a recording artifact.

- An increase in ABP starting at 2200s and a subsequent increase in Levophed dose led us to hypothesize an increase in $R_a$ starting at 2200s. The time difference between the Levophed dose change and the point at which ABP starts to increase can again be attributed to a recording artifact.

C.2 Peripheral Resistance Estimation using the Windkessel Model

The Windkessel model is a simple three-element circuit model of arterial dynamics. Figure C-2 shows the circuit analog of the Windkessel model. The current source, which drives
the circuit with impulses, represents the pumping heart, ejecting blood into the circulation instantaneously. The resistor represents the peripheral resistance whereas the capacitance models the arterial compliance ($C_a$).

Through the application of circuit theory, it can be shown that pulse pressure ($PP$) is proportional to stroke-volume, with the constant of proportionality being the arterial compliance.

The blood pressure data can therefore be used to calculate $R_a$ in the following manner:

$$R_a = 60 \cdot \frac{\overline{ABP}}{PP \cdot HR \cdot C_a}$$

where $\overline{ABP}$ refers to beat-to-beat averaged ABP and HR represents the heart rate. A quantity proportional to $R_a$ can be obtained as $C_a$ is constant in the Windkessel model:

$$R_a \sim 60 \cdot \frac{\overline{ABP}}{PP \cdot HR}$$

This quantity can be used as a relative estimate of $R_a$, which we shall refer to as the Windkessel estimate.

Figure C-3 shows a plot of the Windkessel $R_a$ estimate using the patient ABP data. The plots of the patient ABP data and Levophed medication are also shown. The Windkessel $R_a$ estimate behaves exactly opposite to our intuition. Whenever ABP decreases, along with
the Levophed dose, the Windkessel estimate of $R_a$ increases and vice-versa. One possible explanation for this behavior is the intervention by the control system. Whenever ABP decreases, the control system intervenes to increase ABP and therefore increases $R_a$. However, it must be taken into account that the derived estimate of $R_a$ assumed a constant $C_a$, whereas physiologically, $C_a$ exhibits a non-linear volume-pressure relationship [31].

Based on an arctangent model of aortic mechanics, Langewouters and co-workers [32] proposed a method of calculating $C_a$ which incorporates the non-linear behavior:

$$C_a = \frac{A_{max}/\pi P_1}{1 + \left(\frac{P_a}{P_1}\right)^2} \quad \text{(C.1)}$$

here $P_a$ refers to arterial blood pressure. $A_{max}$, $P_0$, and $P_1$ are constants denoting the maximum thoracic aortic cross-sectional area, inflection point of pressure, and width-parameter respectively. These constants are derived from aortic pressure-area relationships. Through population studies, Wesseling and co-workers [33] determined the values of these constants.
based on gender and age. We applied Equation C.1 to our patient data to obtain $C_a$ that varies non-linearly with ABP. The calculated $C_a$ was then incorporated into the Windkessel model to obtain the updated Windkessel $R_a$ estimate that takes the $C_a$ non-linearity into account.

Figure C-4 shows the updated Windkessel $R_a$ estimate. The updated estimate overlaps to some degree with our assumptions. The decrease in $R_a$ that we assumed from 500 – 700s is present in the updated estimate, so is the increase in $R_a$ that we assumed from 2200s onwards. However, the starting points of these changes are not aligned with our assumptions. We hypothesized a decrease in $R_a$ from 500s, whereas in the updated estimate $R_a$ decreases from the start. A similar starting-point mismatch is observed for the increase in $R_a$ that we assumed started at 2200s. Moreover, the updated estimate shows an increase in $R_a$ during the times of bolus administration. We are not quite sure as to why the estimate is showing an

---

1The calculation of the non-linear $C_a$ was provided to us courtesy James Sun, who also introduced us to the work of Langewouters and Wesseling [32, 33].
increase in $R_a$ in that region. Ignoring the region of bolus administration and the subsequent recorded drop in Levophed dose, and assuming long time-lags exist to record the changes in medication, we can somewhat correlate the changes in the updated $R_a$ estimate to the Levophed medication. The decrease in the estimated $R_a$ from the start can be caused by the decrease in Levophed dose which is recorded at approximately 500s. Similarly, the increase in $R_a$ which starts at approximately 1300s can be related to the increase in Levophed dose which is recorded at approximately 2250s, however, this lag of more than 15 minutes is slightly long to be attributed to a recording artifact, but it is possible.

C.3 Concluding Remarks

In this section, we used the Windkessel model to estimate $R_a$ for the patient case we considered in Chapter 5. The idea was to use a simple arterial side model to estimate $R_a$ using actual patient data in an attempt to validate the assumptions we made when simulating the patient. The Windkessel $R_a$ estimate turned out to exhibit exactly the opposite behavior to our assumptions. However, the Windkessel estimate itself is not very reliable as it makes several simplifying assumptions including instantaneous ejection and constant $C_a$. To incorporate the non-linear $C_a$ into the Windkessel estimate, we used a method proposed by Langewouters and co-workers [32]. The updated $R_a$ estimate had some overlap with our assumptions and was seen to be somewhat correlated to the changes in Levophed medication. However, the updated estimate did exhibit some inexplicable behavior in the region of bolus administration.

The analysis performed in this section serves to show the difficulty in estimating $R_a$ using only ABP data. Given only ABP data, we are limited to using simple arterial side models that make several simplifying assumptions and ignore important components with which the arterial side interacts, such as the venous compartment. Thus, such models are not very representative of the underlying physiology and can lead to misleading results. One simple solution to this problem is increased cardiac output recordings in the ICU setting which can be used to calculate $R_a$. 100
Bibliography


