ANALYSIS AND SENSITIVITY STUDY OF ZERO-DIMENSIONAL MODELING OF HUMAN BLOOD CIRCULATION NETWORK

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Mechanical Engineering

By

ROUSSEL RAHMAN
B.S., Bangladesh University of Engineering and Technology, 2014

2017
Wright State University

George Huang, Ph.D.
Thesis Director

Joseph Slater, Ph.D.
Chair, Department of Department of Mechanical and Materials Engineering

George Huang, Ph.D.

James Menart, Ph.D.

PhilippeSucosky, Ph.D.

Robert EW Fyffe, Ph.D.
Vice President of Research and Dean of the Graduate School
ABSTRACT


The systemic circulation has a large number of vessels; therefore, 3-D simulation of pulse-wave propagation in the entire cardiovascular system is difficult and computationally expensive. Zero-Dimensional (Zero-D) and One-Dimensional (1-D) models are simplified representations of the cardiovascular network; they can be coupled as supplements to regional 3-D models for closed-loop multi-scale studies or be simulated as self-sufficient representations of the blood-flow network. Unlike Zero-D models, 1-D models can provide linear space-wise information for the vessels. However, Zero-D models can prove to be more useful in particular cases; as flexibility in adjusting parameters facilitate in tailoring the model to specific needs. A prevalent reservation regarding the Zero-D models has been the inconsistency of parameter adjustment. A primary objective of this work is to build a closed loop cardiovascular model with a consistent, easily replicable methodology so that the model (1) can be adopted in multi-scale studies and (2) can provide a quick clinical tool for patient-specific studies. Fifty-five large arteries were represented individually and the rest of
the cardiovascular network was lumped into several equivalent components. This way, arbitrary parameter adjustments have been restricted to the microcirculation and venous sections only. The model was validated by comparing simulated hemodynamic properties with clinical measurements and simulations from a comparable 1-D model. The Zero-D simulations have been shown to be in excellent agreement with the 1-D predictions, despite their discrete nature in space being contrary to linearly continuous 1-D counterpart. An advantageous characteristic of the developed model is the retention of physiological definitions, especially for the arterial network. Therefore, the model can be conveniently modified for patient-specific simulations. The generality of the method and closed-loop nature of the model also allow to inquisitively study various mathematical assumptions in blood flow modeling and experimental techniques. As an example, a possible source of non-physiological wave reflections has been studied in this thesis. The developed Zero-D model was found to be quite sensitive to the diastolic function of the left ventricle (LV). Therefore, several aspects of the mathematical modeling of ventricular elastance and LV-aorta coupling have been investigated in terms of measured responses from a healthy heart. Moreover, a few conventional assumptions of Zero-D modeling have been studied and found to be quite accurate with respect to 1-D simulations. Finally, the scopes for future studies and suitability of the model to certain applications have been discussed.

**Keywords:** Zero-dimensional modeling; Blood circulation network; Cardiovascular system; Arterial network; Ventricular elastance
# Table of Contents

List of Figures .................................................................................................................................................. viii

List of Tables ...................................................................................................................................................... xi

Acknowledgements........................................................................................................................................... xii

Chapter 1  Introduction ....................................................................................................................................... 1

1.1 Human Cardiovascular System: Physiology and Anatomy ................................................................. 4

1.1.1 Heart and Pulmonary Circulation ....................................................................................................... 6

1.1.2 Systemic Circulation and its Blood Vessels .................................................................................... 8

1.1.3 Blood: Distribution and Properties .................................................................................................... 11

1.2 Mathematical Modeling of Cardiovascular System: Review ............................................................ 12

1.2.1 Review of Zero-Dimensional Modeling Methods ......................................................................... 14

1.3 Motivations and Objectives .................................................................................................................. 17

1.3.1 Objectives and Goals ...................................................................................................................... 20

Chapter 2  Methodology .................................................................................................................................... 22

2.1 Formulation of Zero-Dimensional Governing Equations .................................................................... 22

2.1.1 Flow Resistance, R .......................................................................................................................... 28
2.1.2 Vessel Compliance, C ................................................................. 29

2.1.3 Fluid Inertance, L ............................................................... 30

2.2 Calculation of RLC Parameters ...................................................... 30

2.2.1 Constant RLCs for Arteries ......................................................... 31

2.2.2 Variable RLCs for Arteries ......................................................... 32

2.3 Junction Treatment ........................................................................ 32

2.4 Peripheral Circulation ................................................................. 33

2.4.1 Terminal Reflection Co-efficient and Terminal Resistance .......... 35

2.5 Heart Model .............................................................................. 36

2.5.1 Modeling of Cardiac Contraction and Relaxation ......................... 38

Chapter 3 Model Construction and Simulation Settings .......................... 41

3.1 Specification of Model Parameters .................................................. 43

3.2 Specification of Simulation Conditions ............................................. 44

3.2.1 Space-time Discretization and Stability ....................................... 44

3.2.2 Boundary Conditions .................................................................. 45

Chapter 4 Results and Validation ...................................................... 47

4.1 Heart ......................................................................................... 48

4.2 Arterial Network ......................................................................... 52
4.3 Pressure Drop in Peripheral Circulation ..................................................... 63

4.4 Sensitivity of the Model to RLC Parameters ............................................. 64

4.5 Fixed vs Time-varying RLC Parameters .................................................. 68

4.6 Effect of Ventricular Elastance ................................................................. 70

Chapter 5 Conclusions .................................................................................. 75

5.1 Scopes of Application ................................................................................ 78

5.2 Scopes of Future Work .............................................................................. 79

Appendix 1: Arterial Network ....................................................................... 80

Appendix 2: Heart Model ................................................................................ 82

Appendix 3: Venae Cavae ............................................................................. 83

Appendix 4: Peripheral Circulation ............................................................... 84

References ...................................................................................................... 86
List of Figures

Figure 1.1: Simplified depiction of human blood flow through the cardiovascular system, (red=rich in $O_2$, blue=rich in $CO_2$) [3]........................................................................................................................................5

Figure 1.2: Structure of typical systemic vessel (except capillaries) [57].................................................................................9

Figure 1.3: Distribution of (a) cardiac output (b) Blood Volume [4].............................................................................................11

Figure 2.1: (a) General orientation of a sample vessel (b) 1-D representation of the vessel; redrawn from [52]........................................................................................................................................22

Figure 2.2: Concept of a control volume or compartment for a vessel in 1-D to Zero-D transformation ...........................................................................................................................................24

Figure 2.3: Inverse L-element single compartment for Zero-D modeling (P_e set to zero in current work)........................................................................................................................................28

Figure 2.4: (a) Compliances in series (b) Equivalent compliance; at arterial bifurcations..............................................33

Figure 2.5: A peripheral channel consisting of a terminal resistance (R_0) and lumped-parameter models for micro- and venous circulation........................................................................................................34

Figure 2.6: Lumped-parameter heart model developed through electrical analogy. [16] Notation of parameters: E, elastance; L, inertance; R, viscous resistance; C, compliance; B, Bernoulli’s resistance; S, viscoelasticity coefficient; P_i, intrathoracic pressure; P_pc, pericardium pressure.
Subscripts: ra, right atrium; rv, right ventricle; tv, tricuspid valve; pv, pulmonary valve; pua, pulmonary artery; puc, pulmonary capillary; puv, pulmonary vein; la, left atrium; lv, left ventricle; mv, mitral valve; av; aortic valve........................................................................................................................................37

Figure 3.1: Flow of information (and blood) in the modeled cardiovascular network......................................................41

Figure 3.2: Arterial model consisting of 55 major arteries [7]........................................................................................................42
Figure 3.3: Construction of the entire Zero-D model of the blood circulation network. Notations: rectangular symbols in red denote individual arteries, labeled according to vessel IDs in appendix 1. Parallelogram-shaped symbols in purple are peripheral channels, labeled as in appendix 4. Blue, circular symbols represent the venae cavae. Dashed lines are used to indicate extension lines for illustrating connections, physically not present in the cardiovascular system or the developed model.

Figure 4.1: (a) Pressures and (b) volumes of the chambers of heart during a cardiac cycle; simulations from both models are compared against literature data [60, 62].

Figure 4.2: Changes in pressure and volume in aorta, left ventricle and left atrium from Zero-D simulations (HR=60 bpm).

Figure 4.3: Blood flow in selected vessels of systemic circulation: computational results from Zero-D and 1-D models are compared with literature data (average and standard deviation). Number in parenthesis denotes vessel ID. References: [7] in general; 01, 10, (13, 31), (28 & 30), 34, 38, SVC) from [60, 63, (64), (65), 66-68] respectively.

Figure 4.4: Zero-D simulations are compared against in-vivo measurements adopted from literature, references within. To note, cardiac cycles were adjusted to match the cardiac parameters of simulation (Appendix 2).

Figure 4.5: Pressure and flow waveforms in ascending aorta (To note: the time axis is different from figure 4.2 and as per the parameters of simulation).

Figure 4.6: Pressure and flow waveforms in two arteries branching towards superior vena cava.

Figure 4.7: Pressure and flow waveforms in the arteries of renal circulation, branching towards inferior vena cava.

Figure 4.8: Sensitivity to (a) resistance (b) inertance (c) compliance.

Figure 4.9: Simulations with variable and averaged RLC parameters show marginal differences, and no obvious improvement with respect to 1-D simulations.

Figure 4.10: (a) Pressure (b) flow waves for elastances modeled with equations (2.30) - (2.32). A time interval of flow wave is zoomed and panned in (c).
Figure 4.11: Corresponding normalized elastance functions for figure (4.10) ......................................................71

Figure 4.12: (a) Pressure in left ventricle (b) flow through aortic valve. Sudden shut-off of aortic valve shown in inset ........................................................................................................................................73

Figure 4.13: Pressure and flow waves in aorta from 1-D simulations for elastance functions in equation (2.31) -(2.32) ..................................................................................................................................................73
List of Tables

Table 1.1: Distribution of systemic vessels and their typical lumen diameter (D) and wall thickness (h) [4, 5, 6, 8].................................................................................................................. 8

Table 4.1: Comparison between simulated cardiac parameters and In-vivo measurements in Brachiocephalic artery for healthy, young adults. (*: Male; **: Female). References are included within. .............................................................................................................................................49

Table 4.2: Mean values for ascending aorta..........................................................................................................................58

Table 4.3: Comparisons of mean pressure and flow distribution. The variables were normalized in terms of aortic pressure and flow rate in table 4.2..........................................................................................................................59

Table 4.4: Pressure distribution in microcirculation (Note: the mean pressures are presented at the inlet of the sections) ........................................................................................................................................63

Table 4.5: Changes in mean values with changes in RLC parameters..........................................................................................64

Table A1: Physiological data for arteries, taken from [58].............................................................................................................80

Tables A2 and A3: Parameter used in heart model, adopted from [2, 7, 16] and adjusted.................................82

Table A4: Parameter used in venae cavae, adopted from [58].................................................................................................83

Table A5: Parameter used in peripheral circulation, adopted from [58] and adjusted.................................84
Acknowledgements

To my Abbu (Father), who was a physician by profession; but, a mathematician with all his heart. His extreme and contagious numero-philia is his greatest impression on my mind. This work is my tribute to him; I know he would have loved to see the fusion of his life and love in my thesis on mathematical modeling of human blood flow.

To my thesis advisor, Dr. George Huang. Apart from the obvious reasons, I am especially grateful for allowing me to run wild with my ideas and for the patience in reining me in when necessary.

To my undergraduate advisor and life-time mentor, Dr. Md. Zahurul Haq, who is never tired of my incessant questions.

Finally, to my loved ones, who would not need any words to know what I want to say to them.
Chapter 1

Introduction

The delicate nature of the human body frequently eliminates the most commonly used method in scientific studies, trial-and-error, to reach the solution. Therefore, experimental setups and Computational Fluid Dynamics (CFD) are the tools extensively used to study the blood circulation system of a human body. Zero-Dimensional (Zero-D) and One-Dimensional (1-D) models are simplified representations of the cardiovascular phenomenon in human blood flow network. Their necessity rises from the complexity of human vasculature. To provide a glimpse of the complexity, the total linear length of the systemic blood vessels is a staggering 60,000 miles approximately; which is ~2.5 times of the earth’s circumference [78]. Understandably, development of a complete closed-loop 3-D model of the entire network can be safely assumed to be impossible, at least in foreseeable future, despite the ever-increasing computational riches of modern era. On one hand, the singularity of every human body significantly undermines the possibility that a single, comprehensive circulatory model exists for the entire human race. On the other hand, because of the enormity of the number of vessels, it is extremely difficult to create a complete 3-D model even for one individual; as the ensuing computational cost would also exceed any figments of imagination.
Therefore, Zero-D and 1-D models present a convenient way to study the flow conditions in the human cardiovascular system. 1-D models are represented as a system of Partial Differential Equations (PDEs) with the assumption that the flow parameters and properties primarily change in linear space-time. 1-D models are significantly faster than 3-D models to simulate, but are susceptible to the similar restrictions because of the number of vessels and their combined length to model. Also, specialized treatments are required to solve the PDEs governing the flow. Therefore, vascular sections beyond the intended scope of investigation are often pooled together into Zero-D or lumped-parameter models to complement 1-D models. Zero-D models are the derivatives of one more step of simplification of 1-D linear counterparts. In zero dimensions, the space dependence is discretized by considering one or more vessels as a point, or more accurately, a compartment in the circulatory network. The governing equations are ordinary differential equations; therefore, they can be solved through much simpler techniques and much faster with any average computer. The models are also quite robust and stable; consistent solutions can be reached with few simple convergence criteria [1]. Zero-D modeling is not new as a concept, rather the first CFD attempts to model the human cardio-vasculature had been through similar models; as the simplicity makes Zero-D models convenient for solving both analytically and numerically, by hand or with the help of simple calculators. Because of the general use of Zero-D modeling techniques in *lumping* multiple vessels into fewer equivalent components, Zero-D models are also
known as lumped-parameter models. A detailed discussion of the applications, merits and perils of 1-D and Zero-D models is provided in the following sections.

