EXTRACTING NEW INFORMATION FROM THE SHAPE OF THE BLOOD PRESSURE PULSE

by

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Abstract

Clinically, the most frequently used indices of cardiovascular performance are heart rate, stroke volume, cardiac output, and blood pressure. Virtually no quantitative information from the shape of the blood pressure pulse is ever used. This thesis addresses the issue of extracting clinically useful information from the shape of the diastolic portion of the blood pressure. A simple third-order, lumped parameter circuit model has been proposed to characterize the wave shape changes in terms of the mechanical features of the systemic arterial system. An attempt to validate the model was made using an independent measure of flow in the radial artery, but the measured results were suspect. However, the model has been used to study the response of five subjects to the Valsalva maneuver. The model attributed the changes in wave shape during the maneuver primarily to changes in peripheral vascular resistance and distal compliance. Furthermore, the onset of the increased resistance occurred consistently 5–7 seconds after the increase in intrathoracic pressure. As this application illustrates, the model has the potential to become a clinically useful tool because it may allow the clinician to monitor changes in peripheral resistance using only the blood pressure waveform.

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Chapter 1

Introduction

A serious athlete often evaluates the effectiveness of his training by monitoring his pulse rate. A clinician measures a patient's systolic and diastolic blood pressure in the brachial artery by listening for the Korotkoff sounds. These are common ways in which non-invasive measurements give us important information about cardiovascular function. The information gained from the above techniques is rather limited. However, with the development of new pressure transducers and computers, there is a greater prospect of extracting even more information about the cardiovascular system from simple, non-invasive measurements.

Clinically, the most frequently used indices of cardiovascular performance are heart rate, cardiac output, stroke volume, and blood pressure. Virtually no quantitative information from the shape of the blood pressure pulse is ever used. If the changes in the wave shape become better understood, clinically important parameters might be extracted from the blood pressure pulse. For example, the changes in the blood pressure waveform that occur with some pathophysiological condition like cardiomyopathy or arteriosclerosis might be recorded and used in the future to monitor the progress made through treatment. The analysis of the radial artery blood pressure waveform might also provide valuable information about age-related changes in the cardiovascular system. Finally, wave shape analysis might be used to study the dynamic nature of the cardiovascular control system. Under controlled cardiovascular stresses, for instance, it might be possible to monitor and quantify the response of the cardiovascular control mechanisms—in particular, beat-by-beat changes in peripheral
resistance.

The general goal of this thesis is to determine what useful information about the dynamics of the cardiovascular system can be extracted from the shape of the radial artery blood pressure pulse. This project has been divided into three tasks.

1. Develop a model to account for the major features of the blood pressure wave shape in the radial artery.

2. Validate the model.

3. Perform an experiment using this model to extract information about the systemic arterial system.

In this project the radial blood pressure will be measured using a new instrument that is based on arterial tonometry, a method of continuous, non-invasive measurement of the arterial blood pressure (Appendix B).

1.1 Blood Pressure Wave Shape

The blood pressure pulse that originates in the aorta undergoes a number of changes as it propagates through the arterial system. In this section two different types of wave shape changes are discussed—changes in wave shape with anatomy and changes in wave shape with cardiovascular stress. The anatomical wave shape changes are described first, and then the changes that accompany cardiovascular stress are discussed.

1.1.1 Anatomical Wave Shape Changes

The behavior of the blood pressure in the aorta and the large elastic arteries is often modeled by the windkessel model, a parallel RC circuit (Section 2.3). In this model the heart is represented by a current source which supplies a bolus of blood to the systemic arterial system. The effects of the arterioles and capillaries, the peripheral circulation, are lumped together as a resistance $R$, and the arteries are modeled by a single lumped capacitance $C$, a measure of the distensibility of the arteries. The model
Figure 1.1: Changes in the blood pressure waveform as a function of distance from the heart. (From McDonald, D. A., Blood Flow in Arteries, 2nd ed., Williams & Wilkins, Baltimore, 1974, p. 332.)
predicts that the arterial blood pressure decays exponentially with a time constant $RC$ during diastole. This response can be compared with the aortic blood pressure in Figure 1.1 during diastole.

Although the decay in the aortic blood pressure during diastole can be approximated by a decaying exponential, the blood pressure waveform observed in the distal arteries shows that such an approximation is no longer entirely valid (Figure 1.1). The changes in the shape of the blood pressure pulse as it travels from the aorta to the distal arteries are related to a number of important anatomical changes in the arteries. The first notable change is that the number of arteries greatly increases further from the heart. The large elastic arteries close to the heart branch into other arteries, each of which also branches several times. These branches, or bifurcations, are potential sites for reflections of the blood pressure pulse. The arteries are also tapered. The diameter of the arteries gradually decreases with increasing distance from the heart. Furthermore, the mechanical properties of the arteries also undergo significant change. Close to the heart the arteries are large and elastic, but they gradually become stiffer and more muscular further from the heart.

Figure 1.1 illustrates the changes that take place in the shape of the blood pressure pulse further from the heart. Some of these changes include:

1. The high frequency components of the blood pressure pulse become attenuated. Notice in particular that the dicrotic notch gradually disappears.

2. A number of changes occur in the systolic portion of the waveform. The systolic upstroke becomes steeper, the maximum pressure increases, and the systolic portion of the pulse becomes narrower.

3. A hump appears on the diastolic wave of the blood pressure pulse.

1.1.2 Dynamic Wave Shape Changes

As discussed above, a number of wave shape changes take place as the blood pressure pulse propagates through the arteries. The extent to which the shape of the blood pressure pulse changes depends directly on the properties of the arterial system.
Figure 1.2: Comparison of blood pressure wave shape changes during a Valsalva maneuver. A. Control—Subject at rest just before the Valsalva maneuver. B. During Valsalva maneuver—blood pressure wave shape about 10 seconds after the increase in intrathoracic pressure.
In other words, the blood pressure pulse observed in some distal artery contains information about the arteries and peripheral vascular resistance.

During a cardiovascular stress the cardiovascular system may change the mechanical properties of the blood vessels. For example, peripheral resistance and venous tone are dynamically modulated by the autonomic nervous system. The blood pressure wave shape will, in general, change during such alterations in the mechanical properties of the blood vessels. Figure 1.2 shows the extent to which the wave shape can change during a particular cardiovascular stress, known as the Valsalva maneuver (Section 4.1.1).

1.2 Outline of Thesis

This thesis is concerned with changes in the shape of the radial artery blood pressure pulse. The first part of this project is to propose an explanation in the form of a model for the wave shape changes discussed above. Once a particular explanation, or model, has been developed, the model must be validated, and the usefulness of the information derived from the model must be evaluated. The organization of the thesis is as follows:

- Chapter 2: The properties of the systemic arteries and the mechanisms behind the anatomically-related wave shape changes are discussed. Then, some of the approaches used to model various aspects of the cardiovascular system are reviewed.

- Chapter 3: A model is proposed to account for the major features of the blood pressure wave shape.

- Chapter 4: The mathematical and physiological methods used in this thesis are discussed.

- Chapter 5: The results from the parameter estimation and model validation are presented.
• Chapter 6: The conclusions are discussed along with some possible areas for future work.
Chapter 2

The Systemic Arterial System

During each contraction of the heart, a volume of blood is ejected into the aorta resulting in a blood pressure wave that propagates through the systemic arterial system. As the blood pressure pulse travels down the aorta and through its branches, a number of changes take place in the wave shape. Since the goal of this project is to determine the important mechanisms behind dynamic wave shape changes (Section 1.1.2) and to develop a model from which information about the arterial system can be extracted, the relevant properties of the arterial system are discussed. The first section contains a discussion of the structure and relevant properties of the systemic arteries. In the following section a linear distributed model is derived and used to describe the mechanisms behind the anatomical wave shape changes (Section 1.1.1). Finally, the use of lumped parameter models in describing various aspects of the arterial system and the methods used by other investigators to monitor peripheral vascular resistance and arterial compliance are reviewed.

2.1 The Systemic Arteries

Many of the changes that occur in the pressure and flow waveforms can be attributed directly to the mechanical properties of the blood vessels. Because these properties depend on the surrounding tissue and location in the circulation in addition to the intrinsic properties of the blood vessel wall, the systemic, pulmonary, and coronary arteries all have very different properties. Since this thesis deals exclusively with observations of the blood pressure in the radial artery, only the systemic arteries are
2.1.1 The Structure and Composition of the Arterial Wall

The cross-section of an artery reveals that the arterial wall consists of three concentric layers—the intima, media, and adventitia (Figure 2.1). The first layer, the intima, contains the endothelium, a single cell layer that covers all surfaces in contact with the blood in the lumen. Although the intima is functionally very important, it contributes almost nothing to the overall mechanical properties of the artery. The media, which is separated from the endothelium by a subendothelial layer of collagen fibers and the internal elastic lamina, consists of elastin, collagen, and smooth muscle cells. The composition of this layer varies considerably throughout the different regions of the circulation.

In the large central arteries the media contains multiple concentric layers of elastic tissue separated by thin regions of connective tissue, collagen fibers, and smooth muscle cells. The smooth muscle cells in these arteries are oriented primarily in the circumferential direction. The smooth muscle cells connect the concentric elastic
laminae and generate tension in the arterial wall in response to the depolarization of the cell membranes.

Further from the aorta the media undergoes a number of changes. The content of elastin decreases while the amount of collagen, the number of smooth muscle cells, and the relative wall thickness increase. In addition to the increase in smooth muscle in these arteries, there is also a restructuring of the cells. In these arteries, known as the muscular arteries, the muscle cells are connected end to end and form continuous rings of muscle that lie parallel to the elastic laminae. As the arteries get smaller, the number of layers of elastic fibers and smooth muscles decreases.

The outermost layer, the adventitia, is a layer of loose connective tissue that merges with the neighboring tissue. The connective tissue contains some elastin, but it is composed mostly of stiff collagenous fibers. For the aorta and its branches it is reasonable to assume that the mechanical properties discussed below are determined primarily by the media [19].

2.1.2 The Properties of the Systemic Arteries

The mechanical properties of the systemic arteries are largely determined by the presence of elastin, collagen, and smooth muscle cells in the media of the arterial wall. Elastin, a protein substance, is mechanically very similar to rubber. Elastic fibers, which have a Young's modulus of approximately $3 \times 10^8 \, Nm^{-2}$, obey Hooke's Law and produce elastic tension automatically as the vessel expands. In the arteries the elastic fibers respond to the small displacements in the arterial wall that accompany the small blood pressure pulsations. Collagen, another protein substance found in the blood vessel wall, is arranged as a mesh of slack fibers. With a Young's modulus of approximately $10^8 \, Nm^{-2}$, however, it is considerably stiffer than elastin. Unlike the elastic fibers, the slack collagen fibers do not exert their tension until the vessel has been stretched. In the arteries the collagen fibers respond to the displacements in the blood vessel wall that are too large for the elastic fibers. Although the smooth muscle cells influence the geometry of the smaller vessels and regulate blood flow, they can also affect the mechanical properties of the smaller arteries. The elasticity of smooth muscle is approximately the same as elastin, but its properties can be influenced by
sympathetic nervous stimulation and pharmacologic interventions.

In the above paragraph the individual components of the blood vessel wall were described. In the remainder of this section the arterial properties resulting from the composite of the above materials are considered. Since the purpose of the remainder of this section is to introduce some of the arterial properties relevant to the study of wave shape changes, the discussions are brief, but for more information see references [13, 14].