In this work, the human arterial network has been modeled in zero-dimensions with fifty-five large arteries being individually represented. The rest of the vasculature, including the heart, has been represented by several equivalent lumped models to form a closed loop. The simulations have been compared against clinical data (if available), and also with the predictions of a validated 1-D model [2]. This 1-D model uses a shock-capturing Time Variation Diminishing (TVD) scheme to solve the PDEs and demonstrates excellent agreement with clinical and experimental data for problems involving varying and discontinuous mechanical properties. In this work, it has been shown that the developed Zero-D cardiovascular model can emulate hemodynamic conditions predicted by the 1-D model reasonably well, with proper adjustments and within the restricted scope. Comparison with 1-D model provides an important advantage: to distinctively identify the effects of Zero-D assumptions only. On the basis of the discrepancies, the sources have been studied and methods of adjustments have been explored to overcome those differences. The physiological definitions of the arterial section have been retained in this Zero-D model, unlike many of its predecessors. Therefore, a significant advantage is the capability of studying various assumptions in numerical modeling and validation of experimental measurements. As an example, the cardiac function of the left ventricle has been studied in terms of its elastance function.
As the premise of this work has been set in application of principles of fluid mechanics in human cardiovascular system, the human body has often been depicted as an extremely sophisticated machinery. The physiological events have been interpreted in terms of fluid dynamics governing equations; therefore, the traditional clinical terminology and comparable mechanical nomenclature have been used interchangeably.

1.1 Human Cardiovascular System: Physiology and Anatomy

The human body consists of many organs and mechanisms performing different functions in periodic manner and in close co-ordination with each other. Blood performs an integral task in this synchronized work environment. To perform respective functions, the organs require energy and this energy is received from the chemical reactions. The extents of the reactions are dependent upon the amount of oxygen and other reactants supplied by the blood. Therefore, the cardiovascular or the circulatory system can be considered as the transportation system for oxygen and nutrients through the carrier fluid, blood. The flowing blood performs other important functions as well; such as, periodic removal of carbon-di-oxide and temperature regulation [3, 4]. The cardiovascular system is a closed-loop network, primarily consisting of the heart, the pulmonary circulation, the systemic network (Figure 1.1) and, of course, the blood within. The O$_2$-CO$_2$ exchange occurs in the microcirculation of the capillaries; with the direction of exchange being opposite for systemic and pulmonary circulations.
Another important portion of the blood flow is the coronary circulation, which sustains the heart itself. However, coronary vessels have not been included in the model and therefore, are not discussed in this thesis.

Figure 1.1: Simplified depiction of human blood flow through the cardiovascular system, (red=rich in $O_2$, blue=rich in $CO_2$) [3].
1.1.1 Heart and Pulmonary Circulation

The pulsatile blood flow is induced by the periodic spatial pressure gradient generated by the heart. The heart, with its chambers, periodically contracts and relaxes during a cardiac cycle to pump blood throughout the body. The heart has four chambers; two atria and two ventricles, separated into left and right segments (Figure 1.1). The hydraulic analogy of the ventricles are pumps, which are connected in series to perform the pumping action and thereby, creating the necessary pressure gradient for the circulation through the systemic circulation spread across the entire body [3].

Four cardiac valves situated between chambers, open and close due to pressure differences and ensure that the flow is unidirectional by protecting against backflows. The CO₂–rich blood returning from the systemic circulation, enters the heart through the Right Atrium (RA) and flows through the Tricuspid Valve (TriV) to the Right Ventricle (RV). The first pumping action is performed by the RV, raising the pressure and when this pressure exceeds that of the pulmonary artery, blood flows into the lungs as the Pulmonary Valve (PulV) opens. Within the pulmonary circulation, CO₂ is released and blood is refilled with oxygen. Thereafter, blood re-enters the heart through the Left Atrium (LA) and flows through the Mitral Valve (MitV) into the Left Ventricle (LV). LV performs the second pumping action on the blood to raise its pressure even further and blood enters the systemic circulation as the Aortic Valve (AorV) opens. The oxygen-rich blood is depicted in red in the cardiovascular network in figure (1.1) and CO₂-saturated blood in blue.
Blood pressure increases as it flows through the chambers of heart and the lung, although it is the ventricles that impart the majority of driving pressure potential. In each cardiac cycle, atria and ventricles go through respective phases of systole and diastole, with 1:2 ratio of respective durations under resting conditions in healthy human beings [4]. During ventricular systole, the ventricles contract and towards the end of the systole, PulV and AorV opens to allow blood to flow to pulmonary and systemic circulation, The RV pumps deoxygenated blood at low pressure (mean ~15 mm Hg) through the low-resistance pulmonary circulation and the LV drives oxygenated blood at high pressure (mean ~90 mm Hg) through the high resistance systemic circulation [4]. During diastole, PulV and AorV remain shut and the atrioventricular valves open as the ventricles refill receiving the blood from the atria. The heart rate in a healthy human at rest is approximately 60-75 beats per minute; consequently, the usual duration of a cardiac cycle is ranges between 0.8-1.0 second with the typical stoke volume of the heart being within 70-80 mL [4, 5]. Therefore, the normal range of cardiac output, i.e., the volume of blood ejected per cardiac cycle is within 5-6 L/min. This periodic contraction and relaxation is associated with the elastances of the heart’s chambers, which are often used as the defining parameters of heart’s functioning in CFD simulations. The elastance of chamber is a time varying quantity during systole (Section 2.5.1) and hence, the rate of volume contraction also varies during a cardiac stroke.
1.1.2 Systemic Circulation and its Blood Vessels

Systemic circulation distributes the blood to the organs and muscles of the human body, hence performing the previously mentioned functions of the blood flow. Blood from the heart enters the systemic circulation through the aorta before branching out into the arterial network of progressively smaller arteries. Thereafter, blood flows through the microcirculatory segment of arterioles (smallest arteries), capillaries and venules to the venous section. Oxygen is stripped away from the blood by the organs and tissues of the body predominantly within this microcirculation. Contrary to the events in the arterial network, venules and veins keep merging in the direction of the flow into larger veins. Finally, at the very end of the systemic circulation, blood return to the heart through superior and inferior venae cavae, two of the largest veins (often regarded as one single vein, for example in [6]) of the human body.
This work primarily focuses on the arterial network of the systemic circulation. Fifty-five large arteries have been individually modeled and the rest has been *lumped* into several equivalent components. The geometric, structural and material properties of the blood vessels, along with the flow situations in them, are of great importance in the context of this work; therefore, have been discussed in the light of the considerations used for modeling purposes.

![Structure of typical systemic vessel (except capillaries)](image)

*Figure 1.2: Structure of typical systemic vessel (except capillaries)* [57]

Blood flow in the human body is associated with a pulse wave propagation along the systemic circulation. This pressure wave propagation through the enormous length of the systemic circulation is possible only because the blood vessels are compliant, instead of being rigid tubes [3, 4]. The compliance allows the vessels to store energy.
by expanding of the vessels during ventricular systole, and the potential energy is released to maintain the driving pressure required for flow. The vessels expand and contract to create regional pressure differences and consequently, generate a pulsatile flow.

Similar to the elastances of the heart’s chambers, the compliance is a product of the elastic nature; in fact, the two terms are reciprocal of each other (section 2.1.2). Arteries are the most compliant vessels present in the systemic circulation and the compliance decreases as the flow moves downstream to venous sections, which is understandable as the further downstream and closer to the heart, the less is the requirement for storing energy. This phenomenon can be loosely and presumably interpreted as the energy and material management system installed by the years of evolution of human body.

Though arterial vessels are tapered and curved in shape, in CFD studies (including this one) they are often assumed as straight tubes of varying cross-sectional area. This assumption on the vessel geometry is more suitable for smaller arteries, capillaries and the veins. Also, the area of the vessels becomes more uniform in later parts of the systemic circulation, with even the large veins having very marginal changes in lumen diameter throughout [7]. The pressure is the highest at the start of the systemic circulation and the arterial network is the high-pressure zone of the systemic circulation [4]. The largest artery of the cardiovascular system is the aorta, where the pressure and the flow rate are also the highest as the entirety of cardiac output from the heart travels through this single vessel. The total pressure drop in systemic
circulation is approximately 90-100 mm Hg; only 1% of that occurs in the aorta [4, 8] and the mean pressure drop across the main arteries is only ~2 mm Hg [4]. The pressure drop mainly occurs in the small vessels (arterioles, capillaries, venules), due to the increased resistance to the flow from reduced lumen area. For instance, the total arteriolar resistance is ~100 times and total capillary resistance is ~25 times larger than that of the ascending aorta; with the venules and veins contribute 5 percent of the total systemic resistance [8]. Though capillaries have a smaller order of diameter than arterioles, capillaries are larger in number and provide more pathways for the flow (Table 1.1), to have an overall lower resistance than arterioles.

1.1.3 **Blood: Distribution and Properties**

*Figure 1.3: Distribution of (a) cardiac output (b) Blood Volume [4]*
Blood constitutes of plasma (~55%) and cellular elements (~45%) [3, 4]. Plasma is a highly aqueous solution, in which the red blood cells, white blood cells and platelets are carried. Blood is a non-Newtonian fluid; however, the extent of non-Newtonian behavior varies in different vessels. At shear rates in the order of 1000 1/s (typical for large systemic arteries) and higher, the dynamic viscosity of the blood remain unchanged [3, 9], and the blood can be approximated as a Newtonian fluid. This assumption holds true in the large systemic arteries; but, not in the vessels of smaller diameters, such as the capillaries [5, 9]. Overall, the whole blood has a density of ~1050 kg/m$^3$ and an apparent dynamic viscosity in the range of 3-4 mPa-s [4, 9, 10].

The approximate volume of blood in a 70-kg human is 5 liters; which is about 7% of total body weight [11]. The blood distribution in different organs are shown from two perspectives in figure (1.3).

1.2 Mathematical Modeling of Cardiovascular System: Review

The heart (pulse) rate of the human body is perhaps the most easily perceptible and quantifiable cardiovascular phenomenon. Unsurprisingly, one of the first known steps towards mathematical modeling of blood flow in human vasculature, by Galen (129-210 AD), were through the study of strength and frequency of the blood pulse [12]. Modern understanding of cardiovascular phenomenon was initiated by William Harvey (1677-1761), as he noticed the cyclic nature of the blood flow in the body and made another important discovery that the arterial pulse is caused by the contraction of the heart [13]. Reverend Stephen Hales (1677-1761) introduced the concept of
Windkessel effect, which can be considered as the first steps towards Zero-D modeling of a cardiovascular phenomenon. Later, the effect was described mathematically by Otto Frank [14].

Many significant contributions in mathematical interpretation of cardiovascular phenomenon came from the contributions in the field of fluid dynamics. Sir Isaac Newton had devised the necessary mathematical tools for studying fluids and conceptualized the fluid resistance in the form of viscosity. The basis of modern endeavors was formed by Leonhard Euler in 1775 [15], when he derived the partial differential equations from the conservation of mass and momentum of an inviscid fluid. Supposedly, he did not recognize the wave-like nature of the blood flow and was not able to find a solution for the pulse wave propagation [5]. Then, Thomas Young gave the first scientific explanation of the oscillatory nature of the flow and proposed an intuitive relation [12]; which, in current bio-mechanical parlance, can be described as a correlation between vessel compliance and wave propagation velocity. This correlation was based upon Newton’s theory of sound velocity in fluid mediums. Afterwards, Moens and Korteweg were independently able to derive an equation for the wave speed for thin, elastic vessels [5], which is now known as the Moens-Korteweg relationship. Though the relation does not account for the viscous effects, it is still being used extensively in CFD simulations [7, 16-18] and has been used in this work as well, through adopting the calculated wave speeds from the referred literature. The wave propagation in 1-D space is described by a system of hyperbolic or parabolic partial differential equations [10]. Therefore, when Bernhard Riemann
developed the method of characteristics in 1860 for solving partial differential equations [19], it became a vital cog of 1-D modeling endeavors and a cornerstone for modern CFD studies, in general.

This work primarily focuses on Zero-D modeling of the arterial network on the basis of the 1-D simulations. In the following section, the successes and obstacles of related works are discussed.

1.2.1 Review of Zero-Dimensional Modeling Methods

Zero-D models are most commonly expressed by hydraulic-electrical analogies; with flow resistance (R), fluid inerterance (L) and vessel compliance (C) being respective derivatives of resistor, inductor and capacitor of circuit theory. The compliance describes the energy or pressure potential storing abilities of elastic arteries and the resistance that describes the viscous dissipation in vessels. The inertance is a relatively new addition to the concept, emulating the inertia of the fluid and consequent disinclination towards sudden changes in flow wave. While the overall hemodynamics can be predicted by the resistance in a Poiseuille flow consideration, the LC parameters are essential in capturing the pulsatile nature of blood flow.

The Windkessel model, mathematically formulated by Frank [14], was a single-compartment RC model for the entire systemic circulation, with components in parallel connection. This model neglected the venous section by attributing a zero pressure to it and was developed to capture the elementary characteristics of the systemic artery network. Despite the crude outlook and an obvious restriction of a
single time constant, the two-element Windkessel is able to emulate the pressure decay in the aorta over the period of diastole and is still in use in clinical estimation of total arterial compliance with known peripheral resistance and the aortic pressure pulse waveform [4, 23]. Landes [20] introduced an additional resistive element in series with the RC Windkessel model and the resulting RCR model has been extensively studied by Westerhof et al. [72], rendering another label for the RCR model as the Westkessel model. This second resistance, representing the characteristic impedance of the arterial network, was defined as the ratio of oscillatory pressure and flow-rate when zero reflective waves [5, 10] and the total resistance was maintained the same as of the RC model [21]. However, in-vivo studies showed that underestimations of peak aortic flow and mean arterial pressure, and non-physiological aortic pressure and flow waveforms in comparison to a realistic arterial impedance model with the same ventricular action [22]. Another configuration of the three element RCR model was proposed by Burattini and Natalucci [24]. Landes [20] and Westerhof et al. [26] then individually incorporated the inertial effect of blood flow and extended the RCR model to different RLCR configurations. In a bid for more accurate representation of the systemic circulation, the Zero-D models were extended to multi-compartment constructions. While the earlier descriptions were appropriate to treat the systemic vasculature as a whole, the characteristics of the individual vessels are included in individual representation of the arteries in multi-compartment methods; therefore, these models provide better scopes for detailed studies of cardiovascular diseases. Noordergraaf et al. [27],
Avolio [28], and O'Rourke and Avolio [29] had constructed complete, open-loop models for the systemic arterial network with this principle. Some multi-branched multi-compartment models had also been developed [27, 29-36] to investigate the hemodynamics of vessel branches in both human and canines. More recently in the 2000s, Formaggia and Veneziani [37] and Milišić and Quarteroni [1] developed the detailed derivations of four typical configurations for individual vessel segments. De Pater et al [38] suggested that “the transmission line can be represented to any desired accuracy by a lumped section”, This statement was proved in [1], and methods and corresponding stability criteria were developed for discretizing vessels along the length into multiple Zero-D elements, even in one single vessel. In such a representation, the resulting model can capture the pulse wave propagation and has been demonstrated to very accurately emulate 1-D predictions. In the present work, the large arteries are represented as individual, single compartments and the simulations were run per the stability criteria derived in [1].

For the heart, Suga et al. [39] proposed a varying elastance model in representing the left ventricle; the ventricular pressure being defined a function of the ventricular elastance and the change of volume from its unstressed value. The change of ventricular volume is determined by the conservation of mass in the chamber. The ventricular elastance is developed as a time-varying function based on in-vivo measurement of the ventricular activity over the cardiac cycle. This model has been extensively adopted by researchers [31, 33, 40-43]. Differing alternatives to the varying elastance model have been described in [36, 44-46]; the variations are based
on muscle force, myocardial wall tension and even assuming the heart as a spherical compartment and also from a purely mathematical point of view without any consideration of ventricular dynamics. The concept was later adopted for the right ventricle and the atria as well, some of the recent works being [2, 7, 16]. This current work uses a heart model inspired by the same principle of time-varying elastance.

*Multiple branches for each artery*

1.3 Motivations and Objectives

The perils associated with 3-D and 1-D modeling of the entire cardiovascular system have already been discussed. In this section, the advantages of Zero-D modeling overall and the purposes of this work are discussed in terms of the requirement of proper boundary conditions and the importance of closed-loop formulation of the circulatory network.

3-D and 1-D models of segments of the cardiovascular system have been and are in widespread practice for computational bio-fluid dynamics studies. An associated difficulty in such endeavors is the common one as in any CFD studies: the appropriateness of boundary conditions. The effectiveness of CFD simulations and accuracy of results are very much dependent on this point. Understandably and ideally, the most accurate boundary conditions would be the recent patient data for the local model. However, in case of the unavailability of proper resources and scope for extracting *in-vivo* data, researchers are often forced to approximate the boundary conditions with highly idealized functions or numerical inputs. For example, in an
arterial stenosis study, the flow conditions at the boundaries would change due to the presence of the plaque. But, for many relevant researches, the boundary conditions are adopted from statistical data of healthy control groups; a few from myriad examples are [43-45]. The consequence is the inclusion of an uncertainty in otherwise excellent studies of cardiovascular diseases. Also, the open loop nature of the study reduces the model’s capability to capture the global hemodynamics. Following the earlier example, downstream vessels of a stenosed artery goes through vasodilation to ameliorate the effects of increased flow resistance [4]. For a strictly local model, the changes will not be included in the simulation if the boundary condition is not adjusted.

A major reason behind the increasing popularity of CFD in studying human blood circulation is that the computational methods provide convenient ways to glean the details of hemodynamic conditions from limited patient data; similarly, the flexibility offers a way to address or bypass the aforementioned concerns. A growing recent trend has been to include the entire network or extended sections at the boundaries in simulation, through simplified in 1-D or Zero-D standalone models and multiscale models; a few examples of many are in [16, 17, 48, 71, 73]. This way, associated global effects can be included; by eliminating the necessity of imposing boundary conditions in closed-loop formations and in open-loop studies, by applying the boundary conditions in distant localities where the effects are marginal. Contrary to the open-loop networks, the closed-loop formation does not require any direct boundary conditions. Rather, the problem is reduced to setting flexible initial conditions for the
model. An accurate, flexible closed-loop network of the entire cardiovascular system is, therefore, an attractive proposition. Numerous 1-D models have already been established to provide simulations in excellent agreement with the *in-vivo* measurements [2, 5, 7, 51]. However, 1-D governing equations are partial differential equations of either hyperbolic or parabolic nature and require mathematically involved solution techniques (such as, Riemann variable transformation [2]). Consequently, delicate treatment is required at the discontinuity of the junctions as well. Each bifurcation involves three branches and the problem is usually defined through a set of six equations, to be solved for six unknowns per junction [10]. Conversely, Zero-D governing equations are ordinary differential equations that can be solved with much simpler numerical methods and the junction treatment is equally easier. The Zero-D model of this work adopts a simplifying assumption through common pressure requirement at the bifurcations to handle the discontinuity (section 2.3). Moreover, the closed-loop multiscale and 1-D models usually require several sections to be modeled in Zero-D as well. The numerical challenge of these simplified representations is to ensure wave propagation without causing excessive errors in amplitude (dissipation) and in phase (dispersion) [10]. Consequently, Zero-D modeling parameters often require adjustments through a trial-and-error or numerical optimization process to fit patient data. Combined with the high-level abstraction of lumped models, the adjustments can render an arbitrariness to the physiological interpretation. The varying methods used in different works and resulting inconsistency in parameters is a point of both concern
and interest, and requires further exploration [50]. While the option of parameter adjustment in lumped models is advantageous from a mathematical perspective, it also permits an ambiguity to persist in the method. Consequently, clinical decision-making based on simulated data can be difficult.

1.3.1 Objectives and Goals

From the review in section (1.2) and the discussion of the advantages and problems associated with Zero-D models, it can be understood that the modeling technique comes with the cost of a trade-off among computational accuracy, modeling simplicity and ease of interpreting result. A general goal of this project was to analyze the extent of this trade-off and find an optimum solution.

Therefore, the primary objective of this work was to develop a closed-loop Zero-D model of the cardiovascular system, with a detailed arterial network following a consistent methodology bereft of any arbitrary parameter adjustments. The methodology discussed in chapter 2 will show that the large systemic arteries are modeled individually with parameters directly determined from the physiological definitions. Numerical adjustments have been limited to the lumped models of peripheral circulation only. The accuracy of the Zero-D model to emulate pulse wave propagation along the systemic network was analyzed with respect to the simulations of a previously validated 1-D model adopted from [2]. A derived objective of this work was to specifically identify the limitations and sensitivities of Zero-D modeling techniques. As the Zero-D governing equations can be derived with a few
simplifications of 1-D equations, this objective was pursued comparing with simulations from a 1-D model proven to provide accurate simulations of vascular hemodynamics. In light of the ease of physical interpretations of the developed model, several assumptions and sensitive issues of Zero-D modeling are also investigated.
Chapter 2
Methodology

2.1 Formulation of Zero-D Governing Equations

The governing equations for Zero-D modeling of blood flow have been derived from the 1-D governing equation and a detailed formulation is provided in this section. In 1-D formulation, the blood vessels are approximated to be axisymmetric straight tubes of varying cross-sectional area ($A$) with the assumption that the local curvatures are sufficiently small [52] and the significant changes in flow characterization variables, pressure ($P$) and flow rate ($Q$), are assumed to be in the longitudinal direction of the vessels. Therefore, any flow variable $\Psi \in \{P, Q\}$ is averaged over the area of the cross-section so that the variable can be defined as function of linear space and time only (figure 2.1); i.e., $\Psi = \Psi(x, t) = \int_{A(\sigma)} \Phi d\sigma$.

Figure 2.1: (a) General orientation of a sample vessel (b) 1-D representation of the vessel; redrawn from [52]
The resulting 1-D governing equations in terms of \((A, Q)\) variables \([2, 7, 10, 52]\)

\[
\frac{\partial A}{\partial t} + \frac{\partial Q}{\partial x} = 0 \tag{2.1}
\]

\[
\frac{\partial Q}{\partial t} + \frac{\partial}{\partial x} \left( \frac{Q^2}{A} \right) = -A \frac{\partial P}{\partial x} + \frac{f}{\rho} \tag{2.2}
\]

For full derivation of the equations, please refer to \([10, 52]\). The above equations can also be reached by integrating 3-D incompressible Navier-Stokes equations over the cross-sectional area of the vessel \([53]\). Equations (2.1) and (2.2) are the 1-D representations of conservation of mass and momentum, respectively. The friction force per unit length is denoted by \(f\), which can be expressed as

\[
f = -\beta \pi \mu \frac{Q}{A};
\]

where \(\mu\) is the dynamic viscosity of the blood and \(\beta\) is a constant for the shape of the velocity profile. From \textit{in-vivo} studies of healthy human beings, it has been found that the blood flow velocities in large arteries assume a flat, blunt profile for the most part of the cross-section \((\beta = 22)\) and in smaller vessels (such as capillaries) become increasingly parabolic \((\beta = 8)\) \([5, 10, 54]\). For this work, the flat profile option has been adopted for the arterial network, as the individually modeled arteries are the largest of systemic circulation. Equation (2.2) can be rewritten as

\[
\frac{\partial Q}{\partial t} + \frac{\partial}{\partial x} \left( \frac{Q^2}{A} \right) = -A \frac{\partial P}{\partial x} - \beta \pi \mu \frac{Q}{A} \tag{2.3}
\]

For Zero-D formulation, the quantities \(\Psi \in \{A, P, Q\}\) are averaged over a finite distance depending upon the desired level of discretization. According to the

23
objectives of the work, this distance has been set as the entire length of vessel, i.e.,

\[ l = |x_{out} - x_{in}| \] (figure 2.2).

\[
\Psi = \Psi(t) = \int_l \Psi \, dx \Rightarrow \Psi(t) = \frac{1}{l} \int_{x_{in}}^{x_{out}} \Psi(x, t) \, dx
\]

Therefore, the boundary conditions become

\[
P_{in}(t) = P(x_{in}, t), \quad Q_{in}(t) = Q(x_{in}, t)
\]
\[
P_{out}(t) = P(x_{out}, t), \quad Q_{out}(t) = Q(x_{out}, t)
\]

\[\text{Figure 2.2: Concept of a control volume or compartment for a vessel in 1-D to Zero-D transformation}\]

Integrating the continuity equation in (2.1) over the vessel length

\[
l \frac{d\hat{A}}{dt} + Q_{out} - Q_{in} = 0
\]

\[\Rightarrow \frac{d\hat{A}}{dt} + \frac{Q_{out} - Q_{in}}{l} = 0 \quad (2.4)\]

At this point, the quantities are dependent upon time only and to note, consequently the PDE description of conservation of mass in equation (2.1) has become an ordinary differential equation in (2.4).
For the momentum equation, two further approximations are made.

(i) Contribution of the advection term is negligible
(ii) Changes in lumen area and wave speed along the length is negligible compared to the changes of pressure and volumetric flow rate.

Integrating the momentum equation in (2.3) over the length with above approximations, the ODE representation can be formulated.

\[
\frac{d\dot{Q}}{dt} = -\frac{A}{\rho} (P_{\text{out}} - P_{\text{in}}) - \frac{\beta \pi \mu}{\rho} \frac{\dot{Q}}{A} \Rightarrow \frac{d\dot{Q}}{dt} = \frac{1}{\rho l/A} (P_{\text{in}} - P_{\text{out}} - \frac{\beta \pi \mu l}{A^2} \dot{Q})
\] (2.5)

To rewrite the governing equations in terms of the flow variables \((P, Q)\), the following 1-D relations were adopted and adjusted for Zero-D modeling.

\[
P(x, t) = P_e(x, t) + \psi(x, t) \quad [2, 7] \quad (2.6)
\]

\[
\psi = K(x) \phi(x, t) + P_o \quad [2, 7] \quad (2.7)
\]

\[
\frac{\partial P}{\partial t} = \frac{\partial P_e}{\partial t} + K \frac{\partial \phi}{\partial t} \quad (2.8)
\]

\(K(x)\) is a positive function of Young's modulus and wall thickness of the vessel [7, 55], both of which can be reasonably assumed to remain unchanged within a vessel. Therefore, \(K\) can be considered to be a constant within a vessel.

The function \(\phi\) is expressed as [7]

\[
\phi(x, t) = \left( \frac{A(x, t)}{A_o(x)} \right)^m - \left( \frac{A(x, t)}{A_o(x)} \right)^n ; \quad (2.9)
\]

\(m = \begin{cases} 0.5; & \text{arteries} \\ 10; & \text{veins} \end{cases} \quad n = \begin{cases} 0; & \text{arteries} \\ 1.5; & \text{veins} \end{cases}\)
The wave speed, $c$ can be expressed as [7]

$$c = \sqrt{\frac{A \partial \psi}{\rho \partial A}} \quad (2.10)$$

The equations (2.6)–(2.10) can be used to develop an ODE description for the pressure-area relation. From equation (2.7)

$$\psi = k\phi + P_o \Rightarrow \frac{\partial \psi}{\partial A} = k \frac{\partial \phi}{\partial A}$$

Now, the wave speed can be rewritten from equation (2.10).

$$c^2 = \frac{A}{\rho} k \frac{\partial \phi}{\partial A} \quad (2.11)$$

$$\Rightarrow c^2 = \frac{A}{\rho} k \frac{\partial \phi}{\partial t}$$

$$\Rightarrow \frac{\partial A}{\partial t} = \frac{A}{\rho c^2} k \frac{\partial \phi}{\partial t} \quad (2.12)$$

Using equation (2.8) in (2.12)

$$\frac{\partial A}{\partial t} = \frac{A}{\rho c^2} \left( \frac{\partial P}{\partial t} - \frac{\partial P_e}{\partial t} \right) \quad (2.13)$$

Setting the external pressure as constant, using assumption (ii) and integrating equation (2.13) over the length, the following ODE relation can be deduced.

$$\frac{d\hat{A}}{dt} = \frac{A}{\rho c^2} \frac{d\hat{P}}{dt} \quad (2.14)$$

Incorporating equation (2.14) in equation (2.4)

$$\frac{d\hat{P}}{dt} = \frac{Q_{in} - Q_{out}}{lA/\rho c^2} \quad (2.15)$$
Introducing the electrical analogy to equation (2.15) and (2.5) respectively,

\[ \frac{d\hat{P}}{dt} = \frac{Q_{in} - Q_{out}}{C} \]  
\[ \frac{d\hat{Q}}{dt} = \frac{1}{L}(P_{in} - P_{out} - R\hat{Q}) \]  

where,

\[ R = \frac{\beta \pi \mu l}{A^2}; \quad L = \frac{\rho \rho}{A}; \quad C = \frac{lA}{\rho c^2} \]

The relations in (2.18) are the definitions of model parameters: \( R, L, C \); which respectively represent the flow resistance, fluid inertance (inertia of the blood) and vessel’s compliance [10]. The properties of blood are assumed to constant and therefore, the set of RLC are geometrically determined parameters of the vessel. These parameters are comparable to the resistance, inductance and capacitance of electrical circuits and consequently, a blood vessel can be analogously represented as an RLC circuit. The interpretations of these parameters are discussed in the following sections. Equations (2.16) and (2.17) are the general governing equations for zero-D modeling of a single blood vessel where \( \hat{P} \) and \( \hat{Q} \) are the state variables. The definitions of the state variables and the boundary conditions depend on the configuration of the network. There are several choices [10,50]; for this work, inverse \( L \)-element configurations have been used (figure 2.3). The state variables have, therefore, been set as \((\hat{P}, \hat{Q}) = (P_{in}, Q_{out})\) and the values \((P_{out}, Q_{in})\) have been used as the boundary conditions (more accurately, known input variables for the compartment [10]).
Now, the final governing equations can be expressed as

\[
\frac{dP_{in}}{dt} = \frac{Q_{in} - Q_{out}}{C} \tag{2.19}
\]

\[
\frac{dQ_{out}}{dt} = \frac{1}{L} (P_{in} - P_{out} - R Q_{out}) \tag{2.20}
\]

Figure 2.3: Inverse L-element single compartment for Zero-D modeling \((P_e\) set to zero in current work)

### 2.1.1 Flow Resistance, \(R\)

The parameter \(R = \frac{\beta \pi \mu l}{A^2}\), represents the resistance encountered by the flow due to the viscous behavior of the blood [10]. Mean pressure and flow rate is associated with the resistance through Darcy's law [4].

\[
Q = \frac{\Delta P}{R}
\]

With viscosity assumed to be constant in large arteries, the resistance is proportional to the length of the vessel and inversely proportional to the squared area of flow. Understandably, microcirculation vessels offer very high resistances to the flow. The pressure drops are proportional to the resistances, if the flow rate remains fixed. Therefore, the largest pressure drop of the entire cardiovascular system occurs in the
microcirculation. The metrics are already provided in chapter 1 and the results section shows the pressure drop in the developed model.