As mentioned above, elastin is very extensible and plays a major role in the small displacements of the arterial wall for low distending pressures. Collagen, on the other hand, is relatively inextensible and is more important in bearing the radial stress at higher distending pressures. The composite operates such that at lower pressures the elastin dominates, but as the pressure increases, the collagen fibers with a much higher Young's modulus take over. For significant changes in the distending pressure, the relative contributions of elastin and collagen in bearing the stress change. Therefore, the elastic modulus of the arterial wall is a non-linear function of pressure [4].

In addition to the nonlinear stress-strain relationship discussed above, the arteries also have time-dependent properties. While the strain in a purely elastic material depends only on the applied stress, the deformation in a viscoelastic material depends both on the stress and strain rate. Viscoelastic materials may exhibit such behaviors as

- Creep—If a load is suddenly applied to an elastic material, it is deformed immediately, and it maintains the strain as long as the load is applied. A viscoelastic material continues to extend after the initial extension.

- Stress Relaxation—For an elastic material there is a linear relationship between the stress and strain. If the material is subjected to a constant strain, then it develops a constant stress. The stress in a viscoelastic material decreases in time.

- Hysteresis—Viscoelastic materials generate stress-strain loops when subjected to a cyclic stress.
Another very significant difference between elastic and viscoelastic materials is that a viscoelastic material dissipates energy when it is deformed; an elastic material only stores energy. Under steady state conditions these properties are neglected, but they can be significant in pulsatile systems such as the arteries. Therefore, in studying the systemic arterial system, the frequency of the pulsations and the viscoelasticity of the vessels must be considered.

Vasomotor tone, the state of contraction of the smooth muscle in the blood vessels, influences both the geometry and the elasticity of the arteries. Sympathetic stimulation of the smooth muscle is known to influence the cross-sectional area of the arterioles and muscular arteries. The relationship between sympathetic tone and the diameter of the conduit arteries was investigated by Gero and Gerová [19]. They demonstrated that the diameter of the femoral and carotid arteries are only slightly influenced by the carotid sinus baroreceptors under normal circumstances. Small decreases in the cross-sectional area of the arteries result in increased arterial resistance to blood flow. Since any increase in resistance in the arteries will be negligible compared to the changes in the arterioles and the microcirculation, the changes in the vessel caliber resulting from changes in vasomotor tone can generally be ignored in the systemic arteries.

Changes in vasomotor tone can also change the mechanical properties of the muscular arteries. When the smooth muscle cells contract, a number of physical changes can take place in the arterial wall. The vessel diameter decreases slightly while the wall thickness increases. The orientation of the structural elements in the arterial wall can be altered. A corresponding change in the mechanical properties of the arterial wall is expected. The precise effects of the change in vasomotor tone, however, have been the source of much controversy in the literature and are shown to depend on the conditions of the experiment [14, 19]. Generally, the contraction of the smooth muscles increases the arterial stiffness in the muscular arteries [3, 8]. This is not surprising since the tensile force generated by the contraction of the smooth muscle would be expected to act in conjunction with the elastin and collagen to bear the stress, thereby increasing the stiffness on the artery. In general, vasoconstrictors increase the elastic modulus while vasodilators decrease it.
2.1.3 Age-related Changes in the Systemic Arteries

Aging is associated with a number of changes in the cardiovascular system. Not only does the systemic arterial pressure progressively increase with age, but the structure and properties of the arteries also undergo some characteristic changes [13]. The elastin in the walls fragments and becomes calcified. The content of collagen, which can splint elastin into stiffened positions, increases. The overall effect of these changes is that the vessels become much less distensible, a condition often referred to as "hardening of the arteries".

2.2 Wave Propagation Models

The modeling of the circulation of blood through the cardiovascular system began in 1628 when William Harvey published that blood flows through a closed circuit. Stephen Hales in 1733 made the first blood pressure measurements and provided the first description of the "windkessel" properties of the arteries. He described the arteries as reservoirs that store blood during part of the cardiac cycle and then contract to maintain the flow during the remainder of the cycle. In 1899 Otto Frank used these ideas and developed his quantitative, but simple windkessel theory of the arterial system. These models are discussed in the next section.

At the end of the eighteenth century the study of pulse wave propagation effects in the arterial system began. In 1775 Euler developed a non-linear distributed model for blood flow, but he was unable to solve the equations. Viscous effects were added later, and the modified Euler model was finally solved for blood flow in 1958 by Lambert [33]. Young (1809) studied the modes of pressure wave propagation in the systemic arteries and derived the main propagation mode's velocity. His expression for the velocity is equivalent to the Moens-Korteweg velocity used today. In 1898 Lamb introduced the effects of the vessel wall and developed the equations of motion for the wall. Witzig (1914) used these equations and studied the propagation of waves in distensible tubes. Although his work went virtually unnoticed until recently, it forms the basis for modern pulse transmission theories of the arterial system. He was the first to show the effects of viscosity on the wave propagation characteristics and
the fluid impedance. Womersley in the late 1950's included both viscosity and the
effects of wall motion into his model. His work is regarded as a complete treatment
of the effects of viscosity in pulsatile flow. A review of the mathematical modeling of
the arteries between 1950 and 1970 is given by Cox [10]. A number of investigators
demonstrated the usefulness of transmission line models to study the cardiovascular
system [26, 30, 36, 37] and developed models of the complete circulation [1, 26].

The models discussed above can be divided into two categories depending on
their purpose and their complexity. The first type of model, the simple lumped
parameter model, is usually developed for a specific purpose. These models, which are
often based on the windkessel idea, are used to extract information from the system.
Since there is generally not enough information in a measurement to estimate all the
parameters in a complicated model, the number of parameters is necessarily kept
small. The distributed models, on the other hand, are developed to test a theory and
to add further to the understanding of a complicated system. In the remainder of this
section the mechanisms behind the blood pressure wave shape changes are studied. A
linear distributed model is derived to clarify some of the ideas presented. Deviations
from the assumptions in the model will be discussed when necessary.

2.2.1 Linear Distributed Model

Many researchers have developed pulse wave propagation models starting from the
conservation of mass and momentum in the arteries [26, 30, 33]. In this section such
a model is derived\(^1\). To simplify the derivation viscous effects are neglected and the
velocity is assumed to vary only in the axial direction. Consider the shaded region
in Figure 2.2. Applying the conservation of mass to the shaded section in Figure 2.2
yields

\[
\frac{\partial Q}{\partial z} + \frac{\partial A}{\partial t} = 0
\] (2.1)

From the conservation of momentum, the Navier-Stokes equation,

\[
\rho \frac{\partial v}{\partial t} + \rho v \frac{\partial v}{\partial z} = -\frac{\partial p}{\partial z}
\] (2.2)

\(^1\)The derivation in this section is taken from Mark, R. G., Classnotes for HST-542J, 1988.
Figure 2.2: A longitudinal cross-section of an artery with a section of transmission line.
Substituting \( v = Q/A \) into the above equation, differentiating, and using Equation 2.1 reduces the above expression to

\[
\frac{\partial Q}{\partial t} + \frac{\partial}{\partial z} \left( \frac{Q^2}{A} \right) = -\frac{A}{\rho} \frac{\partial p}{\partial z}
\]  

(2.3)

Since the wave generally propagates at a velocity much greater than the actual velocity of the blood and the axial changes in the cross-section are assumed to be small,

\[
\frac{\partial Q}{\partial t} >> \frac{\partial}{\partial z} \left( \frac{Q^2}{A} \right)
\]  

(2.4)

Neglecting the non-linear term and rewriting Equation 2.1 gives the following system of equations

\[
\frac{\partial Q}{\partial t} + \frac{A}{\rho} \frac{\partial p}{\partial z} = 0
\]  

(2.5)

\[
\frac{\partial Q}{\partial z} + \frac{\partial A}{\partial \rho} \frac{\partial p}{\partial t} = 0
\]  

(2.6)

which completes the derivation of a simple linear distributed model.

### 2.2.2 A Transmission Line Model

In this section the distributed model developed above is shown to be equivalent to an ideal transmission line. A more general development of such transmission line models is given by Taylor [36, 37] and Noordergraaf [26] who included attenuation in their models.

Substituting pressure for voltage and flow for current in the model in Figure 2.2 and deriving the ideal transmission line equations gives

\[
\frac{\partial P}{\partial z} = -L \frac{\partial Q}{\partial t}
\]  

(2.7)

\[
\frac{\partial Q}{\partial z} = -C \frac{\partial P}{\partial t}
\]  

(2.8)

where the resistance has been neglected since viscous effects are considered to be negligible as in the above derivation. Using the results from Appendix A, the transmission line equations can be rewritten as

\[
\frac{\partial P}{\partial z} + \frac{\rho}{A} \frac{\partial Q}{\partial t} = 0
\]  

(2.9)
\[ \frac{\partial Q}{\partial z} + \frac{\partial A}{\partial p} \frac{\partial P}{\partial t} = 0 \]  \hspace{1cm} (2.10)

which is equivalent to model developed by applying the conservation of mass and momentum to the section of the artery.

Given that the models are the same, all the techniques used in transmission line analysis carry over and can be applied to the study of the systemic arterial system. To begin two familiar results can be written immediately using the expressions for the capacitance and inductance per unit length derived in Appendix A. The wave speed \( c \) is

\[ c = \sqrt{\frac{1}{LC}} = \sqrt{\frac{Eh}{\rho d}} \]  \hspace{1cm} (2.11)

which is the Moens-Korteweg velocity. The characteristic impedance of a segment of artery is

\[ Z = \sqrt{\frac{L}{C}} = \frac{\rho c}{A} \]  \hspace{1cm} (2.12)

In the next section the mechanisms behind the waveshape changes are discussed with the aid of the techniques of transmission line analysis.

2.2.3 Mechanisms Behind the Wave Shape Changes

As mentioned in Chapter 1, the blood pressure pulse undergoes a number of changes as it propagates through the arterial system. Figure 1.1 illustrates these changes. First of all, the high frequency components of the wave, like the incisura, are attenuated. The systolic upstroke becomes steeper, the pulse pressure increases, and the systolic portion of the wave becomes narrower. Lastly, a hump appears during the diastolic part of the pulse. In the rest of this section the mechanisms behind these changes are discussed.

Reflections:

The arterial system is a branching collection of tapered vessels with varying elastic properties. At any point where the arterial properties change, a partial reflection of the pressure wave can occur. A reflection site can be anything from a change in vessel caliber to a bifurcation in a vessel. Since there are many such sites throughout the
arterial system, it is not surprising that reflections do in fact occur, but how important are these wave reflections? Before answering this question, the transmission line analysis in the previous section will be used to derive some parameters for a reflection site—the reflection and transmission coefficients.

Figure 2.3 shows a bifurcation in an artery. At the junction two conditions must be satisfied. The pressure in each vessel must be equal, and mass must be conserved. Expressed mathematically, these conditions are

\[ p_i + p_r = p_1 = p_2 \]  \hspace{1cm} (2.13)

\[ Q_i - Q_r = Q_1 + Q_2 \]  \hspace{1cm} (2.14)

The conservation of mass equation can be rewritten in terms of the pressure and characteristic impedances.

\[ \frac{p_i - p_r}{Z_0} = \frac{p_1}{Z_1} + \frac{p_2}{Z_2} \]  \hspace{1cm} (2.15)

The reflection and transmission coefficients can be derived from the above equations.

\[ R = \frac{p_r}{p_i} = \frac{Z_0^{-1} - (Z_1^{-1} + Z_2^{-1})}{Z_0^{-1} + (Z_1^{-1} + Z_2^{-1})} \]  \hspace{1cm} (2.16)

\[ T = \frac{p_1}{p_i} = \frac{Z_0^{-1}}{Z_0^{-1} + (Z_1^{-1} + Z_2^{-1})} \]  \hspace{1cm} (2.17)
Figure 2.4: Multiple branches in the systemic arterial system.

When \( R = 0 \), there is no reflected wave and the junctions are matched. Assuming that the wave velocity is the same in all branches, the reflection coefficient can be rewritten as

\[
R = \frac{A_0 - A_1 - A_2}{A_0 + A_1 + A_2}
\]

(2.18)

where \( A_0 \) is the area of the parent branch, and \( A_1 \) and \( A_2 \) are the areas of the daughter branches. In the case with a variable number of daughter vessels, a matched junction implies that

\[
\frac{1}{A_0} \sum_{i=1}^{N} A_i = 1
\]

(2.19)

Many of the major branches in the arterial system have area ratios between approximately 1.15 and 1.25, and these junctions result in small reflection coefficients [24]. Many of the junctions in the cardiovascular system are well matched.

Even though many of the junctions may be well matched, reflections do occur and are important factors in altering the wave shape. According to McDonald, it is important to distinguish between two types of reflections—discrete and distributed reflections. Discrete reflections are large reflections of a single component that result in a discrete deformation. Distributed reflections, however, are reflections composed of many indistinguishable components that are scattered in time and influence the
wave shape. These reflections, for instance, alter the shape of the systolic portion of the arterial pulse. Furthermore, the resistive vessels that terminate the arterial system represent a closed end and create positive reflections.

The distributed reflections are responsible for low frequency changes in the wave shape. The pressure wave is reflected from many sites in the arterial system. For long wavelength components of the pressure wave, the reflected waves are in phase and add constructively. In this case the arterial tree behaves like a single tube with a single reflection site at the end [26]. As the wavelength decreases, however, the reflections gradually become out of phase. For the smallest wavelengths of the pressure wave, the phase difference between the numerous reflected components increases further, and the reflections mutually cancel.

There is also some evidence of discrete reflection sites. Impedance plots in the aortic arch show that there is a principle reflection site at the aortic bifurcation [8]. The best evidence of discrete reflections comes from the work of Murgo and Westerhof [25]. In some subjects they noticed an additional component late in the systolic part of the pulse. They called the initial portion of the wave the percussion wave, and the additive component the tidal wave. They also noticed that any tidal wave present in the control waveform would disappear during the strain phase of the Valsalva maneuver (Section 4.1.1), and that an accentuated tidal wave would often appear during the post-release phase. In order to find the reflection site, they inserted a catheter with a number of transducers into the aorta and recorded the pressure during the maneuver. They found that the reflection site was at the origin of the renal arteries.

Consider the arrangement of vessels in Figure 2.4. In an ideal transmission line one might expect to find resonance and standing wave patterns on the section between junctions $J_1$ and $J_2$. If the length $L$ were equal to an integral number of half wavelengths of any component in the pulse, then that component would be amplified. McDonald measured the positions of nodes and anti-nodes for the first four components of the pressure wave in the arteries of dogs, but because of attenuation true resonance was not observed [24]. There is always an amplitude difference between the incident and reflected components, and complete cancellation does not occur at the nodes.
Figure 2.5: Taper of the artery

One might also expect to find multiple reflections from junctions $J_1$ and $J_2$, but as McDonald points out these are also not significant. Only the first reflection is important because the reflected components are strongly attenuated [24]. The incident wave is attenuated by viscous effects, but as discussed below the taper in the arteries amplifies the wave. The reflected component, on the other hand, is attenuated by both viscous effects and the change in arterial diameter. Therefore, multiple reflections and standing wave patterns in the arterial system are negligible.

Taper:

The gradual decrease in arterial diameter and increase in the elastic modulus of the arteries with increasing distance from the heart results in the increase in pulse pressure. The continuous variation in area and distensibility can be represented as a series of reflection sites as shown in Figure 2.5. In analyzing this system, Caro et al. assumed that at each reflection site all the energy is transmitted; there is no reflected energy [8]. Equating the energies,

$$\frac{p_i^2}{Z_i} = \frac{p_t^2}{Z_t} \quad (2.20)$$

and assuming that the thickness to diameter ratio remains constant across the site

$$\left(\frac{p_t}{p_i}\right)^2 = \frac{A_i}{A_t} \sqrt{\frac{E_t}{E_i}}. \quad (2.21)$$
Thus, a decrease in area and an increase in the Young’s modulus both increase the amplitude of the transmitted wave relative to the incident wave.

The other changes in the systolic portion of the blood pressure pulse are related to the elastic non-linearity, the stiffening of the arteries with increasing pressure. Because the artery becomes stiffer as the distending pressure increases and because the wave speed is proportional to the Young’s modulus (Equation 2.11, the forward wave speed during systole is greater than that during diastole. The peaks in the blood pressure travel faster than the valleys, and the resulting systolic portion of the pulse becomes both steeper and narrower.

Attenuation:

There are two sources of attenuation in the arterial system—viscosity and viscoelasticity. Viscosity reduces the speed of propagation and attenuates the blood pressure. Linear theory predicts that the gradient of the pressure and the flow waveforms should be the same shape, but there are some differences. Blood viscosity accounts for some of the differences. Viscosity alone, however, is not sufficient to account for all the attenuations in the blood pressure. Energy dissipated in the arterial walls is important, and the viscoelastic properties of the arteries must be considered. The attenuation coefficient for the arteries is frequency dependent; higher frequencies are damped more than lower ones.

2.3 Lumped Parameter Models

Most lumped parameter models of the systemic arterial system are based on the observations of Hales (1733) and Frank (1899). With each contraction of the heart some of the energy forces blood through the distal vessels, but by far, most of the energy inflates the aorta, increasing the transmural pressure. During diastole the large arteries recoil and force the blood forward through the circulation. The large, elastic arteries damp out the pressure fluctuations caused by the heart and maintain blood flow throughout the cardiac cycle.

In Frank’s windkessel model the arteries are represented by a compliant chamber which is electrically equivalent to a capacitor. The effects of the peripheral circulation
are lumped into a single resistance, and lastly, the heart is modeled by a current source. Some of the blood ejected by the heart "charges" up the capacitor and the rest leaks out into the peripheral resistance.

\[ Q_i = C \frac{dp_a}{dt} + \frac{p_a}{R} \]  \hspace{1cm} (2.22)

where \( p_a \) is the arterial pressure and \( Q_i \) is the input from the heart. Solving for the arterial pressure \( p_a(t) \) gives

\[ p_a(t) = p_0 e^{-t/RC} + \frac{1}{C} e^{-t/RC} \int_0^t Q_i(\tau) e^{-\tau/RC} d\tau \]  \hspace{1cm} (2.23)

and predicts an exponential decay in the pressure during diastole. The simple windkessel model is shown in Figure 2.6.

A number of problems with the windkessel models are often mentioned in the literature [8, 22]. The source of much of the criticism is that these models neglect wave propagation effects. According to the windkessel theory, the pressure increases simultaneously throughout the entire arterial system. The windkessel model also disregards the effects of the distributed reflections during systole (Section 2.2). These models predict that (Equation 2.22)

\[ Q_i \propto \frac{dp_a}{dt} \]  \hspace{1cm} (2.24)

Experimental data suggests, however, that

\[ Q_i \propto p_a - p_{ed} \]  \hspace{1cm} (2.25)
<table>
<thead>
<tr>
<th>Artery</th>
<th>Length(cm)</th>
<th>Velocity(cm/sec)</th>
<th>$\lambda_1$(cm)</th>
<th>$\lambda_4$(cm)</th>
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</thead>
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<td>Brachial</td>
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<td>925</td>
<td>231</td>
</tr>
<tr>
<td>Radial</td>
<td>24.5</td>
<td>1065</td>
<td>1065</td>
<td>266</td>
</tr>
</tbody>
</table>

Table 2.1: The Variation of some quantities throughout the systemic arterial system. (Data compiled from Schaaf et al. 1972).

where $p_{ed}$ is the end diastolic pressure. Another source of criticism involved the use of wave propagation phenomena with windkessel theory. For example, until the late 1950's the primary application of the windkessel theory involved the estimation of stroke volume. For this calculation it was generally assumed that the arterial system had a finite length and that a fundamental standing wave reflected back and forth [24]. McDonald studied this phenomena of standing waves in the arterial system, and as mentioned on page 26, he concluded that they could not exist because the attenuation of reflected waves was too great.

Despite these problems with the windkessel model, many investigators have continued using these models. The reasons for the continued success of windkessel theory can be divided into two categories—theoretical and practical. The first theoretical argument is based on the idea that a distributed system can be replaced by a lumped parameter model if the wavelengths of the excitations are much greater than the dimension of the system. Simon et al. [32] and Guier et al. [20] mentioned this argument when they justified their use of the windkessel model. As Noordergraaf explained (see page 25), for low frequencies the arterial system can be approximated by a tube with a single reflection site [26]. Table 2.1 shows the wavelength of the first and fourth harmonics of the blood pressure pulse in various systemic arteries. Comparison of these values shows that the wavelengths of the first four components are greater than the lengths of the arteries..

Additional support for the use of the windkessel model, at least the diastolic
portion, is provided by Jones [21]. He studied the relationship between the pulse wave and windkessel theories. He decomposed the arterial pulse into a superposition of the several delayed reflections. From this representation of the arterial pressure, he derived a first-order correction for the systolic portion of the blood pressure pulse, and more importantly, he also concluded that the windkessel model gave good predictions of the pressure response in the large arteries during diastole.

Although some aspects of the windkessel theory can be supported theoretically, the most important reason for its continued success is its conceptual and mathematical simplicity. Many investigators have used these models to derive important information from the systemic arterial system (see [2], for a brief review). Guier et al. [20] used a simple windkessel model to estimate stroke volume on a beat-by-beat basis during the presence of large pressure variations. Wesseling et al. [40] used a four segment model to extract the peripheral resistance, the internal arterial radius, arterial compliance, and gain of a section of artery. They claimed that the technique could be important for detecting plaques and other abnormalities in the arteries. Deswysen et al. [12] developed a simple model that accurately described the afterload on the heart. The parameters were estimated from aortic pressure and flow measurements.

A number of investigators have used resonant networks to account for anatomical wave shape changes in the peripheral arteries. For example, Warner [26] used a four pole system with carefully chosen parameters to completely characterize the entire shape of the blood pressure pulse. In separate experiments he was able to fit the pulse in the brachial, femoral, and radial arteries. Spencer et al. [35] used the model shown in Figure 2.7 to account for the shape of the entire pulse in both the aorta and femoral artery using typical parameter values from dog experiments. Although the changes in wave shape are caused by distributed effects (Section 2.2), the fact that the above models fit the pulses suggest that the changes in shape can, in some sense, be attributed to the inertial, compliant, and resistive (viscous and termination) properties of the blood and the arteries.