The resistance dictates the mean flow rate and pressure [5], and does not have any direct contribution in the shape of the pressure and flowrate waveforms; i.e., the pulsatility of blood flow. The shape of pressure and flow waves; i.e., the instantaneous pressure-flow relations, are dependent on the combined response of the transient components; the compliance and inertance. In absence of the pulsatile nature of blood flow, Darcy’s law would have held true for the instantaneous flow parameters as well.

2.1.2 Vessel Compliance, C

The capacitive element, C represent the volume compliance of the vessels that allows them to store large amounts of blood [10]. The volume compliance can be expressed as

\[ C = \frac{\Delta V}{\Delta P} \]

The elastance (E=ΔP/ΔV) is the reciprocal term of the compliance. The stored blood contains potential energy that is released to allow the pressure pulse wave to propagate during diastole. A more compliant vessel will expand more under the similar pressure increments than a stiffer vessel and consequently has a larger energy storage capacity. Accordingly, in equation (2.19), it can be seen that instantaneous pressure changes are directly controlled by the compliance term, whereas the link with resistance and inertance is through the flowrate variable. Another interpretation
from a numerical perspective is that the vessel compliance allows only gradual changes of pressure in the vessels; therefore, eliminates the oscillations from the pressure waveform. This observation is also consistent with the phenomenon observed in reduced vessel compliance due to aging [56]. It has been shown that the pressure wave forms contain more fluctuations with stiffer vessels in the aforementioned work.

2.1.3 Fluid Inertance, L

Blood accelerates during the systole and decelerates in diastole during each cardiac cycle, and the working force induces an inertia in the blood [8]. This inertia is represented by the inertance. Fluid inertance, therefore, prevents abrupt changes in flowrate through a vessel and from a numerical perspective, reduces oscillations in the generated flow wave patterns. The disinclination to changes are more prominent in large vessels, the mass of contained blood being higher. A physiological example of the existing inertance is the flow persistence through the aortic valve, for a limited period when aortic pressure is higher than left ventricular pressure (Figure 4.1).

2.2 Calculation of RLC Parameters

From equations in (2.14), it can be seen that the RLC parameters vary with vessel length, lumen area and wave speed. Even after the Zero-D approximations, the area and wave speed are time-dependent variables, i.e.,

\[ A = A(t) \; ; \; c = c(t) \]
Therefore, with other properties assumed to remain constant,

\[ R = R(t) \; ; \; L = L(t) \; ; \; C = C(t) \]

In most studies, lumen area and wave speed are assumed to be fixed at reference values at reference pressure in a Zero-D vessel [1, 8, 10] and consequently RLC parameters are set as constant as well. In this work, another additional variation with varying RLC parameter has been tried. Comparison of simulations from both variations of Zero-D model with the predictions from the 1-D model, provide the basis for understanding specific contributions of the aforementioned assumption and also for deciding which simplifications can reduce computational complexities without significantly compromising the accuracy. The time varying technique is not attempted for the peripheral vessels, as the anomalous viscous behavior in small vessels mean that the constant viscosity assumption will also be associated and the contributions cannot be separated.

### 2.2.1 Constant RLCs for Arteries

The cross-sectional area of a human artery changes along the length. To simplify this change for Zero-D modeling, the reference area is approximated from the mean of the lumen radii at inlet and outlet. The reference wave speed has been acquired from the reported data in appendix 1.

\[ A = A_0 = \frac{A_{inlet} + A_{outlet}}{2} \]

\[ c = c_0 \text{ at } A = A_0 \]
2.2.2 Variable RLCs for Arteries

The instantaneous lumen area can be determined by combining equations (2.14) and (2.16), and Wave speed $c$ and associated values can be expressed with the equations (2.9) and (2.11).

\[
\frac{dA}{dt} = \frac{A}{\rho c^2} \frac{Q_{in} - Q_{out}}{C} \quad (2.21)
\]

\[
c^2 = \frac{A}{\rho} K \frac{\partial \phi}{\partial A}
\]

\[
\phi(t) = \left( \frac{A(t)}{A_o} \right)^m - \left( \frac{A(t)}{A_o} \right)^n; \quad m = \begin{cases} 0.5; & \text{arteries} \\ 10; & \text{veins} \end{cases}, \quad n = \begin{cases} 0; & \text{arteries} \\ 1.5; & \text{veins} \end{cases}
\]

\[
K = \frac{\rho c_o^2}{m - n}
\]

For arteries, these equations can be combined to form a relation between the instantaneous and reference values of lumen area and wave speed.

\[
c^2 = c_o^2 \left( \frac{A(t)}{A_o} \right)^{0.5} \quad (2.22)
\]

Equations (2.21)- (2.22) can now be used in equation (2.18) to calculate the time-dependent RLC parameters.

2.3 Junction Treatment

The pressure changes at the inlet are governed by the equation in (2.19), through the flow variables and the vessel compliance element. At the arterial bifurcations, the inlet pressure must be unique ($P_{in,1} = P_{in,2}$) for the branches. As the compliances are
connected in parallel according to the electric analogy, the compliances are combined together for an equivalent compliance and a consequent uniform pressure \( P_{in,12} \).

![Diagram of compliances in series and equivalent compliance](image)

**Figure 2.4:** (a) Compliances in series (b) Equivalent compliance; at arterial bifurcations

From equations (2.19) and (2.20), the following system of governing equations for the bifurcations can be derived.

\[
\frac{dP_{in,12}}{dt} = \frac{Q_{in} - Q_{out,1} - Q_{out,2}}{C_{12}} \quad (2.23)
\]

\[
\frac{dQ_{out,1}}{dt} = \frac{1}{L_1} (P_{in,12} - P_{out,1} - R_1 Q_{out,1}) \quad (2.24)
\]

\[
\frac{dQ_{out,2}}{dt} = \frac{1}{L_2} (P_{in,12} - P_{out,2} - R_2 Q_{out,2}) \quad (2.25)
\]

### 2.4 Peripheral Circulation

At the end of the arterial network, the arterioles (including small arteries), capillaries, venules and veins were modeled with equivalent components. Therefore, flow rate and pressure in the arteries are related to the peripheral circulation; especially, the
terminal arteries have the outlet boundary condition dependent on the peripheral channels. It was shown analytically and numerically for peripheral circulation in [8] that the mean values are dependent upon the resistances only. The additional resistance at the inlet, \( R_0 \), is used to account for the reflected waves at the terminals and is discussed in the next section.

To keep the physiological definitions for the large arteries intact, the parameters defined by equations in (2.18) for the large arteries were left unchanged. Instead, the peripheral resistances were adjusted from the values obtained from [58] so that the mean pressures and flowrates are within acceptable range. Each of the lumped models follow the same governing equations as discussed earlier. The inflow resistances link the outlet pressures of terminal arteries and inlet arteriolar pressures through Darcy’s law, as no transient component is present in between.

Figure 2.5: A peripheral channel consisting of a terminal resistance (\( R_0 \)) and lumped-parameter models for micro- and venous circulation
2.4.1 Terminal Reflection Co-efficient and Terminal Resistance

Blood from the heart branches though the network of arteries to reach the microcirculation of the numerous small arterioles and capillaries, where the largest pressure drop of the cardiovascular system takes place. At the terminal section of the arterial network, an inflow resistance \( (R_0) \) is required to prevent non-physiological wave reflections from the peripheral vessels \([59]\). It is to be noted that to account for this particular phenomenon, the input impedance was introduced to the original two-element RC model \([10, 12]\). For simplicity, the impedance has been approximated as a terminal resistance, as proposed and adopted in \([5, 10, 18, 58, 59]\). The value of this resistance was calculated from the definition of terminal reflection co-efficient, \( r_t \) \([5, 10, 59]\).

\[
r_t = \frac{R_0 - \rho c_{0,in}/A_{0,in}}{R_0 + \rho c_{0,in}/A_{0,in}}
\]

Here, \( c_{0,in} \) and \( A_{0,in} \) are the wavespeed and lumen area of the incoming artery, at rest and respectively. To prevent the non-physiological wave reflections, the terminal inflow resistance, \( R_0 \) must match the characteristic impedance \([10, 59]\); which corresponds to the reflection co-efficient being zero. Therefore, the required resistance can be expressed as

\[
R_{0,reqd} = \frac{\rho c_{0,in}}{A_{0,in}}
\]  

(2.26)

This equation was used to set the terminal resistance in the developed Zero-D model.

*To avoid any confusion on reader’s part, the usual upper-case notation for terminal reflection co-efficient omitted in favor of a lower-case representation.*
2.5 Heart Model

A lumped-parameter heart model was developed adopting the methodology from [16] and with modifications from [2, 7]. Additionally, the parameters and several functions were modified and adjusted to (i) match the rest of the cardiovascular system of this work and (ii) study cardiac functions with the Zero-D model developed in this work.

The heart is represented by modeling of the four cardiac chambers, four valves and the pulmonary circulation. The contraction and relaxation of each chamber is emulated by a time varying elastance function, $E_{ch}(t)$. Thereafter, pressure inside the chamber, $P_{ch}(t)$, is defined by equation (2.28), as a function of the elastance and the volume of the chamber. The first term in equation (2.27) defines the time-varying chamber elastance due to the active stimulation of myocardial fibers, with the peak of $E_{ch,A}$ representing the contractility of the myocardium and the second term, $E_{ch,B}$, is the passive elastance representing the stiffness without active stimulation [16].

Here, $e(t)$ is a normalized time-varying function, emulating the active elastance and is expressed as a piecewise function and the values of $e(t)$ range between 0-1. The constant parameters and the normalized elastance are different for each chamber and define individual functions. The volume of each chamber is governed by the conservation of mass.

\[
E_{ch}(t) = E_{ch,A}e(t) + E_{ch,B} \tag{2.27}
\]

\[
P_{ch}(t) = P_e + E_{ch}(t)(V_{ch}(t) - V_{ch,0}) + S \frac{dV_{ch}(t)}{dt} \tag{2.28}
\]
When the valve is open, flow through a valve is described by the following equations, with $P_{up}$ and $P_{down}$ representing the pressures in upstream and downstream regions, respectively. The unidirectional flow through the valves is controlled by imposing a diode-like condition for valve closing: an open valve will remain open until pressure difference is negative and flow is very close to zero; a closed valve will open if and only if upstream pressure exceeds downstream pressure. The condition can be mathematically represented by including a diode resistance in the valve resistance, \[
\frac{dV_{ch}(t)}{dt} = \sum Q_{in, ch} - \sum Q_{out, ch}
\]
as shown in latter equation. The definition of the flow rate being very close to zero in numerical simulation can be set as absolute value being less than the convergence criteria.

\[
\frac{dQ_{\text{valve}}}{dt} = \frac{P_{up} - R_{\text{valve}}Q_{\text{valve}} - P_{down} - B_{\text{valve}}Q_{\text{valve}}}{L_{\text{valve}}} |Q_{\text{valve}}|
\]

\[
R_{\text{valve}} = \begin{cases} 
R_{\text{valve}} & ; P_{up} > P_{down} \\
\infty & ; P_{up} < P_{down} \text{ and } Q_{\text{valve}} \to 0 
\end{cases}
\]

### 2.5.1 Modeling of Cardiac Contraction and Relaxation

The elastances of the atria and ventricles are the controlling parameters of the heart’s contraction and relaxation. The normalized time varying function, \( e(t) \) for the atria was modeled with the piecewise function in (2.29) adopted from [2, 7, 16]. However, for the ventricular elastance, some curious features on diastolic function were observed specifically for the Zero-D models (results shown in section x.x). Therefore, several functions (eqns. 2.30-2.32) of varying diastolic characteristics were used.

\[
e_a(t) = \begin{cases} 
0.5 \left(1 + \cos\left[\frac{\pi(t + T - t_{ar})}{T_{arp}}\right]\right) & ; 0 \leq t \leq t_{ar} + T_{arp} - T \\
0 & ; t_{ar} + T_{arp} - T < t \leq t_{ac} \\
0.5 \left(1 - \cos\left[\frac{\pi(t - t_{ac})}{T_{acp}}\right]\right) & ; t_{ac} < t \leq t_{ac} + T_{acp} \\
0.5 \left(1 + \cos\left[\frac{\pi(t - t_{ar})}{T_{arp}}\right]\right) & ; t_{ac} + T_{acp} < t \leq T
\end{cases}
\]  

Equation (2.30) was developed by fitting experimental data from [16] and was implemented in the heart model to obtain all simulation results, unless specifically stated. Equation (2.31) was adopted from [2, 7] and used to reconstruct corresponding 1-D model. Equation (2.32) was adopted from [16]. These three
ventricular elastance functions differ mainly in isovolumic relaxation phase and are nearly identical during the rest of the duration of cardiac cycle. The three equations were used to analyze the effects of different ventricular elastances through the Zero-D model predictions and the results are presented in section (4.6). The values of the parameters are included in appendix 2.