Goldwyn and Watt [18, 39] applied a third-order model for a similar application; they used their model to characterize the shape of the diastolic wave in the radial artery. However, unlike Warner and Spencer they estimated the parameters. They
tried to use this technique for diagnosis. They estimated the two compliances and an inerance for a number of different blood pressure waveforms corresponding to different pathophysiologica conditions like arteriosclerosis and cardiomyopathy. One problem with their model is that the parameters were not identifiable. Their solution to this problem was to normalize the other parameters to the resistance.

Lumped parameter models have become useful tools for studying the distributed systemic arterial system because of their simplicity. A number of researchers have used these models to develop clinically significant results. Furthermore, windkessel models still be used with little error between the actual system and the model if only the diastolic portion of the pulse is used [21].

2.4 Review of Literature

One area of research that has received much attention in recent years is the use of lumped parameter models to estimate the arterial compliance and peripheral resistance of the systemic arterial system. A number of researchers have developed
methods for the estimation of arterial compliance. Burattini et al. [7] and Cope [9] both used modified windkessel models to study the dependence of arterial compliance on pressure. Defares et al. [11], Simon et al. [32], and Randall [28] investigated the age-related changes in arterial compliance and their relationship to hypertension. All of these studies used a windkessel model with simultaneous pressure and flow measurements taken from the aorta.

Other researchers worked on the problem of monitoring peripheral vascular resistance. Bourgeois et al. [6] measured the time constant of the decay of the aortic pressure in a dog and compared these values with the measured value (mean aortic pressure divided by cardiac output). They found that the time constant measured in the caudal segment of the thoracic aorta was proportional to the measured resistance, and they proposed using a similar site in humans for monitoring peripheral resistance. Toorop et al. [38] developed a method of estimating peripheral resistance and arterial compliance during transient conditions. They used the pressure and flow measured in a cat's aorta to estimate the parameters of a three-element windkessel model. In order to take transients in the blood pressure into account, they subtracted the stored volume from the average flow before calculating the resistance. Yin and Liu et al. [23, 41] estimated arterial compliance and peripheral resistance using aortic pressure and flow data from human subjects. Although in form their model is a simple windkessel, they did not assume that the decay is exponential. Instead, they based their calculations on the stroke volume and the areas under the systolic and diastolic parts of the pressure curve. They incorporated non-linear P-V relationships into the model, and they computed the compliance and resistance without parameter estimation. Correction terms were also introduced to account for pressure transients.

To my knowledge no one has yet addressed the issue of using the wave shape in the radial artery to monitor peripheral vascular resistance. All of the techniques discussed above are invasive and involve measurements taken in the aorta. However, we are interested in monitoring beat-by-beat changes in the peripheral vascular resistance by using a simple, non-invasive measurement of blood pressure in the radial artery. In the next chapter we develop the model used by Goldwyn and Watt [18] for the purpose of monitoring peripheral resistance.
Chapter 3

Model Development

In this chapter a model is developed to account for the dynamic wave shape changes seen in the radial blood pressure pulse. With a continuous, non-invasive measurement of blood pressure and a parameter estimation algorithm, such a model would make long term monitoring of beat-by-beat changes in the mechanical properties of the arterial system possible.

In order for the model to be useful in the above application, it must be rich enough to account for the wave shape changes and yet, simple enough so that the parameters can be reliably estimated. For the reasons discussed in Chapter 2, a lumped parameter model was chosen, and the information was extracted only from the diastolic portion of the pulse. Using only the diastolic wave shape eliminates much of the uncertainty associated with the input flow from the heart. The model assumes that all hearts are the same in that they all eject a bolus of blood into the arterial system and set up the initial conditions for the diastolic decay. Furthermore, the systolic portion of the pulse was neglected because it is the part most affected by such wave propagation effects as taper, dispersion, and elastic non-linearities (Section 2.2). The diastolic part of the aortic pulse, which is influenced less by these distributed effects, is described very well by a simple windkessel model. Thus, using only the information in the diastolic wave decreases the number of parameters in the model and makes it possible to extend the simple windkessel model to apply to the wave shape in the radial artery.

Although the simple windkessel model generates a decaying exponential blood pressure, it is a useful starting point for the development of a new model. By intro-
ducing new energy storage elements into a simple parallel RC circuit, a higher-order model can be developed to take into account the changes in the waveshape seen in the distal arteries. Such a model is developed in this chapter.

3.1 A Simple Mechanical Analogue

Before developing the model for the arterial system, a simple but analogous mechanical system is introduced in order to gain some insight into the behavior of our system. Consider a tube with a hole in the far end. If a bolus of liquid is ejected into the near end of the tube which is subsequently closed, the resultant pressure at any point along the tube will be the combination of two responses. One is the gradual decay of the mean pressure due to leakage through the hole. The second is a resonant response; the pressure wave in the fluid reflects back and forth in the tube leading to an oscillatory behavior that decays as the volume of fluid decreases. If the hole were plugged up, the response would be purely oscillatory. However, as the diameter of the hole increases, both responses gradually appear, but their time constants decrease, speeding up their decay. Furthermore, the amplitude of the oscillatory component also depends on the size of the hole. If the end is closed, there is a large reflected component, but the reflection decreases as the hole diameter increases.

The behavior of this mechanical system is similar to the behavior of the blood pressure in the radial artery. This is similar to Noordergraaf's idea which was explained on page 25. Assuming that the formation of the dicrotic wave, the hump in the diastolic part of the pulse, is due to pressure reflections from the peripheral resistance, then the hole in the tube is analogous to the arterioles. As the cross-sectional area of the arterioles changes, the peripheral vascular resistance changes. Increasing the resistance increases the time constants of decay and results in a larger reflected component. In the limit that the resistance goes to infinity, the pressure would be oscillatory. This behavior can be seen in Figure 1.2. A third-order model is developed in the next section.
3.2 A Lumped Parameter Circuit Model

As seen from the heart, the systemic arterial system can be represented by a lumped compliance for the arteries and a parallel resistance for the arterioles and capillaries. The view from the distal arteries, however, is slightly more complicated, but before developing the new model, the behavior of the arterial system during each contraction of the heart is reviewed.

The arterial blood pressure resulting from the discrete, almost periodic contractions of the heart is pulsatile. During ventricular contraction, a bolus of blood is injected into the aorta where the blood pressure abruptly increases. Some of the energy from the contraction pushes the blood forward through the capillaries, but most of the energy is stored as potential energy in the large elastic arteries that expand to store the ejected volume of blood. The aortic valve closes, and then during ventricular relaxation, the large elastic arteries push the blood forward through the distal arteries and arterioles. During this peripheral runoff, the pressure in the large arteries gradually decays until the next cardiac contraction.

As seen from a distal artery, blood is stored throughout the arterial system: both in the elastic proximal arteries and in the less distensible, muscular ones. It is useful to expand the simple windkessel model by dividing the storage (capacitive) function of the arteries into two distinct components (central and peripheral) separated by an inertance representing the momentum of the column of blood flowing between the two regions (Appendix A.3). The complete model is shown in Figure 3.1.

This circuit has been used by other investigators to describe the changes in the wave shape in the systemic arteries. This model was used by Landes [26] to describe wave shape changes in the systemic arteries and is similar to the one used by Spencer (Figure 2.7). However, as mentioned in Section 2.3, Goldwyn and Watt were the first to use this model to estimate parameters from the wave shape.
3.3 The Complete Solution

The model developed in the previous section can be described by a set of three linear first-order differential equations. These equations, expressed in terms of voltages and currents, are

\[
\frac{d}{dt} V_{ce}(t) = -\frac{1}{C_e} I_l(t) + \frac{1}{C_m} I_s(t) \tag{3.1}
\]

\[
\frac{d}{dt} I_l(t) = \frac{1}{L} V_{ce}(t) - \frac{1}{L} V_{cm}(t) \tag{3.2}
\]

\[
\frac{d}{dt} V_{cm}(t) = \frac{1}{C_m} I_l(t) - \frac{1}{RC_m} V_{cm}(t) \tag{3.3}
\]

with a characteristic equation

\[
\lambda^3 + \frac{1}{RC_m} \lambda^2 + \frac{1}{L} \left( \frac{1}{C_e} + \frac{1}{C_m} \right) \lambda + \frac{1}{RC_eC_mL} = 0 \tag{3.4}
\]

If we let \( \mathbf{x}(t) = (V_{ce}(t), I_l(t), V_{cm}(t))^T \) and let \( y(t) \) denote the output, then the above system of equations can be expressed in state-space representation.

\[
\frac{d}{dt} \mathbf{x}(t) = A\mathbf{x}(t) + B I_s(t) \tag{3.5}
\]

\[
y(t) = C\mathbf{x}(t) \tag{3.6}
\]
where

\[
A = \begin{pmatrix}
0 & \frac{1}{c_c} & 0 \\
\frac{1}{c_c} & 0 & \frac{1}{c_c} \\
0 & -\frac{1}{c_m} & -\frac{1}{mc_m}
\end{pmatrix}
\quad \text{and} \quad
B = \begin{pmatrix}
\frac{1}{c_c} \\
0 \\
0
\end{pmatrix}
\]

The general solution to this system of equations is

\[
\varphi(t) = e^{At} \varphi(0) + \int_0^t e^{A(t-\tau)} BI_s(\tau) d\tau
\] (3.7)

\[
V_{cm}(t) = C \varphi(t)
\] (3.8)

where \( C = (0, 0, 1) \).

### 3.4 Natural Response

The modes of the natural response of the system are given by the roots of the characteristic equation (Equation 3.4). Before presenting the natural response of the model, the impulse response of the second-order system will be discussed since the modes of the third-order system are the sum of the possible modes of the second-order system with a decaying exponential.

#### 3.4.1 Second-order System

In general the dynamics of a second-order, linear, time-invariant system can be described by the differential equation

\[
\frac{d^2}{dt^2} g(t) + 2\zeta \omega_n \frac{d}{dt} g(t) + \omega_n^2 g(t) = f(t)
\] (3.9)

where \( f(t) \) is the forcing function, \( \omega_n \) is the natural frequency, and \( \zeta \) is the damping factor. The characteristic equation of this second-order system is

\[
\lambda^2 + 2\zeta \omega_n \lambda + \omega_n^2 = 0
\] (3.10)

The eigenvalues of this system are

\[
\lambda_{1,2} = -\zeta \omega_n \pm \omega_n \sqrt{\zeta^2 - 1}
\] (3.11)
There are three different cases that arise for different values of $\zeta$.

**Case $\zeta > 1$:**

If $\zeta > 1$, then the roots of the characteristic equation are distinct, real, and negative. The impulse response of the system is the sum of two decaying exponentials

$$h(t) = a_1 e^{-\lambda_1 t} + a_2 e^{-\lambda_2 t}$$  \hspace{1cm} (3.12)

The system is **overdamped**.

**Case $\zeta = 1$:**

When $\zeta = 1$, the radical in Equation 3.11 vanishes, and the two roots are identical

$$\lambda_1 = \lambda_2 = -\omega_n$$  \hspace{1cm} (3.13)

The impulse response is

$$h(t) = b_1 e^{-\omega_n t} + b_2 te^{-\omega_n t}$$  \hspace{1cm} (3.14)

This response which is not strictly a decaying exponential is referred to as **critically damped**.