\[ e_v(t) = \begin{cases} 
0.5 \left(1 - \cos \left[ \frac{\pi t}{T_{vcp}} \right] \right) & ; \ 0 \leq t \leq T_{vcp} \\
\sin \left[ \frac{\pi}{2} \left( 1 + \left( t - T_{vcp} \right) / T_{vpr} \right) \right] * r(t) & ; \ T_{vcp} < t \leq T_{vcp} + T_{vpr} \\
0 & ; \ T_{vcp} + T_{vpr} < t \leq T
\end{cases} \] (2.30)

Where,

\[ r(t) = 1 - \frac{1}{1 + \exp(-100(t - T_{vcp} + T_{vpr}/2))} \]

\[ e_v(t) = \begin{cases} 
0.5 \left(1 - \cos \left[ \frac{\pi t}{T_{vcp}} \right] \right) & ; \ 0 \leq t \leq T_{vcp} \\
0.5 \left(1 + \cos \left[ \pi \left( t - t_{vcp} \right) / T_{vpr} \right] \right) & ; \ T_{vcp} < t \leq T_{vcp} + T_{vpr} \\
0 & ; \ T_{vcp} + T_{vpr} < t \leq T
\end{cases} \] (2.31)

\[ e_v(t) = \begin{cases} 
0.5 \left(1 - \cos \left[ \frac{\pi t}{T_{vcp}} \right] \right) + dl(t) & ; \ 0 \leq t \leq T_{vcp} \\
\exp[-(t - T_{vcp})/\tau] & ; \ T_{vcp} < t \leq T_{vcp} + T_{vpr} \\
0 & ; \ T_{vcp} + T_{vpr} < t \leq T
\end{cases} \] (2.32)

where

\[ dl(t) = \cos \frac{\pi t}{T_{vcp}} * \exp \left( - \frac{T_0 - T_{vcp}}{\tau} \right) \]

\[ \tau = 30.2 * \exp \left( \frac{-HR}{81.2} \right) + 31.4 \]
Other Notations: $T$ denotes time period the cardiac events and $t$ denotes the time instants; subscripts preceded by $a$ and $v$ refer to atria and ventricles, respectively; $cp$: contraction period; $rp$: relaxation period. $T_0$ is the duration of a cardiac cycle. $r(t)$ is a function regulating the rate of isovolumic relaxation in equation (2.30) and $\tau$ is the time constant for isovolumic relaxation in equation (2.32).
Chapter 3

Model Construction and Simulation Settings

The entire model of the cardiovascular system has been divided into four sections, as illustrated in the flow chart in figure (3.1). A complete depiction is presented at the end of the chapter. The heart has been represented as a lumped-parameter model consisting of four chambers, four valves and a pulmonary circulation (Figure 2.6). The aorta is connected to the left ventricle via aortic valve and is the first of the modeled arteries.

Figure 3.1: Flow of information (and blood) in the modeled cardiovascular network

The arterial section is the focal point of interest in this work. Fifty-five major arteries are modeled individually as an RLC compartment, according to the arterial network...
adopted from [7] (Figure 3.2). Each vessel bifurcates into the next generation or connects to the peripheral circulation. The number of bifurcations is, therefore, twenty-seven in the model. The remaining arteries connect to twenty-eight peripheral channels for the blood to pass through the microcirculation to the venous section. A peripheral channel consists of five segments: (i) a resistor, to account for
the terminal reflections and a total of four lumped models, one each for (ii) arterioles (iii) capillaries (iv) venules and (v) veins (Figure 2.5). These peripheral channels ultimately merge at the superior and inferior vena cavae, which are modeled with two individual Zero-D models and connect to the RA section of the heart model. Another additional vena cava (abdominal) is present between several channels of renal circulation and the inferior vena cava. The superior and inferior venae cavae are connected to right atrium of the heart and the loop is completed.

3.1 Specification of Model Parameters

In this work, the parameters for the arterial section are determined through the methodology explained in section (2.1). The rest of the model parameters was adopted and adjusted from several literatures. The heart model adopted from [16] and the parameters were optimized with respect to in-vivo measurements in healthy humans and 1-D simulation data. The parameters of Zero-D simulation of the arterial section were reduced to be functions of geometric dimensions (Equation 2.18). The corresponding geometric data was adopted from [58] and is presented in appendix 1. The parameters of peripheral circulation were adopted from [17, 58] and adjusted to match the mean flow distribution in the arterial network and the waveforms in terminal sections, except the terminal resistances; which were determined through equation (2.26). The venae cavae were modeled with parameters adopted from [58]. The adjusted parameters for the heart model, the peripheral circulation and the venae cavae are presented in Appendices 2-4.
3.2 Specification of Simulation Conditions

Density of blood was set as 1050 kg/m$^3$ and dynamic viscosity to be 3.5 mPa.s. $\beta = 22$ was adopted for a flat-head velocity profile in the vessels. The closed loop network is sensitive to the initial conditions as the total mass of working fluid is defined by the initialization. However, the initialization is non-unique and therefore, can be performed by many appropriate sets of values.

The governing equations were solved with Runge-Kutta-Gill method. The model was simulated with FORTRAN codes, with double precision data type and a convergence criteria of $10^{-6}$. The mean values were calculated by taking a time average over one cardiac cycles. Any optimization of model parameters was performed with Nelder-Mead (simplex) method. The optimization and preprocessing of parameters were performed with NumPy and Scipy libraries of python, also with double precision data type.

3.2.1 Space-time Discretization and Stability

The space discretization is dependent on the choice of vasculature. Due to the choice of systemic arteries as Zero-D elements in this work, space discretization is non-uniform. Therefore, the stability criteria for the compartments were satisfied through the time step of forward Euler time discretization. The corresponding CFL condition, adopted from [1], is

$$\Delta t \leq \sqrt{LC}$$
Therefore, the stability criteria for individual elements are different. For the entire network, the overall condition can be set as

$$\Delta t \leq (\sqrt{LC})_{min}$$

### 3.2.2 Boundary Conditions

The closed-loop cardiovascular model does not require setting any manual boundary conditions in simulation. Rather, the conditions are specified in the formulation of governing equations through the choice of configuration of Zero-D blocks (section 2.1). For an inverse L-element RLC component, the boundary conditions are the inlet flow rate and outlet pressure. More strictly, the boundary condition can be considered as the input parameters for solving the governing equations. Because of the forward time discretization, these inputs are set from the preceding iteration (Figure 3.3) and the flow parameters are all updated simultaneously at each time step.
Figure 3.3: Construction of the entire Zero-D model of the blood circulation network. Notations: rectangular symbols in red denote individual arteries, labeled according to vessel IDs in appendix 1. Parallelogram-shaped symbols in purple are peripheral channels, labeled as in appendix 4. Blue, circular symbols represent the vena cavae. Dashed lines are used to indicate extension lines for illustrating connections, physically not present in the cardiovascular system or the developed model.
Chapter 4

Results and Validation

In this chapter, the results from simulation of the developed Zero-D network are presented and analyzed in terms of the methodology discussed in the previous chapters. Model predictions were validated against clinical and/or experimental data collected from various literature, especially for the mean values of simulations. The variations in vessel structures and conditions in human body render a large range in pulse wave information from in-vivo measurements. Therefore, the scopes for analysis of model performance and sensitivities are limited in terms of these measured responses. On the other hand, mathematical models are easily adaptable in parameters to form a similar basis of comparison. For these reasons, in-vivo data was used for validation purposes only and a validated 1-D model was taken as the reference for studying the accuracy of Zero-D simulations. The 1-D model was reconstructed from [4], which uses a shock capturing method and the simulations provide sufficiently detailed information for the heart and systemic circulation. The corresponding predictions are also in excellent agreement with in-vivo measurements and benchmark studies of other 1-D models in [51]. In chapter 2, the governing equations for Zero-D model were developed by reducing the 1-D
equations. Therefore, an additional advantage of using a 1-D model as the reference is that the differences in simulated properties can be attributed as the characteristics of Zero-D modeling method specifically.

The performance of the entire cardiovascular system is dependent on the accuracy of modeling individual components of the closed-loop, as the predictions from one section generate the boundary conditions for another. The arterial resistances are prescribed according to the methodology in section (2.1-2.2). With the adopted and adjusted parameters for the rest of the systemic vessels, the total systemic resistance of the developed model is calculated to be $1.34 \times 10^8 \text{Pa.s/m}^3$ in a constant RLC consideration, with the normal in-vivo range being $(1.344 \pm 0.183) \times 10^8 \text{Pa.s/m}^3$ [69]. In the following sections, the results are discussed in the direction of blood flow, starting from the heart. Mean predictions from both 1-D and Zero-D models are compared against measurements of healthy human beings and the wave profiles are compared between the models. Additionally, the consequences of the choices and assumptions made in the Zero-D model are analyzed in terms of investigative trials and sensitivity studies; for example, the model was found to be quite sensitive to the left ventricular function, which was extensively studied for a better understanding.

4.1 Heart

The simulated cardiac parameters are compared against in-vivo measurements in table (4.1) and the predictions are shown to be within one standard deviation of the mean of population-averaged data. The heart rate was chosen to be 60 beats per min
for a duration of a cardiac cycle of 1 second. The Zero-D pulse pressure is 43 mm Hg compared to 40 mm Hg of 1-D model. Accordingly, the cardiac output is \( \sim 7\% \) higher for the Zero-D model.

Table 4.1: Comparison between simulated cardiac parameters and In-vivo measurements in Brachiocephalic artery for healthy, young adults. (*: Male, **: Female). References are included within.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Zero-D</th>
<th>1-D</th>
<th>In-vivo measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic Pressure (mm Hg)</td>
<td>121</td>
<td>120</td>
<td>122±8 [60], 125±7*,121±12** [61]</td>
</tr>
<tr>
<td>Diastolic Pressure (mm Hg)</td>
<td>78</td>
<td>80</td>
<td>76±12[60], 73±5*, 70±9** [61]</td>
</tr>
<tr>
<td>Mean pressure (mm Hg)</td>
<td>92.3</td>
<td>93.3</td>
<td>90±12[62]</td>
</tr>
<tr>
<td>End systolic volume of LV (mL)</td>
<td>40</td>
<td>42</td>
<td>47 ±12[62]</td>
</tr>
<tr>
<td>End diastolic volume of LV (mL)</td>
<td>134</td>
<td>130</td>
<td>142 ±12[62]</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>60</td>
<td>60</td>
<td>60-75 [4]</td>
</tr>
<tr>
<td>Cardiac Output (L/min)</td>
<td>5.66</td>
<td>5.29</td>
<td>5.5±2.0[60]</td>
</tr>
<tr>
<td>Mean Pulmonary Artery Pressure (mm Hg)</td>
<td>Systolic</td>
<td>24.1</td>
<td>24.7</td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
<td>12.5</td>
<td>12.7</td>
</tr>
</tbody>
</table>

Figure 4.1: (a) Pressures and (b) volumes of the chambers of heart during a cardiac cycle; simulations from both models are compared against literature data [60, 62]
Figure (4.1) shows the comparison of ventricular functions of the heart. Ventricles perform the necessary pumping action; therefore, a measure of the imparted energy to the blood can be achieved through the pressure-volume relations. The pressures and volumes of the cardiac chambers are within acceptable ranges of *in-vivo* measurements. For the chamber volume, Zero-D simulations yield slightly lower predictions for the RV and equally higher for the LV than 1-D counterparts. A converse trend can be observed for the pressures of the ventricles. Therefore, the overall pumping action by the ventricles are quite similar ultimately.

The systolic and diastolic phases of the cardiac cycle and the valve timings in the Zero-D model can be observed in figure (4.2). The LV-aorta interaction can be seen to be as expected of a real heart. Following a period of ventricular filling, isovolumic contraction of the LV starts with the MitV closing at t=0.2 s and is followed by the steepest pressure change of LV in the cycle. The AorV opens when LV pressure exceeds the aortic pressure, and marks the end of the contraction period with the beginning of ventricular ejection. Aortic pressure closely follows that of LV in this period and eventually exceeds. The peak pressure of the aorta is slightly delayed from the maximum of LV pressure. Also, the flow through aortic valve continues for a certain time period until the valve shuts off and diastole starts. The two examples show the ability of the model to emulate the inertia of the flowing blood.

A period of isovolumic relaxation ensues; it would be shown in the following sections that the Zero-D model deviates from 1-D predictions the most within this period. The second peak of pressure waveform due to the discontinuity effected by valve closing
(namely incisura) is more delayed than the first in Zero-D than 1-D predictions and usual physiological observations. The isovolumic contraction period ends with MitV opening and the ventricular filling period starts to complete the cardiac cycle.

Figure 4.2: Changes in pressure and volume in aorta, left ventricle and left atrium from Zero-D simulations (HR=60 bpm)
With accurate modeling of the cardiac functions, it can be concluded that the heart model is emulating a real heart with sufficient accuracy and providing proper inlet conditions for the arterial network. Therefore, the reason behind the anomalous behavior at the initial period of diastole must lie within the systemic circulation or the coupling of the LV-aorta. This observation was pivotal in understanding a sensitive issue of the Zero-D modeling method and was pursued extensively.

### 4.2 Arterial Network

The arterial network contains 55 systemic arteries in the Zero-D model. The mean flowrates in selected arteries at different sections of the network is compared in figure (4.3). It can be observed that both models predict flow rates in close proximity of the mean of in-vivo data in most cases and within one standard deviation in all cases.

Aorta expectedly has the highest flow rate, as the blood ejected by the heart enters systemic circulation through this artery. As mentioned earlier, the cardiac output predictions are higher for the Zero-D model. Commensurately, the flow rate in all arteries are slightly higher for the Zero-D network, except for the femoral artery. It is to note that the femoral artery is quite close to the terminal section of the arterial network and is relatively small in diameter. In table (4.3), it is shown that the flowrates contain more errors for the smaller arteries of the network, even though the mean pressures remain quite accurate.
Figure 4.3: Blood flow in selected vessels of systemic circulation: computational results from Zero-D and 1-D models are compared with literature data (average and standard deviation). Number in parenthesis denotes vessel ID. References: [7] in general; 01, 10, (13, 31), (28 & 30), 34, 38, SVC) from [60, 63, (64), (65), 66-68] respectively.