**Case $0 \leq \zeta < 1$:**

In this case the roots of the characteristic equation are

$$\lambda_{1,2} = -\zeta \omega_n \pm i\omega_n \sqrt{1 - \zeta^2} = -\zeta \omega_n \pm i\omega_d$$  \hspace{1cm} (3.15)

where $\omega_d$ is the damped natural frequency. The roots are complex conjugates of each other, and the impulse response is

$$h(t) = ce^{-(\omega_n - i\omega_d)t} + c^*e^{-(\omega_n + i\omega_d)t}$$

$$= 2|c|e^{-\omega_n t}\cos(\omega_dt - \theta)$$  \hspace{1cm} (3.16)

This response is a damped sinusoidal function; the system is **underdamped**. For $\zeta = 0$, the response is purely sinusoidal. The response of the third-order system is derived in the next section.
3.4.2 Natural Response of the Model

The characteristic equation for the third-order system is

$$\lambda^3 + \frac{1}{RC_m} \lambda^2 + \frac{1}{L} \left( \frac{1}{C_s} + \frac{1}{C_m} \right) \lambda + \frac{1}{RC_sC_mL} = 0$$  \hspace{1cm} (3.18)

To solve for the eigenvalues of the system, let

$$\phi_1 = \frac{1}{L} \left( \frac{1}{C_s} + \frac{1}{C_m} \right) - \frac{1}{3R^2C_m^2}$$  \hspace{1cm} (3.19)

$$\phi_2 = \frac{1}{RC_mC_sL} - \frac{1}{3RC_mL} \left( \frac{1}{C_s} + \frac{1}{C_m} \right) + \frac{2}{27R^3C_m^3}$$  \hspace{1cm} (3.20)

and let

$$\Phi_1 = \left( -\frac{\phi_2}{2} + \sqrt{\frac{\phi_2^2}{4} + \frac{\phi_1}{27}} \right)^{1/3}$$  \hspace{1cm} (3.21)

$$\Phi_2 = \left( +\frac{\phi_2}{2} + \sqrt{\frac{\phi_2^2}{4} + \frac{\phi_1}{27}} \right)^{1/3}$$  \hspace{1cm} (3.22)

The roots of the characteristic equation are given by

$$\lambda_1 = \Phi_1 + \Phi_2 - \frac{1}{3RC_m}$$  \hspace{1cm} (3.23)

$$\lambda_2 = -\left( \frac{\Phi_1 + \Phi_2}{2} \right) - \frac{1}{3RC_m} + i\sqrt{3}\left( \frac{\Phi_1 - \Phi_2}{2} \right)$$  \hspace{1cm} (3.24)

$$\lambda_3 = -\left( \frac{\Phi_1 + \Phi_2}{2} \right) - \frac{1}{3RC_m} - i\sqrt{3}\left( \frac{\Phi_1 - \Phi_2}{2} \right)$$  \hspace{1cm} (3.25)

Again, as in the second-order system, there are three different cases to be considered.

Case \((\frac{d^2}{4} + \frac{d}{27}) < 0\): Three real, unequal roots.

Because all three roots are distinct, real, and negative, this corresponds to the overdamped case. The impulse is the sum of three decaying exponentials.

$$h(t) = a_1 e^{-\lambda_1 t} + a_2 e^{-\lambda_2 t} + a_3 e^{-\lambda_3 t}$$  \hspace{1cm} (3.26)

Case \((\frac{d^2}{4} + \frac{d}{27}) = 0\): Three real roots. At least two are equal.

This case is analogous to the critically damped case discussed above. A possible impulse response in this case is

$$h(t) = b_1 e^{-\lambda_1 t} + b_2 e^{-\lambda_2 t} + b_3 te^{-\lambda_3 t}$$  \hspace{1cm} (3.27)
Figure 3.2: The impulse response of a third-order system with one real root and two complex conjugate roots is shown for a particular set of parameters.

Case \( \left( \frac{a_1}{4} + \frac{a_4}{2^4} \right) > 0 \): One real root and two complex conjugate roots.
The single real root leads to a decaying exponential term in the impulse response, and the complex roots add a damped sinusoidal term to the following impulse response

\[
h(t) = c_1 e^{-\lambda_1 t} + c_2 e^{-\lambda_3 t} \cos(\lambda_3 t - \theta) \tag{3.28}
\]

In Figure 3.2 the impulse response of the third order system is plotted for a particular set of parameters. The response is the sum of a decaying exponential with a damped sinusoid. Note the similarity between this waveform and the wave shape in the radial artery (Figure 1.2). The details of the parameter estimation procedure is discussed in the next chapter along with the other methods.
Chapter 4

Methods

In the last chapter a simple model was developed to characterize the blood pressure wave shape changes in the radial artery. In this chapter the mathematical and physiological methods used in this thesis are discussed. In the first section the methods used to acquire data from human subjects are reviewed. Then, the model development continues with a discussion of the methods used for estimating the model parameters and validating the model.

4.1 Physiological Methods

In order to test our model, it is necessary to acquire data in which the properties of the arterial system are changing in a controlled or predictable manner. One way to elicit the dynamic wave shape changes seen in Figure 1.2 is to apply a stress to the cardiovascular system. In this section the Valsalva maneuver and the protocol for acquiring the data from human subjects are reviewed.

4.1.1 The Valsalva Maneuver

Before describing the Valsalva maneuver, it is necessary to introduce a little more cardiovascular physiology, namely the concept of venous return. Venous return, as the name implies, is the amount of blood that enters the heart from the systemic veins per unit time. Under normal, steady-state conditions the rate of blood flowing into the right atrium equals the left ventricular output. The driving force behind the venous return is the pressure gradient between the end of the capillaries and the right
atrium. The pressure difference needed to cause sufficient venous return, however, is relatively small because the veins have a low resistance. Furthermore, the systemic veins have a relatively very high compliance and are capable of storing large amounts of blood. In fact, at any time up to 67% of all the blood in the body can be found in the venules, veins, and vena cavae.

The Valsalva maneuver is initiated with an abrupt increase in intrathoracic pressure which can be caused by forcefully expiring against a closed glottis. With the step increase in chest pressure, there is a corresponding rise in arterial blood pressure by the same amount *(phase I)*. The intrathoracic veins, arteries, and the heart are compressed. The resultant increase in right atrial pressure causes a decrease in the venous return. Since the blood is prevented from entering the thoracic cavity, it accumulates in the veins. Consequently, the cardiac output and arterial blood pressure soon begin to drop. The cardiovascular control system (baroreceptor) responds by causing vasoconstriction and cardioacceleration. This part of the response is often referred to as *phase II* or the strain phase. When the high intrathoracic pressure is released, the arterial blood pressure abruptly decreases *(phase III)*, but soon rises as the cardiac output dramatically increases due to increased venous return. The blood pressure can actually overshoot the blood pressure prior to the Valsalva maneuver, and a compensatory bradycardia (a slow heart rate) results. The heart rate and blood pressure gradually return to their original levels *(phase IV)*. The response of the blood pressure to the Valsalva is shown in Figure 4.1.

### 4.1.2 Experimental Methods

In these experiments the response of healthy human subjects to the Valsalva maneuver was studied. For each subject the blood pressure and blood velocity were recorded in opposite arms along with the electrocardiogram. The blood pressure was measured using an instrument based on arterial tonometry\(^1\). The velocity was measured using Doppler ultrasound\(^2\). More information on the instrumentation is available in Appendix B.

\(^1\)Colin Electronics Co., Ltd.—Model CBPM 3000

\(^2\)Parks, Medical Electronics, Inc.—Model 1059 Vascular Mini-lab III
Response of Blood Pressure during Valsalva

Figure 4.1: The response of the blood pressure to the Valsalva maneuver.
Each subject was seated in a chair with his arms resting on the arm rests to decrease the likelihood of motion artifact. Two Valsalva maneuvers were elicited. The ECG and blood pressure were recorded throughout the experiment onto VCR tape. The velocity was recorded for one minute prior to the Valsalva maneuver, during the maneuver, and then for another minute. The subject was given about another minute to become completely equilibrated, and the above procedure was repeated.

The Valsalva maneuvers were uncalibrated; no manometer was used to maintain a particular increase in intrathoracic pressure. Each subject increased and held his intrathoracic pressure by some arbitrary amount for 15 seconds.

The data were subsequently digitized and transferred to a SUN 386i workstation where the best Valsalva from each subject was analyzed.

The protocol for this study was approved by the MIT Committee on the Use of Humans as Experimental Subjects (Appendix C).

4.2 Parameter Estimation

In Sections 3.3 and 3.4 both the complete solution and the natural response of the model were presented. For the reason discussed on page 33, however, only the natural response will be considered for the remainder of the thesis. There are two main issues that must be discussed within this section on parameter estimation. This first is the determination of the starting point of the analysis, and the second is the method used to estimate the parameters.

4.2.1 Determining the Starting Point of the Analysis

Recall from Section 1.1.1 that the dicrotic notch which is present in the aortic blood pressure pulse is attenuated and no longer visible in the radial blood pressure pulse, making it difficult to know where diastole starts. In the analysis of the Valsalva maneuver data the starting point was arbitrarily chosen. By default, the analysis began $28\text{msec}$ after the maximum systolic blood pressure, but in cases where large reflections or other artifacts occurred before the dicrotic wave, the starting point was chosen to be the time where the wave shape began to take on the shape described by
the model.

Because this model describes only the natural response of this system ($Q_i = 0$), the dependence of the starting point on the estimated parameters was investigated. The parameters were estimated for many different starting points in the diastolic wave. The initial time was chosen arbitrarily as discussed above, but then it was moved forward in time for $60msec$ at $4msec$ steps. For each beat the initial guess of the parameters was kept the same, and this procedure was repeated throughout the Valsalva maneuver. The results are contained in Section 5.4.