The wave forms of Zero-D simulation are compared with in-vivo measurements adopted from various literature in figure (4.4). The comparisons are made for three arteries located in contrasting sections of the arterial network. The pressures and flow rate profiles fall within the in-vivo range in this comparison as well. As mentioned in the introductory section, human body is unique and unsurprisingly, in-vivo measurements contain large variations. Figure (4.4a) contains an apt example of the differences; the maximum peak pressure of the provided patient data is \(~40\%\) larger in terms of the lowest one. The pulse pressure also has a large range, which is observable in table (4.1) as well. For other arteries, the in-vivo measurements falling in close range of Zero-D simulations are included only (Figure 4.4: c, e).
Figure 4.4: Zero-D simulations are compared against in-vivo measurements adopted from literature, references within. To note, cardiac cycles were adjusted to match the cardiac parameters of simulation (Appendix 2)
The duration of cardiac cycle will change according to the heart rate with the changing requirements of energy during different activities. For the purpose of comparison, the cardiac cycles of *in-vivo* data were scaled to match the cardiac parameters used in simulation (Appendix 2); therefore, the aortic valve opening and closing is set at a common time instant. Due to the large variations in patient data, it is difficult to conclusively determine the accuracy of simulation. However, a cardiovascular model should, at first and at the very least, be able to capture the hemodynamic trends in human vasculature. The comparisons in figure (4.4) illustrate the ability of the Zero-D model in that respect. In pressure waves, many intricate characteristics are present and these minute changes are well captured in simulation; including the dicrotic notches or the ‘incisura’. This second pressure peak is caused by the discontinuity of flow at aortic valve shut-off; for the ensuing analysis of accuracy, it is important to note the delay in simulation of this peak in ascending aorta only. Apart from this initial phase of the diastole, the rest of the features is well predicted by the computational model for all three cases shown in figure (4.4: a, c, e). The physiological flow rates are shown in terms of the population averaged data from [77] and the set of data provided were converted into upper and lower ranges to depict the ability of the Zero-D model in emulating the trend.

After the validation that the Zero-D predictions are within prescribed ranges of patient data and a confirmation that the model is able to capture the patterns of wave propagation, the accuracy of the simulations can be analyzed in terms of the higher order 1-D model. The two models were built with identical parameters in the arterial
network; therefore, the simulations can be extensively studied in terms of an equivalent frame of reference.

Figure (4.5) shows the waveforms of flow variables in the ascending aorta and the level of agreement between the simulations of the two models. The peaks of both

![Graph showing pressure and flow waveforms in ascending aorta.](image)

*Figure 4.5: Pressure and flow waveforms in ascending aorta (To note: the time axis is different from figure 4.2 and as per the parameters of simulation)*
variables are close to the 1-D predictions (within 1% for pressure and 7% for flow rate). Additionally, the mean values are of similar order as well (Table 4.2). As discussed in section (2.1), the wave patterns are regulated by the transient components of the hydraulic circuit. Accurate predictions of mean values, peaks, troughs and shapes of the curves in general, indicate that the LC parameters are calculated accurately for the ascending aorta. Both models yield identical results during systole and the deviation occurs as the pressure and flow rate drops during diastole. The second pressure peak (incisura) can again be observed to be quite delayed for the Zero-D model and the differences decrease after the corresponding time instant. The persistence of this phenomenon in every comparison confirms that the deviation is indeed non-physiological. From the observation that the discrepancies lie in the vicinity of the incisura and after the aortic valve closes, it can be deduced that the issues are with diastolic function only. As the concerns are present in pressure curve specifically, an intuitive conclusion can be that the calculated compliance is not accurate. However, the pulse pressure is controlled by the compliance and its near identical values to 1-D predictions rule out that possibility. From many iterative studies, it was found that increasing the compliance would result in lower pulse pressure. A robust method by adjusting the entire network was also tried and it was found that the model can be adjusted with the numerical optimization methods (such as, Nelder-Mead). However, this solution comes at the expense of inducing arbitrariness of parameter setting, as the required aortic compliance in optimized model was found to be beyond any physiological
estimates and directly contradicts the objectives of this work. Therefore, the pursuit of the source can be reduced to the connected vasculature, which would be discussed in the later sections.

The robust optimization is still useful, when a section of the circulation has numerical importance only; such as to provide boundary conditions to the region of interest. This observation is consistent in this work as well, with the peripheral circulation being required to provide the necessary inlet-outlet conditions for the larger vessels. Therefore, the aforementioned robust optimization was consigned to the microcirculation only.

A comparative analysis of the mean values of propagated waves in arterial network, are presented in table (4.3). The pressure range is quite small in the large arteries and the cardiac output is also different for the two models in 1-D and Zero-D. For the convenience of comparison, the parameters are normalized and expressed as percentage of aortic hemodynamics (Table 4.2). The deviations are calculated in terms of 1-D simulations.

<table>
<thead>
<tr>
<th>Mean values</th>
<th>Zero-D</th>
<th>1-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure (mm Hg)</td>
<td>101</td>
<td>101</td>
</tr>
<tr>
<td>Flow rate (mL/s)</td>
<td>94.2</td>
<td>88</td>
</tr>
</tbody>
</table>

Table 4.2: Mean values for ascending aorta
Table 4.3: Comparisons of mean pressure and flow distribution. The variables were normalized in terms of aortic pressure and flow rate in table 4.2.

<table>
<thead>
<tr>
<th>ID</th>
<th>Vessel Name</th>
<th>Normalized Pressure (% of Aortic Pressure)</th>
<th>Normalized Flow rate (% of Aortic Flow)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Zero-D</td>
<td>1-D</td>
</tr>
<tr>
<td>2</td>
<td>Aortic arch I</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>3</td>
<td>Brachiocephalic artery</td>
<td>100.0</td>
<td>100.1</td>
</tr>
<tr>
<td>4</td>
<td>Right subclavian artery I</td>
<td>99.9</td>
<td>100.0</td>
</tr>
<tr>
<td>5</td>
<td>Right carotid artery</td>
<td>99.9</td>
<td>99.9</td>
</tr>
<tr>
<td>7</td>
<td>Right subclavian artery II</td>
<td>99.8</td>
<td>99.8</td>
</tr>
<tr>
<td>8</td>
<td>Right radius</td>
<td>97.1</td>
<td>96.8</td>
</tr>
<tr>
<td>9</td>
<td>Right ulnar artery I</td>
<td>97.1</td>
<td>98.6</td>
</tr>
<tr>
<td>10</td>
<td>Aortic arch II</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>13</td>
<td>Thoracic aorta II</td>
<td>99.9</td>
<td>99.9</td>
</tr>
<tr>
<td>14</td>
<td>Intercostal artery</td>
<td>99.9</td>
<td>99.7</td>
</tr>
<tr>
<td>15</td>
<td>Left subclavian artery I</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>17</td>
<td>Left subclavian artery II</td>
<td>99.8</td>
<td>99.8</td>
</tr>
<tr>
<td>20</td>
<td>Celiac artery I</td>
<td>99.8</td>
<td>99.6</td>
</tr>
<tr>
<td>24</td>
<td>Gastric artery</td>
<td>98.8</td>
<td>98.4</td>
</tr>
<tr>
<td>25</td>
<td>Abdominal aorta I</td>
<td>99.8</td>
<td>99.8</td>
</tr>
<tr>
<td>27</td>
<td>Abdominal aorta II</td>
<td>99.7</td>
<td>99.9</td>
</tr>
<tr>
<td>29</td>
<td>Abdominal aorta III</td>
<td>99.6</td>
<td>99.9</td>
</tr>
<tr>
<td>44</td>
<td>Right ulnar artery II</td>
<td>96.3</td>
<td>97.6</td>
</tr>
<tr>
<td>54</td>
<td>Left posterior tibial artery</td>
<td>92.3</td>
<td>96.2</td>
</tr>
<tr>
<td>55</td>
<td>Left anterior tibial artery</td>
<td>92.3</td>
<td>96.9</td>
</tr>
<tr>
<td></td>
<td>Average for 55 arteries</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
The mean pressures are in excellent agreement, the difference being mostly within 1% (the average difference is also below 1%). The mean pressures are regulated predominantly by the local resistances and downstream pressure; therefore, the accuracy of mean pressures shows the accuracy of resistance estimations for the arterial section. The flow rate distribution, on the other hand, is dependent on the resistance of the entire channel. It can be observed that several arteries contain larger differences than the average of ~17%. The low flow rates in these arteries and the resistances in the peripheral circulation are the contributors to these differences. This observation is supported by the location of the largest differences; which is invariably a terminal vessel connected to the peripheral section (ID: 14, 54) or branches into two terminal vessels (ID: 5, 9, 44) of the arterial network. However, there are also two other contributing factors. These vessels relatively small in diameter and contain comparatively low flow rates; the constant dynamic viscosity assumption in the governing equations is more appropriate for the larger vessels with higher shear rates. Also, the low flow rates would be more susceptible to the numerical errors. The first observation regarding peripheral circulation still should be the major contributor, as small arteries (ID: 7,17) in the intermediate section contain smaller differences and is less than the average difference.

Similar patterns can also be observed in the arterial wave forms in figure (4.6) and the effect of peripheral transient components. The brachiocephalic artery is branches into right subclavian and right carotid arteries, none of which is connected to the peripheral section; whereas, one of the branches of subclavian artery is a terminal
artery (right vertebral artery). Consequently, the deviations in flow waves are larger for subclavian artery. However, the mean flow rates do not share the trend (difference<average). Therefore, it is the associated inertances and compliances, not the peripheral resistances, that are the primary contributors in this case.

![Graphs showing pressure and flow waveforms in two arteries branching towards superior vena cava](image)

*Figure 4.6: Pressure and flow waveforms in two arteries branching towards superior vena cava*

The propagation of pulse wave is illustrated in figure (4.7), in successive arteries of the lower body. A distinctive characteristic is the improved accuracy of the pressure wave simulation; which can be attributed to the reduced dependence on the diastolic function of the LV. For example, the abdominal aorta does not have a prominent reflected pressure wave due to valve shut off as in the aorta or the brachiocephalic
artery. Accordingly, the downstream arteries have further improved agreement with 1-D simulations.

Figure 4.7: Pressure and flow waveforms in the arteries of renal circulation, branching towards inferior vena cava
Therefore, the Zero-D model is quite sensitive to the ventricular function, more specifically during diastole. This sensitivity was extensively investigated and the findings presented in section (4.6).

4.3 Pressure Drop in Peripheral Circulation

In this work, the network of large arteries was the focus of interest and the role of peripheral circulation was reduced to providing proper boundary conditions for the terminal arteries. A robust optimization method (as discussed in section 4.2) was applied to ensure appropriate pressure drop and the parameters adopted from [58] were adjusted according to the flow distribution. While the pressure drops (table 4.4) are within the prescribed ranges [4, 69], the exact values could not be used in optimization due to the unavailability of such information. The importance peripheral parameters have already been shown and the associated lumped models are intended to be studied further.

Table 4.4: Pressure distribution in microcirculation (Note: the mean pressures are presented at the inlet of the sections)

<table>
<thead>
<tr>
<th>Mean Pressure (mm Hg)</th>
<th>Terminal Arteries of the network</th>
<th>Arterioles, Capillaries and venules</th>
<th>Venous section</th>
<th>Venae Cavae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum</td>
<td>100</td>
<td>99</td>
<td>32.1</td>
<td>6.15</td>
</tr>
<tr>
<td>Minimum</td>
<td>91.9</td>
<td>86</td>
<td>17.9</td>
<td>6.11</td>
</tr>
</tbody>
</table>
4.4 Sensitivity of the Model to RLC Parameters

In the developed model, each artery is defined by a set of RLC parameters. In this section, the contribution of each parameter is explored and discussed with a sensitivity analysis in the Right Carotid Artery (RCA). The sensitivity analysis was performed by increasing and decreasing one parameter by a factor, keeping all other model parameters of the entire network unchanged. The RCA is one of the carriers of blood to the brain. While it carries a significant amount of blood, the flow rate is not large enough to affect the rest of the circulation significantly. Also, a comparatively large discrepancy (~34%) is present in the flow rate between the 1-D and Zero-D predictions. For these reasons, the RCA has been chosen to illustrate the sensitivity to the parameters.

<table>
<thead>
<tr>
<th>Reference parameters</th>
<th>Change from Reference</th>
<th>Mean Pressure (mm Hg)</th>
<th>Mean Flow rate (mL/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R&lt;sub&gt;ref&lt;/sub&gt;, L&lt;sub&gt;ref&lt;/sub&gt;, C&lt;sub&gt;ref&lt;/sub&gt;</td>
<td>-</td>
<td>100.9</td>
<td>281.4</td>
</tr>
<tr>
<td></td>
<td>R = R&lt;sub&gt;ref&lt;/sub&gt; * 3</td>
<td>101.0</td>
<td>277.0</td>
</tr>
<tr>
<td></td>
<td>R = R&lt;sub&gt;ref&lt;/sub&gt; / 3</td>
<td>100.9</td>
<td>283.2</td>
</tr>
<tr>
<td></td>
<td>L = L&lt;sub&gt;ref&lt;/sub&gt; * 3</td>
<td>101.0</td>
<td>281.6</td>
</tr>
<tr>
<td></td>
<td>L = L&lt;sub&gt;ref&lt;/sub&gt; / 3</td>
<td>100.9</td>
<td>281.3</td>
</tr>
<tr>
<td></td>
<td>C = C&lt;sub&gt;ref&lt;/sub&gt; * 5</td>
<td>100.7</td>
<td>281.0</td>
</tr>
<tr>
<td></td>
<td>C = C&lt;sub&gt;ref&lt;/sub&gt; / 5</td>
<td>101.0</td>
<td>281.5</td>
</tr>
</tbody>
</table>
The resistance of the RCA is almost twice of aortic resistance, according to the calculated values from the physiological data presented in appendix 1. It has already been showed, both numerically and analytically, that the resistance parameter regulates the mean values [5, 8, 10, 18] and in the previous sections of this work as well. The mean flow rate expectedly decreases as resistance is increased (table 4.5) and the converse being true as well. The relatively small changes confirm that the mean flow is more dependent on the resistance of entire channel than the local one.

For the flow wave (figure 4.8a), increased resistance result in both forward and backward flow. As the mean pressure in RCA (also in most arteries of the network) is quite close to the maximum mean pressure of the cardiovascular system, the changes are not easily perceptible. For both the wave forms, resistance changes were only accompanied by scaling of amplitudes, without affecting the shape or curvature.

The inertance and compliance terms emulate the pulsatile nature of blood flow and their sensitivity can be observed in table (4.5) and figures (4.8: b-c). The mean parameters remain largely unaffected, but the wave patterns are significantly influenced by the changes. An important distinction of the influences can be observed in comparing the figures in (4.8). There is no change in the timings (no phase change) for the changes in flow resistance; unlike the transient LC- parameters.