4.2.2 Method for Estimating the Parameters

The behavior described in Section 3.1 is best characterized by a system that has one real root and two complex conjugate roots. So for

$$\left( \frac{\phi_2^2}{4} + \frac{\phi_1^3}{27} \right) > 0,$$  \hspace{1cm} (4.1)

the eigenvalues of the system are $(\lambda_1, \lambda_2 + i\lambda_3, \lambda_2 - i\lambda_3)$. The two components of the natural response can be represented mathematically by

$$p_{\text{decay}}(t) = a_1 e^{-\lambda_1 t}$$  \hspace{1cm} (4.2)

$$p_{\text{resonant}}(t) = a_2 e^{-\lambda_2 t} \cos(\lambda_3 t - \theta)$$  \hspace{1cm} (4.3)

In order to estimate the model parameters, we assume that the diastolic portion of the blood pressure can be represented by the sum of Equations 4.2, 4.3, and a constant offset.

$$p_{\text{rad}}(t) = a_0 + a_1 e^{-\lambda_1 t} + a_2 e^{-\lambda_2 t} \cos(\lambda_3 - \theta)$$  \hspace{1cm} (4.4)

The structural parameters $(a_0, a_1, a_2, \lambda_1, \lambda_2, \lambda_3, \theta)$, in general, are uniquely identifiable and have been estimated using the Levenburg-Marquardt method of performing non-linear least-squares [27]. The parameters $(\lambda_1, \lambda_2, \lambda_3)$ are then used to estimate the

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model parameters using the following relationships.

\[
\frac{1}{RC_m} = \lambda_1 + 2\lambda_2 \tag{4.5}
\]

\[
\frac{1}{L} \left( \frac{1}{C_e} + \frac{1}{C_m} \right) = 2\lambda_1 \lambda_2 + \lambda_2^2 + \lambda_3^2 \tag{4.6}
\]

\[
\frac{1}{RC_aC_mL} = \lambda_1 \left( \lambda_3^2 + \lambda_2^2 \right) \tag{4.7}
\]

These equations express the four model parameters—\(R, C_e, C_m,\) and \(L—\)in terms of three structural parameters. Therefore, given only \(\lambda_1, \lambda_2,\) and \(\lambda_3,\) it is not possible to identify all four model parameters unless one of the parameters is determined independently. If we assume that the compliance of the large, elastic arteries is constant over the pressure range of the Valsalva maneuver, then the other model parameters can be determined from

\[
R = \frac{1}{C_e} \left[ \frac{4\lambda_1 \lambda_2^2 + 2\lambda_2 \left( \lambda_3^2 + \lambda_3^2 + \lambda_3^2 \right)}{\lambda_1 \left( \lambda_2^2 + \lambda_3^2 \right) \left( \lambda_1 + 2\lambda_2 \right)} \right] \tag{4.8}
\]

\[
C_m = C_e \left[ \frac{\lambda_1 \left( \lambda_2^2 + \lambda_3^2 \right)}{4\lambda_1 \lambda_2^2 + 2\lambda_2 \left( \lambda_3^2 + \lambda_3^2 + \lambda_3^2 \right)} \right] \tag{4.9}
\]

\[
L = \frac{1}{C_e} \left[ \frac{\lambda_1 + 2\lambda_2}{\lambda_1 \left( \lambda_2^2 + \lambda_3^2 \right)} \right] \tag{4.10}
\]

In the estimation of the model parameters from the Valsalva data the central compliance \(C_e\) was set equal to one. Under this condition the model gives information only on the relative changes in resistance, inertance, and the distal compliance.

The question of how well a model fits the data involves more than simply looking at the agreement between the best-fit and the data. One must also consider the uncertainties in the estimated parameters [29, 27]. The Levenburg-Marquardt algorithm as implemented in Numerical Recipes in C [27] automatically generates a covariance matrix to evaluate the parameter uncertainties. Strictly speaking the covariance matrix only gives error estimates on the estimated parameters in the case that the residual errors are normally distributed. The diagonal elements of the matrix are estimates of the error variances for each parameter, and the off-diagonal elements are the covariances between two parameters. Nevertheless, the matrix is useful for
the evaluation of the parameter estimates from our model. It does not provide error estimates, but it can show if the parameter estimates are reliable, or if any parameters are correlated. This matrix is used to determine the reliability of the estimated parameters in Section 5.2.

4.3 Model Validation

In the development of any model it is important to verify the predicted results with the results from an independent measure if possible. In this section the model validation methods are described.

The model presented here estimates relative values for the peripheral resistance, distal compliance, and inerterance on a beat-by-beat basis. The most important parameter for our application, which is also the easiest to measure, is resistance. Therefore, in order to validate our model an independent value of resistance was measured.

During steady-state conditions when the mean blood pressure is constant, the resistance can be measured by computing

$$R_{meas} = \frac{\text{mean blood pressure}}{\text{mean blood flow}} \tag{4.11}$$

The mean blood pressure was computed on a beat-by-beat basis by integrating over the entire pulse. The Doppler velocity was measured and averaged over each beat instead of the flow. A number of issues regarding the velocity measurement require further discussion.

First of all, as mentioned in Appendix B, the velocity measurement is uncalibrated; neither the gain nor the offset of the velocity signal were known. Accounting for the gain was no problem. An arbitrary gain was calculated by setting the ratio from Equation 4.11 equal to one before the Valsalva maneuver, and thus, all subsequent computed values were expressed relative to this first value. On the other hand, knowing the offset is important. If the measured resistance is calculated by

$$R_{meas} = k \frac{P_{\text{mean}}}{Q_{\text{mean}} - Q_0} \tag{4.12}$$

where $Q_0$ is the offset, then the uncertainty in the offset can have serious consequences.
such as a negative measured resistance. Therefore, at the end of each Valsalva maneuver a zero velocity signal was recorded onto the VCR tape.

Another issue is the use of the velocity measurement instead of the flow. The flow through the arteries is pulsatile and is related to the velocity $u(r)$ by

$$Q = \int_0^a 2\pi r u(r) \, dr$$  \hspace{1cm} (4.13)

where $a$ is the radius of the artery which depends on time and the mean pressure. If the cross-sectional area were constant, then the average velocity would be proportional to the average flow, but this is not the case in the arterial system. The mean cross-sectional area is determined by the mean pressure, and the deviations in diameter result from the pressure pulsations about the mean pressure during each beat. Therefore, in general, it is not valid to assume that the ratio of mean pressure to mean velocity is proportional to the measured resistance given by Equation 4.11, but under certain conditions we assume that this connection can be inferred. We assume that the ratio of the mean pressure to mean velocity is proportional to the measured resistance under the following circumstances:

- The mean pressure must be constant so that the assumption of steady-state is valid. If the mean pressure is changing, then the volume of blood stored in the arteries is changing.

- The mean pressure during different physiologic conditions must be approximately the same so that the mean cross-sectional areas are the same.

- The changes in cross-section due to the pulse pressure during different physiologic states should be negligible compared to the mean cross-sectional area.

The measured results are included in Section 5.3.
Chapter 5

Results

The response to the Valsalva maneuver was recorded in eight subjects using the protocol discussed in Chapter 4. In this chapter the data are presented, the performance of the model in fitting the data is evaluated, and the results of the Valsalva maneuver are discussed.

5.1 Data from the Valsalva Maneuver

Of the eight subjects that took part in this study only five produced satisfactory data. Three of the subjects were rejected for a couple of reasons. Subjects 3 and 5 who were unfamiliar with the Valsalva maneuver had an atypical response. The most likely reason for the irregular response was that neither subject maintained an increased intrathoracic pressure. Either they allowed the pressure to vary, or they maintained an elevated mouth pressure instead of an increased intrathoracic pressure. With subject 6 there was a significant decrease in signal quality during phase II of the Valsalva maneuver. This subject tried to hold a large increased intrathoracic pressure, and the loss of signal is believed to have resulted from either the tightening of the wrist or to motion artifact toward the end of the strain phase of the maneuver. Because of these problems only the responses from five subjects are discussed below.

The data recorded from the five subjects are shown in Figures 5.1–5.5. Part A of these figures shows the ECG, radial blood pressure, and blood velocity. Part B gives an expanded view of the blood pressure during the maneuver. Typical waveforms from the different phases of the maneuver—control, strain, and post-release— are
also shown.

The responses are very typical and show many of the features that were discussed in Section 4.1.1. For example, consider the response of subject 8 which is representative of the group. At $t = 384s$, there is an abrupt increase in arterial pressure marking the beginning of the Valsalva maneuver. The increased intrathoracic pressure compresses the veins and decreases the stroke volume, causing a significant decrease in pulse pressure. The cardiovascular system compensates by increasing the heart rate and constricting the peripheral vessels. As the heart rate is increased (see the ECG), the blood pressure and velocity waveforms become more oscillatory, and the velocity develops a larger negative component. The gradual increase in blood pressure during the latter part of phase II is a result of the above control mechanisms.

At $t = 399s$, the intrathoracic pressure is abruptly decreased to its normal level. There is a corresponding drop in the arterial pressure, but the rapid increase in cardiac output increases the blood pressure and velocity. The blood pressure overshoots its baseline level and causes temporary bradycardia. As the blood pressure and heart rate return to normal, the blood pressure waveform returns to the shape it had prior to the maneuver.

The response of the other subjects were slightly different. The differences, however, are attributed mainly to the strength of the Valsalva maneuver, the amount by which the intrathoracic pressure was increased. For instance, the changes discussed above were not as dramatic in subject 1 who increased his chest pressure by only a small amount. The initial increase in blood pressure was less. The changes in heart rate and pulse pressure were less dramatic during phase II, and the pressure overshoot after the release in the elevated chest pressure was not as noticeable. The remainder of this chapter focuses on the changes in the blood pressure waveform.
Subject 1: Response to the Valsalva maneuver

Figure 5.1A: The response of subject 1 to the Valsalva.
Figure 5.1B: The changes in blood pressure during the Valsalva of subject 1.
Figure 5.2A: The response of subject 2 to the Valsalva.
Figure 5.2B: The changes in blood pressure during the Valsalva of subject 2.
Subject 4: Response to the Valsalva maneuver

Figure 5.3A: The response of subject 4 to the Valsalva.
Figure 5.3B: The changes in blood pressure during the Valsalva of subject 4.
Subject 7: Response to the Valsalva maneuver

![Graph showing ECG, Radial BP (mmHg), and Doppler Velocity over time.]

Figure 5.4A: The response of subject 7 to the Valsalva.
Figure 5.4B: The changes in blood pressure during the Valsalva of subject 7.
Subject 8: Response to the Valsalva maneuver

Figure 5.5A: The response of subject 8 to the Valsalva.
Figure 5.5B: The changes in blood pressure during the Valsalva of subject 8.
5.2 Parameter Estimation

Before discussing the overall response to the Valsalva maneuver, the performance of the model on a beat-by-beat basis must be discussed. The issue of how well the model fits the dramatic changes in the wave shape throughout the maneuver is addressed in this section.

Figures 5.6–5.8 show three examples of typical beats during the control, post-release, and strain phases, respectively. With each figure the best-fit curve is shown with the covariance matrix. The first examples show how well the model can fit the data. The residual error between the best-fit curve and the data is small, and the parameter estimates are reliable. In the third example, the residual error is negligible, but the two parameters—\( a_1 \) and \( a_2 \)—are unidentifiable as seen by the covariance matrix. In this case one could continue iterating to find a better solution but end up with the same fit and the same residual error with very different parameters. Close inspection of the model and the data reveal that the unidentifiability of these parameters is expected. Physiologically, during the strain phase the peripheral vascular resistance increases due to vasoconstriction. In the model if the resistance increases, the voltage across the capacitor \( C_m \) becomes less damped and more oscillatory. The exponent of the decay term approaches zero, and the whole term approaches a constant \( a_2 \). Since two constants are not uniquely identifiable, \( a_1 \) and \( a_2 \) are indistinguishable. Furthermore, the uncertainty in \( a_1 \) and \( a_2 \) in the high resistance, high heart rate region suggests that a more appropriate model might be a constant with a damped sinusoid, a second-order system. This observation is confirmed by the data. In short, in the strain phase of the Valsalva maneuver the model predicts that the resistance increases, but no quantitative information can be extracted from the model. In Appendix D similar figures are provided from the same subject at various points throughout the Valsalva maneuver to illustrate more closely how the wave shape changes and how well the model fits the data.

In general, the third-order model fits the data quite well and is rich enough to account for the changes in the radial blood pressure wave shape (Appendix D), but there are a few particular regions where some residual error occurs. In beats with a
long decay time, for instance, a phase difference sometimes develops between the data and the best-fit curve ($t = 408.2s$ in Figure 5.7). Another region where some error occurs is at the hump in the diastolic wave. Whether because of reflections before the hump or because of constraints from the decay after the hump, some residual error often results in fitting the hump (Figure 5.9). Despite these areas, the model accounts for the wave shape changes quite well.
Figure 5.6: Example diastolic waveform before the Valsalva maneuver.
Figure 5.7: Example diastolic waveform from the post-release phase.
Figure 5.8: Example diastolic waveform from the strain phase.