The inertance has a greater influence on the flow wave. Increment of the parameter is accompanied by a phase lag and delayed peak flow and the converse is true for decrement. On the other hand, non-physiological oscillations in case of reduction from reference inertance. This can be explained by an analogy from control theory.
The system can be considered as critically damped in case of the reference value and the response is therefore, smooth and bereft of any noise. For an increase from the reference, overdamping and a consequent phase lag occur generating an excessively

*Figure 4.8: Sensitivity to (a) resistance (b) inerterance (c) compliance*
smoothened response with reduced amplitude. The system is under-damped with a reduction from critical reference parameter; hence, unable to generate a smooth, non-oscillatory flow response.

Vessel compliance has similar influences on the pressure wave, but has some different singular characteristics as well. When under-damped, a lot of noise is present in the pressure response (Figure 4.8c). However, an increment from the reference does not necessarily result in smoother response; rather, it is the reference value that yields the most noise-free results. Increased compliance can be interpreted as more storage of energy and the excess energy can result in non-physiological fluctuations as well. This observation is further supported by the time duration of fluctuations. Unlike inertance, the oscillatory response is only limited to the diastolic phase, with the rate of pressure rise during systole being near identical in all three cases. It is during the diastole that the stored energy is released.

Compliance parameter, therefore, is an extremely important parameter in accurate Zero-D modeling and require delicate treatment. Compliance of vessels and diastolic function have already been mentioned in the same sentence quite few times in thesis. They are indeed quite interdependent and an insight into the correlation is provided in section (4.6).

Slight changes in pressure and flow waves can also be observed due to changes in inertance and compliance, respectively. This is expected, as the governing equations are a set of coupled ODEs and changes are not exclusive.
4.5 Fixed vs Time-varying RLC Parameters

One simplifying assumption commonly applied in Zero-D simulations is the use of reference area and wave speed in determination of the RLC parameters [1, 16, 18, 59]. In this work, the consequences of this assumption have been studied. As the pressure is a function of lumen area, the two variables maintain a similar waveform in time, and the changes are interconnected via equation (2.14). Exploiting this pressure-area relationship, simulations with variable and averaged RLC parameters show marginal differences, and no obvious improvement with respect to 1-D simulations.

Figure 4.9: Simulations with variable and averaged RLC parameters show marginal differences, and no obvious improvement with respect to 1-D simulations.
relation, a method was devised to calculate the time-varying RLC parameters (Section 2.2.2). The calculated area from equation (2.21) was implemented in (2.22) to determine the instantaneous wave speed in a vessel and the corresponding values were used to update the RLC parameters at each time step of the simulation. This method was implemented in the entire arterial network to obtain the results presented in figure (4.9).

It can be seen that the variable RLC consideration does not affect the results to a great extent, with any noticeable change being restricted to the diastolic phase. The magnitudes and time-instants of the peak pressure and flow are identical, which is also true for the pulse pressure; however, the time instant of the reflected wave improves slightly. The deviations from 1D predictions also remain quite similar, with no obvious signs of improvement. On the basis of these observations, it can be deduced that the calculations can be simplified with the reference lumen area and wave speed. Therefore, the concept of the time-dependent RLCs were not adopted in the rest of the study.

An investigation of the mean area and wave speed from the variable RLC simulations reveal the reasons for the non-improvement. Mean values were found to be within 10% of the reference values of fixed-parameter simulation. Consequently, the mean of the variable RLC parameters differed very little from constant counterparts as well.
4.6 Effect of Ventricular Elastance

It is the heart that generates the pressure gradient required to drive blood through the intricate cardiovascular network. The pumping action is dependent on the elastance of cardiac chambers; therefore, accurate emulation of the contraction and relaxation of the heart through the elastance functions is of utmost importance in accurate modeling of the cardiac functions. As the developed model is a closed-loop representation of the cardiovascular system, appropriate elastance functions are essential for proper boundary condition at the inlet of the systemic circulation. Several elastance functions of different characteristics, from either curve-fitting of measured data or from precious works (Section 2.3), were studied to understand its effect on Zero-D modeling.

It was found that the changes in atrial elastance only resulted in minor changes, which were mitigated by the rest of the heart model to maintain proper outflow conditions. However, the Zero-D model was found to exceptionally sensitive to the ventricular functions. More specifically it is the diastolic function of the left ventricle that proved to have major influences on the Zero-D model.

Figure (4.10) illustrates the these influences. With all other parameters kept unchanged, the Zero-D model was simulated with the three different elastance functions in equations (2.30) -(2.32). It can be noticed that the simulations yield almost identical results during systole; but, the pressure and flow waveforms contain additional wave reflections during diastole. These oscillations remain within a
physiologically acceptable range in case of equation (2.31); but, significantly increase for equation (2.32). This oscillatory phenomenon was observed to affect the aorta and its neighboring vessels the most, with oscillations dying down further downstream in the arterial network.

The reasons can be pursued in the compliances of systemic arteries. It has been established quite extensively that increased vessel stiffness during aging or stenosis
results in more wave reflections in human vessel [56, 58, 70]. More specifically, it has been shown that a direct correlation exists between arterial compliance and left ventricular afterload [22]. A resulting interpretation of the wave reflections in the Zero-D model can be that the discontinuous pressure changes due to valve shutting off are too strong for the modeled aortic compliance to absorb by itself and hence requires several vessels to perform the task. This hypothesis was tested and found to be accurate; as increased aortic compliance resulted in reduced oscillations.

After the numerical insight into the problem, various ventricular elastance functions were studied to pin-point the source of the non-physiological wave reflections. The findings are presented in this section.

In figure (4.11), the three elastance functions are plotted together and figure (4.12) shows the corresponding left ventricular pressure and flow through aortic valve. The only difference in these three elastance functions is in the ventricular relaxation phase. The elastance in (2.32), corresponding to the most oscillations, has an abrupt change in curvature at the start of the relaxation period (t =0.34s). A comparison with figure (4.10) reveal that the oscillations start at the same exact time instant. At this specific time point, the aortic valve suddenly shuts off and an abrupt change accompanies in the ventricular pressure as well. Equation (2.31) does not effect these abrupt changes and does not result in significant oscillations.
The elastance in equation (2.30) was developed specifically to prevent any abrupt changes and emulates the smooth diastolic pressure and flow wave of 1-D simulation with the best accuracy. Additionally, the following aspects were studied to substantiate the aforementioned reasoning and to reach a conclusion.

(i) Duration of ventricular relaxation

(ii) Rate of change in elastance function at the end of the relaxation

Figure 4.12: (a) Pressure in left ventricle (b) flow through aortic valve. Sudden shut-off of aortic valve shown in inset.

Figure 4.13: Pressure and flow waves in aorta from 1-D simulations for elastance functions in equation (2.31) - (2.32)
These parameters were found to be less influential. Equation (2.30) yields non-oscillatory results; despite having a reduced effective relaxation period than the other two, with the most rapid drop of elastance and pressure after the initial phase.

Therefore, it can be concluded that the change in curvature at the discontinuity of the piecewise elastance function causes the abrupt changes in hemodynamic conditions and results in sudden valve closing and the non-physiological oscillations in the Zero-D model. It was also investigated if the same oscillations occur in 1-D simulations as well. From the results shown in figure (4.13), it can be seen that even though the valve shut off is still abrupt at the start of ventricular relaxation, the 1-D model does not result in oscillatory waveforms. A likely reason is the shock-capturing TVD scheme used in the 1-D model adopted from [1]. Comparisons with other 1-D models are necessary to conclusively determine if all 1-D models are similarly robust and whether only Zero-D models are susceptible to spurious wave reflections.

Based on the near-perfect simulation in systolic phase and the troubles in diastolic region, there is a possibility that the results can be further improved by considering separate arterial parameters for the two phases. Apart from the analysis of this section, the marginal improvement of diastolic function due to variable RLC consideration in section (4.5) also suggest in similar veins. However, there is no previous work or mathematical evidence to support the intuitive hypothesis based on the patterns of numerical simulation. Further clinical and mathematical explorations are required to either substantiate or refute the observation.
Chapter 5

Conclusions

The review of Zero-D models reveals that the use of Zero-D modeling has been largely limited to lumping large sections of circulatory network into very few components. The variation of these lumped models are numerous and corresponding parameters are also similarly varied. Although there are certain benefits from each approach and provided results satisfactory of the purposes, the physical interpretation of the parameters can be lost in the mathematical nuances [18]. In [38] it was proposed and in [1] it was analytically and numerally proved, any desired level of accuracy in hemodynamic simulation can be achieved with proper treatment. The proof was performed by discretizing a single vessel into many elements. In this work, a closed-loop model of the cardiovascular system is built by individually modeling fifty-five large arteries of systemic circulation. Each of the arteries is represented by an inverse L-element RLC component and the parameters were derived from geometric and mechanical properties. The heart and the rest of the circulation were represented by lumped-parameter models adopted from various literature. Model simulations were compared with in-vivo data (when possible) and the simulations from a previously validated 1-D model adopted from [16]. The 1-D model uses a shock-capturing method and has been proven to yield accurate simulations of blood flow conditions;
therefore, provided a convenient reference with information otherwise unavailable through measurement techniques.

The Zero-D simulations were found to be largely in agreement with the in-vivo measurements and 1-D simulations. The heart model yielded an accurate representation of the cardiac and pulmonary functions; thus, provided appropriate inflow boundary conditions to the systemic circulation. In the arterial network, the mean pressures were in close proximity of the 1-D simulations (Average <1%) and the mean flow rates were calculated to be within acceptable ranges of patient data. However, the flow rates in arteries close to the terminal sections contained relatively larger differences (>30%) from 1-D simulations, compared to the average difference (~17%) for the entire network. Due to the implementation of inverse L-element RLC component, the mean pressures are controlled by the local resistances and outlet pressure of the vessel. On the other hand, flow rates are more dependent on the total resistance of the fluid flow. In consideration of the aforementioned characteristics, a conclusion was reached that the peripheral resistances are causing the deviation between the flow distributions of the two models.

Similarly, the waveforms of pressure and flowrate in the arterial network was found to be quite accurate. For the pressure wave, a noticeable difference was observed in the diastolic phase, especially for the arteries experiencing a strong reflected wave due to the aortic valve closing. Additionally, the waveforms in arteries with larger dependence on the peripheral flow conditions, were significantly affected by the transient components of the peripheral circulation. The peripheral circulation was
not a focus of this work, with its purpose being solely to generate appropriate boundary conditions for the arterial network. For the purpose, adopted data from literature was optimized and adjusted for approximate values for the parameters.

The effect of RLC parameters on mean flow conditions were studied in many previous works. The influences on the waveforms were studied through a sensitivity analysis on right carotid artery in this work. The resistance changes resulted in scaling of amplitude of the waveforms only, while the transient components were found to be contributing in both phase and amplitude. Similar to the behavior of transient circuits, the pressure and flow waves are regulated by compliance and inertance, respectively.

Moreover, a variation of the modeled cardiovascular system with variable RLC parameters was compared with the original model with constant parameters for individual arteries. Only a slight improvement was observed in the diastolic function and was not generally implemented in this work.

The ventricular elastance was vigorously studied with the developed model, as a point of sensitivity was found in modeling the wave propagation during diastole. It was found that any sudden changes of curvature in elastance function can result in abrupt changes in the left ventricular pressure. The consequent sudden shut off of the aortic valve resulted in strong waves in the neighboring vessels, which was too strong for the aortic compliance to prevent from propagating. Therefore, curvature of the ventricular elastance function plays an important role in closed loop Zero-D model.
5.1 **Scopes of Application**

The arterial network of the model follows a methodology based on geometric properties of the vessels. With the closed-loop formulation eliminating the necessity of knowing exact boundary conditions, the model can be adjusted conveniently to emulate patient-specific conditions. Moreover, the developed Zero-D model is capable for reproducing 1-D predictions quite accurately with run time in the order of seconds. Therefore, the model simulations can be used as an aid for clinical decision-making. The computational expenses are also extremely low; therefore, making the model suitable for general purpose use before embarking on highly invested studies.

Another important use of this tool is in multi-scale modeling. Any of the systemic arteries can be substituted by a 1-D/3-D model of locality and the model is capable of complementing the regional model with accurate boundary conditions by accounting for the global changes due to a diseased condition. Also, in case of unknown global parameters, the hemodynamic conditions in the Zero-D section of the multiscale model can be studied and compared to identify any regions affected by local anomaly.

The Zero-D model contains only one set of data per artery. In cases where more continuous information is required, the vessel should be discretized into larger number of Zero-D components; or be replaced with a higher order model. Another limitation of the model is that the venous section is pooled into several lumped models. Also, a study in the microcirculation region cannot be aided to great extent
by the current model. Therefore, the recommendations for future work are based on overcoming these limitations.

5.2 Scopes of Future Work

An immediate work that can be pursued is the inclusion of a detailed venous section. Unlike the arteries, veins are largely uniform in radius [7]; therefore, the average area consideration for the compartments should be more accurate for the veins.

The peripheral circulation was not thoroughly studied in this work. However, the effect of the peripheral circulation is evident in the results of simulation. With accurate parameters for the microcirculation, the developed model would result in further improved simulations.