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Figure 5.9: Waveform illustrating residual error in fitting the diastolic hump.
5.3 Estimated Parameters from the Valsalva Maneuver

The estimated model parameters—$R$, $C_m$, and $L$—for the Valsalva maneuver are shown for each subject in Figure 5.10–5.14. All subjects showed an increase in estimated resistance during phase II of the Valsalva maneuver. The estimated resistance consistently increased abruptly over a few beats between 5–7 seconds after the increase in the intrathoracic pressure in all subjects. The beat-to-beat fluctuations in resistance during the strain phase are artifactual; they reflect the unreliability of the parameter estimates in this region (see previous section). Furthermore, the abrupt decrease in estimated resistance at the release of the intrathoracic pressure is also an artifact. In this case the model interprets the decrease in arterial pressure as a diastolic decay, and hence, predicts a lower estimated resistance. During phase IV of the Valsalva maneuver all subjects except subject 7 showed a gradual decay in estimated resistance over a period of 4–5 seconds. The estimated distal compliance shows a consistent decrease that parallels the increase in estimated resistance in all subjects while the estimated inertance shows less of a consistent change throughout the Valsalva maneuver.
Figure 5.10: Estimated parameters from subject 1 during the Valsalva maneuver.
Figure 5.11: Estimated parameters from subject 2 during the Valsalva maneuver.
Figure 5.12: Estimated parameters from subject 4 during the Valsalva maneuver
Subject 7: Estimated Model Parameters during Valsalva

Figure 5.13: Estimated parameters from subject 7 during the Valsalva maneuver.
Figure 5.14: Estimated parameters from subject 8 during the Valsalva maneuver.
5.4 Sensitivity of Estimated Parameters to the Starting Time

As mentioned in Chapter 4, the start of diastole is not easily detected in the radial blood pressure pulse because of the attenuation of the dicrotic notch. The results of the evaluation of parameter sensitivity to the starting point of diastole in the data are summarized in this section.

The estimated resistance was derived from the parameters estimated using the procedure outlined in Section 4.2. Figures 5.15 and 5.16 show the estimated resistance throughout the Valsalva maneuver for different starting points in the data. The estimated resistance determined from the initial starting point \( t_0 \) are shown in the foreground; the values estimated with a starting point 60msec later are shown in the background. Figure 5.15 shows some variation during phase II, but this is attributed mainly to the unreliability of the estimated parameters in the region, not to the starting point in the data. In the case shown in Figure 5.16, the parameter estimates appear to be fairly robust throughout the Valsalva maneuver even during the strain phase. However, a rotated view of Figure 5.16 (not shown) shows the only exception found in the subjects studied. For a few beats during phase IV of the Valsalva maneuver the blood pressure pulse had a relatively large reflected component prior to the diastolic hump. As the starting point was moved forward in time the fit at the diastolic hump improved, and the estimated resistance increased.

Besides the one exception described above, these results show that in general the initial starting point in the data does not influence the estimated resistance so long as the parameter estimates are reliable for that beat.
Figure 5.15: Variation of estimated resistance with the choice of the starting point of the data—Example 1.

Figure 5.16: Variation of estimated resistance with the choice of the starting point of the data—Example 2.
5.5 Measured Results

In this section the results drawn from the measured velocity and pressure are discussed (Figures 5.17–5.21). One of the first noticeable features in the average velocity is its variability. In all subjects the velocity measurement appears unstable. The wander of the velocity signal throughout the Valsalva maneuver is attributed to motion artifact. As discussed in Appendix A, the velocity is measured using a hand held probe which is placed over the radial artery. Any motion by the operator or subject could significantly change the measured velocity. Aside from the signal variability all subjects consistently showed a drop in average flow during phase II of the Valsalva maneuver. During phase III the flow decreases temporarily again, but soon increases as more blood is pumped into the systemic arterial system.

The mean blood pressure, unlike the average flow, shows almost no variability apart from the changes expected from the Valsalva maneuver. The mean blood pressure tracings are very similar for all subjects. They all show the initial increase in mean pressure due to the increased intrathoracic pressure. During phase II the mean pressure decreases as a result of the decrease in stroke volume. There is a dip in the mean pressure when the intrathoracic pressure drops, and in all subjects except subject 1 there is an initial overshoot in the mean pressure during the post-release phase before it decays back to its normal level. One last observation is that the mean pressure during the latter part of phase II is approximately the same as the baseline pressure.

The last tracing shown in Figures 5.17–5.21 is the ratio of the mean blood pressure to mean velocity, which under steady-state conditions is assumed to be proportional resistance. The first noticeable feature in the data is the occurrence of a large spike immediately after the strain phase in the first three subjects. This abrupt increase results from the almost zero flow measured during phase III of the Valsalva maneuver. The same phenomenon is also seen during phase II of the response from subject 4. These spikes in the ratio of mean pressure to mean flow suggest that our method of measuring the zero velocity was subject to error. Since the zero of the velocity signal is not known, only qualitative information can be extracted from this data as well.

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Relative changes in the measured values cannot be quantified.

The general behavior of the ratio of mean pressure to mean velocity, however, is similar throughout the maneuver in all subjects. Almost immediately after the intrathoracic pressure is increased, the "measured resistance" increases, reaches a peak within 5–7 seconds (except in subject 2 where it takes approximately 10 seconds), and gradually decreases to a value greater than its baseline value at the end of the strain phase. During phase IV the ratio of mean pressure to mean flow decreases further and eventually settles to its baseline value.

The transient behavior of the mean pressure during the early part of phase II causes the blood volume stored in the arteries to change, and the ratio of mean pressure to mean flow cannot be equated with resistance. If one knew the value of the distal compliance and measured flow instead of velocity, one could measure the resistance during these transients by subtracting the stored volume from the mean flow before computing the resistance [38]. However, in our case we can only consider the resistance in those regions which meet the conditions outlined in Section 4.3—before the Valsalva maneuver, during the latter part of phase II, and toward the end of the post-release phase. In these regions the mean blood pressure is approximately constant and is approximately equal, and the differences in the pulse pressure between the two regions are assumed to be negligible.

Figures 5.22–5.26 show both the estimated and measured resistances for each subject. Notice that the measured resistance during the latter part of phase II is consistently greater than the measured resistance late in the maneuver. Similarly, the estimated resistance during the same region of phase II is greater that the estimated resistance late in phase IV, confirming that the wave shape changes are due in part to increases in peripheral vascular resistance as expected.
Subject 1: Measured Resistance during Valsalva

Figure 5.17: Measured quantities for subject 1.
Figure 5.18: Measured quantities for subject 2.
Subject 4: Measured Resistance during Valsalva

Figure 5.19: Measured quantities for subject 4.
Subject 7: Measured Resistance during Valsalva

Figure 5.20: Measured quantities for subject 7.
Figure 5.21: Measured quantities for subject 8.
Figure 5.22: Comparison of estimated and measured resistance for subject 1.
Subject 2: Comparison of Resistance Values

Estimated Resistance from Model

Measured Resistance (Mean BP/Mean flow)

Figure 5.23: Comparison of estimated and measured resistance for subject 2.
Subject 4: Comparison of Resistance Values

Estimated Resistance from Model

Measured Resistance (Mean BP/Mean flow)

Figure 5.24: Comparison of estimated and measured resistance for subject 4.
Subject 7: Comparison of Resistance Values

Estimated Resistance from Model

Time (sec)

Measured Resistance (Mean BP/Mean flow)

Time (sec)

Figure 5.25: Comparison of estimated and measured resistance for subject 7.
Subject 8: Comparison of Resistance Values

Estimated Resistance from Model

Measured Resistance (Mean BP/Mean flow)

Figure 5.26: Comparison of estimated and measured resistance for subject 8.
Chapter 6

Discussions and Conclusions

During the Valsalva maneuver dramatic blood pressure wave shape changes have been seen in the radial artery, suggesting that important physiologic information might be extracted from the dynamic waveform changes. A third-order lumped parameter circuit model has been developed. The model has been shown to fit the data very well with little uncertainty in the estimated parameters except during the strain phase of the Valsalva maneuver. Nevertheless, valuable qualitative information was derived using this model from the analysis of the response of five subjects to the Valsalva maneuver. All subjects showed an increase in resistance and a decrease in distal compliance during phase II of the maneuver. Furthermore, the onset of the increase in the peripheral vascular resistance was consistently within 5–7 seconds after the increase in intrathoracic pressure. Although this last result is physiologically reasonable, it is quicker than previously expected.

The development of this model, however, is not yet complete; there are some remaining areas that need more work. One area of necessary work is in the validation of the model. An attempt was made to validate the model in this thesis, but there were a number of problems with the velocity measurement. The first was that the signal was uncalibrated. Not only was the magnitude of the velocity not known, but more importantly, the zero of the velocity signal was not measured accurately. Although an attempt to calibrate the velocity could be made, the signal would still be susceptible to motion artifact. Furthermore, because this work is aimed primarily at the dynamic wave shape changes, a measurement of flow, not velocity, would be
preferable to eliminate the variations due to changes in cross-sectional area in the arteries.

Another area of future work would be to try different interventions in the cardiovascular system to change the peripheral resistance. The Valsalva maneuver was a good choice to begin with because it was simple, resulted in dramatic wave shape changes, and gave much insight into the prospect of monitoring resistance from the radial artery. However, the uncertainty in the estimated resistance during the strain phase limited our ability to evaluate the model. Therefore, a much needed area for future work is the use of other interventions that can changed resistance without significant changes in heart rate, stroke volume, and proximal compliance. For instance, vasoconstrictors and vasodilators might be used to elicit wave shape changes without significant changes in mean blood pressure.

In the future another project might be to develop a scheme for switching from the third-order model to a second-order model in high resistance, high heart rate regions. An example of such a model might consist of a simple windkessel model with an inerntance to account for the kinetic energy of the blood as it flows into the windkessel circuit.

If work continues in these areas, this model might become a clinically useful tool because it has the potential to allow a clinician to monitor changes in peripheral vascular resistance on a beat-by-beat basis from a single, non-invasive measurement of the blood pressure.
Appendix A

Vascular Resistance, Arterial Capacitance, and Inductance

In this appendix the electrical equivalents of vascular resistance, arterial compliance, and inertance are derived.

A.1 Vascular Resistance

In this section an expression for the resistance of a rigid tube with viscous flow is derived. Poiseuille was the first to develop such an expression for the resistance, but he derived it empirically by making precise measurements of blood flow in glass tubing. The result is known as Poiseuille's Law, and it is derived analytically here.

Consider the cylindrical tube with steady, laminar flow shown in Figure A.1. The Navier-Stokes equation with these assumptions and with cylindrical geometry is

\[
\frac{1}{\mu} \frac{d}{dr} \left( r \frac{d}{dr} \right) = \frac{dp}{dx} \approx \frac{\Delta p}{L} \tag{A.1}
\]

where \( \mu \) is the viscosity of the liquid. The solution for the velocity with the boundary conditions that the flow be zero at the wall, \( u(a) = 0 \), and that the flow be a maximum in the center, \( du/dr = 0 \) at \( r = 0 \) is

\[
u(r) = u_0 \left( 1 - \frac{r^2}{a^2} \right) \tag{A.2}
\]

where

\[
u_0 = \frac{\Delta p a^2}{4L\mu} \tag{A.3}
\]
Figure A.1: A cylindrical tube with steady, laminar flow of a Newtonian fluid

Solving for the flow in the tube by integrating the velocity over the cross-sectional area of the tube

\[ Q = \int_0^a 2\pi ru(r)dr = \frac{\pi u_0a^2}{2} \]  \hspace{1cm} (A.4)

Substituting in for \( u_0 \) gives

\[ Q = \frac{\pi a^4}{8L\mu} \Delta p \]  \hspace{1cm} (A.5)

Thus, the resistance of a rigid tube with steady, laminar flow is

\[ R = \frac{8L\mu}{\pi a^4} \]  \hspace{1cm} (A.6)

The resistance is proportional to the length of the tube and inversely proportional to the fourth power of the radius.

A number of assumptions made in the above derivation are not valid in the arterial system. The flow is pulsatile, not steady. The arteries are elastic, not rigid. Their diameters change with pressure. Nevertheless, the above result does provide some valuable information about the resistance to flow in the blood vessels. In the cardiovascular system the vessel cross-sectional area decreases dramatically in the arterioles, and for this reason they are usually modeled by a lumped resistance when modeling the arterial system.
Figure A.2: A small section of artery with the free-body diagram for a cross-section shown on the right.

A.2 Arterial Capacitance

In this section an expression for the compliance of a blood vessel is derived. Assuming that the length of the vessel does not change with changes in the transmural pressure, the capacitance per unit length is defined by

$$ C = \frac{dA}{dp} = 4\pi r \frac{dr}{dp} \quad (A.7) $$

In order to derive an expression for the compliance $C$, consider the free-body diagram in Figure A.2. The internal and external pressures act radially in the blood vessel, and the difference in these pressures extends the vessel wall and causes a circumferential component of stress. Since the segment of artery is in equilibrium, the radial forces must balance.

$$ 2\sigma h \Delta l \sin \frac{\theta}{2} = (p_i r_i - p_e r_e) \Delta l \theta \quad (A.8) $$

where $h$ is the artery thickness. For small $\theta$, $\sin(\theta/2) \approx \theta/2$, and the force balance equation becomes

$$ \sigma h = p_i r_i - p_e r_e \quad (A.9) $$
For a small wall thickness, \( r_i \approx r_e = r \) and

\[
\sigma_\theta = \frac{(p_i - p_e)r}{h} = \frac{pr}{h}
\]  \hspace{1cm} (A.10)

This can be rewritten as

\[
d\sigma_\theta = \frac{r}{h} dp
\]  \hspace{1cm} (A.11)

The stress is also given by Hooke's Law as

\[
d\sigma_\theta = E\frac{dl}{l} = E\frac{dr}{r}
\]  \hspace{1cm} (A.12)

for a cylinder where \( E \) is the Young's modulus. Combining this with Hooke's Law gives

\[
\frac{dr}{dp} = \frac{r^2}{Eh}
\]  \hspace{1cm} (A.13)

Substituting this into Equation A.7 completes the derivation and gives the compliance per unit length as

\[
C = 4\pi r \frac{dr}{dp} = \frac{4\pi r^3}{Eh}
\]  \hspace{1cm} (A.14)

### A.3 Inductance

Inductance, as will be shown in this section, is the electrical equivalent of inerterance. The force acting on the column of liquid is

\[
\text{Force} = (P_1 - P_2)A
\]

\[
(P_1 - P_2)A = \frac{d}{dt} (mv)
\]

\[
= \frac{d}{dt} (\rho l A \frac{Q(t)}{A})
\]

\[
= \rho l \frac{d}{dt} Q(t)
\]  \hspace{1cm} (A.16)

Therefore,

\[
\Delta P = \frac{\rho l \frac{dQ(t)}{dt}}{A}
\]  \hspace{1cm} (A.17)

The pressure drop across the tube is proportional to the change in the flow in the tube with a constant of proportionality will be called the inerterance. The electrical analog
of inercance is inductance since the voltage drop across an inductor is the inductance times $di/dt$. The inercance per unit length of the tube $L$, is

$$L = \frac{\rho}{A}$$

(A.18)
Appendix B

Instrumentation

In this appendix the instruments used to measure the radial blood pressure and blood velocity are described. In the first section the principles of arterial tonometry and its use as a technique for measuring blood pressure are briefly reviewed. In the last section the basic principles behind the Doppler velocity measurements are discussed.

B.1 Arterial Tonometry

There are many techniques for measuring blood pressure ranging from the simple cuff-based instruments that measure systolic and diastolic pressure to the invasive instruments that provide accurate and continuous measurement of blood pressure. Arterial tonometry, a relatively new method for continuous, non-invasive measurement of blood pressure, is described in this section. The discussion is brief and the reader is referred to references [16, 15] for more details.

The basic idea behind arterial tonometry is to place a pressure transducer over some artery, like the radial artery as shown in Figure B.1. $F_1$ in the diagram is the hold-down pressure, and it presses down on the artery, just flattening the surface. The pressure transducer is free to move in response to the intraarterial pressure. The flattening of the artery creates tensile forces, but in the ideal case as shown in the free-body diagram, the tensile forces are orthogonal to the transducer force. When this is the case, the measured force $F$ is a direct measurement of the arterial pressure.

Although the ideas behind arterial tonometry are simple, it was not until recently that these instruments started becoming available. Early in the development of arte-
Figure B.1: Schematic of the tonometer with a free-body diagram (From Eckerle, J. S. et al.)

The instrument used in this work was manufactured by the Colin Electronics Co., Ltd. (Model CBPM-3000). This instrument includes the features discussed in the preceding paragraph, and the blood pressure is calibrated automatically using a cuff.

### B.2 Doppler Velocity

The velocity of the blood in the radial artery is measured by Doppler ultrasound. The basic idea behind this technique is that a change in pitch results when sound reflects off objects in motion, as in the use of radar by the highway patrol. In this case, the sound waves are reflected off red blood cells that are flowing through the
arteries. The change in pitch $\Delta f$ is given by

$$\Delta f = 2fuvk\cos\theta$$  \hspace{1cm} (B.1)

where $f$ is the transmitted frequency, $v$ is the velocity of the red blood cells, $k$ is a tissue dependent constant, and $\theta$ is the angle of incidence between the ultrasound and the red blood cells. The velocity measurement depends on the angle of the probe, and it has been shown that the optimal angle is between 45 and 60 degrees because for higher angles the frequency shift decreases. For high resolution measurements in arteries close to the surface, a high frequency probe ($f = 8-10\ MHz$) is used.

The instrument used in this study was manufactured by Parks, Medical Electronics, Inc. (Model 1059—Vascular Mini-Lab III).

The Doppler probe was held over the radial artery at approximately 45 degrees pointing toward the heart. The analog output from the back of the instrument was recorded onto the VCR tape. This signal, however, was uncalibrated. Neither the gain nor the offset were known. Chapter 4 explains how we dealt with the uncalibrated signal.
Appendix C

Human Studies Approval

The following page is a copy of the letter from the Committee on the Use of Humans as Experimental Subjects granting approval to perform this study.
COMMITTEE APPROVAL

DATE: 11/17/89

TO: Roger G. Mark, M.D., Ph.D.
    E25-519

FROM: H. Walter Jones, Jr., M.D.
    Chairman

APPLICATION NO.: 1922

TITLE: Arterial Blood Pressure Waveform Analysis

RENEWAL DATE:

Your application has been approved by the Committee on the
Use of Humans as Experimental Subjects at its meeting on 11/16/89.
This approval is valid until one year from the above renewal date, at
which time your entire application will be due for annual review.

It is expected that you will promptly notify the Committee if
your subjects experience any undesirable effects. Please inform the
Committee of any changes and when your project is terminated.

The COUHES number assigned to your project is 1922.

In the future, please note this number on all correspondence
referring to this project.

cc: T. Duff, OSP
Appendix D

More Parameter Estimation Results

This appendix contains some examples of the wave shape changes that occur throughout the Valsalva maneuver. With each figure the best-fit curve is given with the covariance matrix. All of these examples come from the same individual, subject 8, and are in the order in which they occurred in the Valsalva maneuver. For more explanation of these results, please refer to Section 5.2.
Figure D.1: Example curve fit from subject 8.
Figure D.2: Example curve fit from subject 8.
Beat Number 10

Figure D.3: Example curve fit from subject 8.
Figure D.4: Example curve fit from subject 8.
Figure D.5: Example curve fit from subject 8.
Beat Number 25

Radial BP (mmHg)

Time (sec)

30273. -30217. 381.11 -15.044 -16.999 -12.644 -3.4380
-30217. 30161. -380.26 15.814 17.180 12.103 3.3703
381.11 -380.26 4.8206 -0.0556 -0.1791 -0.2492 -0.0538
-15.044 15.814 -0.0556 1.1461 0.3573 -0.5147 -0.0599
-16.999 17.180 -0.1791 0.3573 0.1411 -0.1274 -0.0142
-12.644 12.103 -0.2492 -0.5147 -0.1274 0.3933 0.0458
-3.4380 3.3703 -0.0538 -0.0599 -0.0142 0.0458 0.0058

Figure D.6: Example curve fit from subject 8.
Figure D.7: Example curve fit from subject 8.
Figure D.8: Example curve fit from subject 8.
Figure D.9: Example curve fit from subject 8.
Beat Number 45

Figure D.10: Example curve fit from subject 8.
Beat Number 50

Radial BP (mmHg)

Time (sec)

0.2501  -0.0427  0.0515  0.1690  0.0544  -0.0707  -0.0109
-0.0427  0.1518  0.0014  0.1376  0.0483  -0.0348  -0.0042
0.0515  0.0014  0.0116  0.0450  0.0145  -0.0179  -0.0027
0.1690  0.1376  0.0450  0.5921  0.2310  -0.0784  -0.0052
0.0544  0.0493  0.0145  0.2310  0.1273  -0.0248  -0.0027
-0.0707  -0.0348  -0.0179  -0.0784  -0.0248  0.0984  0.0035
-0.0108  -0.0042  -0.0027  -0.0092  -0.0027  0.0098  0.0044

Figure D.11: Example curve fit from subject 8.
Beat Number 55

![Graph showing radial blood pressure over time](image)

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<tr>
<td>418.8</td>
<td>-0.0154</td>
</tr>
</tbody>
</table>

**Figure D.12:** Example curve fit from subject 8.
Beat Number 60

Radial BP (mmHg)

Time (sec)

1.7726  -1.2308  0.2313  0.3554  0.1242  -0.0944  -0.0276
-1.2329  0.9719  -0.1509  -0.1427  -0.0553  0.0335  0.0134
0.2313  -0.1509  0.0313  0.0536  0.0180  -0.0153  -0.0042
0.3554  -0.1427  0.0536  0.3571  0.1286  -0.0355  -0.0076
0.1242  -0.0553  0.0180  0.1286  0.0634  -0.0107  -0.0023
-0.0944  0.0335  -0.0153  -0.0355  -0.0107  0.0442  0.0065
-0.0276  0.0134  -0.0042  -0.0076  -0.0023  0.0065  0.0015

Figure D.13: Example curve fit from subject 8.
Figure D.14: Example curve fit from subject 8.
Bibliography