The ventricular function can be studied further, with the help of more samples of clinical and experimental data. In this work, it has been shown that the model is sensitive to the curvature of elastance function and requires further investigation to understand the extent. Also, experimental studies are required to conclusively determine if the observed phenomenon is a physiological one or a limitation of the Zero-D model. An intuitive hypothesis was presented in section (4.6), that different systemic and diastolic compliance implementation may improve the Zero-D predictions. All results indicate towards the possibility and is intended to be pursued in future.
**Appendix 1: Arterial Network**

*Table A1: Physiological data for arteries, taken from [58]*

<table>
<thead>
<tr>
<th>ID</th>
<th>Vessel Name</th>
<th>l (cm)</th>
<th>r₀ (cm)</th>
<th>r₁ (cm)</th>
<th>c₀ (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ascending aorta</td>
<td>2.0</td>
<td>1.525</td>
<td>1.420</td>
<td>5.11</td>
</tr>
<tr>
<td>2</td>
<td>Aortic arch I</td>
<td>3.0</td>
<td>1.420</td>
<td>1.342</td>
<td>5.11</td>
</tr>
<tr>
<td>3</td>
<td>Brachiocephalic artery</td>
<td>3.5</td>
<td>0.650</td>
<td>0.620</td>
<td>5.91</td>
</tr>
<tr>
<td>4</td>
<td>Right subclavian artery I</td>
<td>3.4</td>
<td>0.425</td>
<td>0.407</td>
<td>5.29</td>
</tr>
<tr>
<td>5</td>
<td>Right carotid artery</td>
<td>17.7</td>
<td>0.400</td>
<td>0.370</td>
<td>5.92</td>
</tr>
<tr>
<td>6</td>
<td>Right vertebral artery</td>
<td>13.5</td>
<td>0.200</td>
<td>0.200</td>
<td>9.64</td>
</tr>
<tr>
<td>7</td>
<td>Right subclavian artery II</td>
<td>39.8</td>
<td>0.407</td>
<td>0.230</td>
<td>5.38</td>
</tr>
<tr>
<td>8</td>
<td>Right radius</td>
<td>22.0</td>
<td>0.175</td>
<td>0.140</td>
<td>10.12</td>
</tr>
<tr>
<td>9</td>
<td>Right ulnar artery I</td>
<td>6.7</td>
<td>0.215</td>
<td>0.215</td>
<td>8.78</td>
</tr>
<tr>
<td>10</td>
<td>Aortic arch II</td>
<td>4.0</td>
<td>1.342</td>
<td>1.246</td>
<td>5.11</td>
</tr>
<tr>
<td>11</td>
<td>Left carotid artery</td>
<td>20.8</td>
<td>0.400</td>
<td>0.370</td>
<td>5.92</td>
</tr>
<tr>
<td>12</td>
<td>Thoracic aorta I</td>
<td>5.5</td>
<td>1.246</td>
<td>1.124</td>
<td>5.11</td>
</tr>
<tr>
<td>13</td>
<td>Thoracic aorta II</td>
<td>10.5</td>
<td>1.124</td>
<td>0.924</td>
<td>5.11</td>
</tr>
<tr>
<td>14</td>
<td>Intercostal artery</td>
<td>7.3</td>
<td>0.300</td>
<td>0.300</td>
<td>7.13</td>
</tr>
<tr>
<td>15</td>
<td>Left subclavian artery I</td>
<td>3.5</td>
<td>0.425</td>
<td>0.407</td>
<td>5.29</td>
</tr>
<tr>
<td>16</td>
<td>Left vertebral artery</td>
<td>13.5</td>
<td>0.200</td>
<td>0.200</td>
<td>9.64</td>
</tr>
<tr>
<td>17</td>
<td>Left subclavian artery II</td>
<td>39.8</td>
<td>0.407</td>
<td>0.230</td>
<td>5.38</td>
</tr>
<tr>
<td>18</td>
<td>Left ulnar artery I</td>
<td>6.7</td>
<td>0.215</td>
<td>0.215</td>
<td>8.78</td>
</tr>
<tr>
<td>19</td>
<td>Left radius</td>
<td>22.0</td>
<td>0.175</td>
<td>0.140</td>
<td>10.12</td>
</tr>
<tr>
<td>20</td>
<td>Celiac artery I</td>
<td>2.0</td>
<td>0.350</td>
<td>0.300</td>
<td>5.86</td>
</tr>
<tr>
<td>21</td>
<td>Celiac artery II</td>
<td>2.0</td>
<td>0.300</td>
<td>0.250</td>
<td>6.54</td>
</tr>
<tr>
<td>22</td>
<td>Hepatic artery</td>
<td>6.5</td>
<td>0.275</td>
<td>0.250</td>
<td>6.86</td>
</tr>
<tr>
<td>23</td>
<td>Splenic artery</td>
<td>5.8</td>
<td>0.175</td>
<td>0.150</td>
<td>7.22</td>
</tr>
<tr>
<td>24</td>
<td>Gastric artery</td>
<td>5.5</td>
<td>0.200</td>
<td>0.200</td>
<td>6.40</td>
</tr>
<tr>
<td>25</td>
<td>Abdominal aorta I</td>
<td>5.3</td>
<td>0.924</td>
<td>0.838</td>
<td>5.11</td>
</tr>
<tr>
<td>26</td>
<td>Superior mesenteric artery</td>
<td>5.0</td>
<td>0.400</td>
<td>0.350</td>
<td>5.77</td>
</tr>
<tr>
<td>27</td>
<td>Abdominal aorta II</td>
<td>1.5</td>
<td>0.838</td>
<td>0.814</td>
<td>5.11</td>
</tr>
<tr>
<td>28</td>
<td>Right renal artery</td>
<td>3.0</td>
<td>0.275</td>
<td>0.275</td>
<td>6.05</td>
</tr>
<tr>
<td>29</td>
<td>Abdominal aorta III</td>
<td>1.5</td>
<td>0.814</td>
<td>0.792</td>
<td>5.11</td>
</tr>
<tr>
<td>30</td>
<td>Left renal artery</td>
<td>3.0</td>
<td>0.275</td>
<td>0.275</td>
<td>6.05</td>
</tr>
<tr>
<td>31</td>
<td>Abdominal aorta IV</td>
<td>12.5</td>
<td>0.792</td>
<td>0.627</td>
<td>5.11</td>
</tr>
<tr>
<td></td>
<td>Artery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>------------------------------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>32</td>
<td>Inferior mesenteric artery</td>
<td>3.8</td>
<td>0.200</td>
<td>0.175</td>
<td>6.25</td>
</tr>
<tr>
<td>33</td>
<td>Abdominal aorta V</td>
<td>8.0</td>
<td>0.627</td>
<td>0.550</td>
<td>5.11</td>
</tr>
<tr>
<td>34</td>
<td>Right common iliac artery</td>
<td>5.8</td>
<td>0.400</td>
<td>0.370</td>
<td>5.50</td>
</tr>
<tr>
<td>35</td>
<td>Right external iliac artery</td>
<td>14.5</td>
<td>0.370</td>
<td>0.314</td>
<td>7.05</td>
</tr>
<tr>
<td>36</td>
<td>Right internal iliac artery</td>
<td>4.5</td>
<td>0.200</td>
<td>0.200</td>
<td>10.10</td>
</tr>
<tr>
<td>37</td>
<td>Right deep femoral artery</td>
<td>11.3</td>
<td>0.200</td>
<td>0.200</td>
<td>7.88</td>
</tr>
<tr>
<td>38</td>
<td>Right femoral artery</td>
<td>44.3</td>
<td>0.314</td>
<td>0.275</td>
<td>8.10</td>
</tr>
<tr>
<td>39</td>
<td>Right external carotid artery I</td>
<td>17.7</td>
<td>0.200</td>
<td>0.200</td>
<td>8.26</td>
</tr>
<tr>
<td>40</td>
<td>Left internal carotid artery I</td>
<td>17.6</td>
<td>0.300</td>
<td>0.275</td>
<td>7.51</td>
</tr>
<tr>
<td>41</td>
<td>Right posterior tibial artery</td>
<td>34.4</td>
<td>0.175</td>
<td>0.175</td>
<td>11.98</td>
</tr>
<tr>
<td>42</td>
<td>Right anterior tibial artery</td>
<td>32.2</td>
<td>0.250</td>
<td>0.250</td>
<td>9.78</td>
</tr>
<tr>
<td>43</td>
<td>Right interosseous artery</td>
<td>7.0</td>
<td>0.100</td>
<td>0.100</td>
<td>15.57</td>
</tr>
<tr>
<td>44</td>
<td>Right ulnar artery II</td>
<td>17.0</td>
<td>0.203</td>
<td>0.180</td>
<td>12.53</td>
</tr>
<tr>
<td>45</td>
<td>Left ulnar artery II</td>
<td>17.0</td>
<td>0.203</td>
<td>0.180</td>
<td>12.53</td>
</tr>
<tr>
<td>46</td>
<td>Left interosseous artery</td>
<td>7.0</td>
<td>0.100</td>
<td>0.100</td>
<td>15.57</td>
</tr>
<tr>
<td>47</td>
<td>Right internal carotid artery I</td>
<td>17.6</td>
<td>0.300</td>
<td>0.275</td>
<td>7.51</td>
</tr>
<tr>
<td>48</td>
<td>Left external carotid artery I</td>
<td>17.7</td>
<td>0.200</td>
<td>0.200</td>
<td>8.26</td>
</tr>
<tr>
<td>49</td>
<td>Left common iliac artery</td>
<td>5.8</td>
<td>0.400</td>
<td>0.370</td>
<td>5.50</td>
</tr>
<tr>
<td>50</td>
<td>Left external iliac artery</td>
<td>14.5</td>
<td>0.370</td>
<td>0.314</td>
<td>7.05</td>
</tr>
<tr>
<td>51</td>
<td>Left internal iliac artery</td>
<td>4.5</td>
<td>0.200</td>
<td>0.200</td>
<td>10.10</td>
</tr>
<tr>
<td>52</td>
<td>Left deep femoral artery</td>
<td>11.3</td>
<td>0.200</td>
<td>0.200</td>
<td>7.88</td>
</tr>
<tr>
<td>53</td>
<td>Left femoral artery</td>
<td>44.3</td>
<td>0.314</td>
<td>0.275</td>
<td>8.10</td>
</tr>
<tr>
<td>54</td>
<td>Left posterior tibial artery</td>
<td>32.2</td>
<td>0.175</td>
<td>0.175</td>
<td>11.98</td>
</tr>
<tr>
<td>55</td>
<td>Left anterior tibial artery</td>
<td>34.4</td>
<td>0.250</td>
<td>0.250</td>
<td>9.78</td>
</tr>
</tbody>
</table>
Appendix 2: Heart Model

Tables A2 and A3: Parameter used in heart model, adopted from [2, 7, 16] and adjusted.

<table>
<thead>
<tr>
<th>CARDIAC CHAMBERS</th>
<th>RA</th>
<th>RV</th>
<th>LA</th>
<th>LV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_A (mmHg.ml^{-1})$</td>
<td>0.030</td>
<td>0.550</td>
<td>0.070</td>
<td>2.750</td>
</tr>
<tr>
<td>$E_B (mmHg.ml^{-1})$</td>
<td>0.055</td>
<td>0.050</td>
<td>0.090</td>
<td>0.080</td>
</tr>
<tr>
<td>$T_{cp} (s)$</td>
<td>0.170</td>
<td>0.340</td>
<td>0.170</td>
<td>0.340</td>
</tr>
<tr>
<td>$T_{cp} (s)$</td>
<td>0.170</td>
<td>0.250</td>
<td>0.170</td>
<td>0.250</td>
</tr>
<tr>
<td>$t_c (s)$</td>
<td>0.800</td>
<td>0.000</td>
<td>0.800</td>
<td>0.000</td>
</tr>
<tr>
<td>$t_r (s)$</td>
<td>0.970</td>
<td>0.340</td>
<td>0.970</td>
<td>0.340</td>
</tr>
<tr>
<td>$S (mmHg.s^{-1}.ml^{-1})$</td>
<td>0.0005*P_{ra}</td>
<td>0.0005*P_{ra}</td>
<td>0.0005*P_{ra}</td>
<td>0.0005*P_{ra}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CARDIAC VALVES</th>
<th>TriV</th>
<th>PulV</th>
<th>MitV</th>
<th>AorV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$B(mmHg.s^{-2}.ml^{-2})$</td>
<td>0.000016</td>
<td>0.000025</td>
<td>0.000016</td>
<td>0.000025</td>
</tr>
<tr>
<td>$R (mmHg.s^{-1}.ml^{-1})$</td>
<td>0.001</td>
<td>0.003</td>
<td>0.001</td>
<td>0.003</td>
</tr>
<tr>
<td>$L (mmHg.s^{-2}.ml^{-1})$</td>
<td>0.0002</td>
<td>0.0005</td>
<td>0.0002</td>
<td>0.0005</td>
</tr>
</tbody>
</table>
Appendix 3: Venae Cavae

Table A4: Parameter used in venae cavae, adopted from [58].

<table>
<thead>
<tr>
<th></th>
<th>Superior Vena Cava</th>
<th>Inferior Vena Cava</th>
<th>Abdominal Vena Cava</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R ) (mm Hg.s.ml(^{-1} ))</td>
<td>0.0005</td>
<td>0.0005</td>
<td>0.0005</td>
</tr>
<tr>
<td>( L ) (mm Hg.s(^2).ml(^{-1} ))</td>
<td>0.0005</td>
<td>0.0005</td>
<td>0.0005</td>
</tr>
<tr>
<td>( C ) (mL.mmHg(^{-1} ))</td>
<td>5.0</td>
<td>7.5</td>
<td>7.5</td>
</tr>
</tbody>
</table>
### Appendix 4: Peripheral Circulation

**Table A5: Parameter used in peripheral circulation, adopted from [58] and adjusted.**

<table>
<thead>
<tr>
<th>Peripheral ID</th>
<th>Incoming artery ID</th>
<th>Goes into</th>
<th>Parameter used</th>
<th>Arterioles</th>
<th>Capillaries</th>
<th>Venules</th>
<th>Veins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$R_0$</td>
<td>$R_1$</td>
<td>$L_1$</td>
<td>$C_1$</td>
<td>$R_2$</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>IVC</td>
<td>1.9860</td>
<td>5.6100</td>
<td>0.0090</td>
<td>0.0540</td>
<td>2.1600</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>IVC</td>
<td>2.4957</td>
<td>16.2400</td>
<td>0.0150</td>
<td>0.0210</td>
<td>6.2400</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>IVC</td>
<td>6.8543</td>
<td>21.3300</td>
<td>0.0180</td>
<td>0.0140</td>
<td>8.2000</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>IVC</td>
<td>4.0112</td>
<td>8.9100</td>
<td>0.0120</td>
<td>0.0330</td>
<td>3.4300</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>IVC</td>
<td>1.0286</td>
<td>3.8500</td>
<td>0.0070</td>
<td>0.0810</td>
<td>1.4800</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>SVC</td>
<td>2.0055</td>
<td>6.4650</td>
<td>0.0080</td>
<td>0.0245</td>
<td>1.6600</td>
</tr>
<tr>
<td>7</td>
<td>28</td>
<td>SVC</td>
<td>2.0055</td>
<td>4.3100</td>
<td>0.0080</td>
<td>0.0680</td>
<td>1.6600</td>
</tr>
<tr>
<td>8</td>
<td>32</td>
<td>SVC</td>
<td>4.4566</td>
<td>30.7400</td>
<td>0.0200</td>
<td>0.0110</td>
<td>11.8500</td>
</tr>
<tr>
<td>9</td>
<td>36</td>
<td>SVC</td>
<td>6.3301</td>
<td>23.4800</td>
<td>0.0180</td>
<td>0.0140</td>
<td>9.0300</td>
</tr>
<tr>
<td>10</td>
<td>37</td>
<td>SVC</td>
<td>4.9387</td>
<td>13.3700</td>
<td>0.0140</td>
<td>0.0230</td>
<td>5.1400</td>
</tr>
<tr>
<td>11</td>
<td>41</td>
<td>SVC</td>
<td>9.8066</td>
<td>30.4400</td>
<td>0.0210</td>
<td>0.0100</td>
<td>11.7100</td>
</tr>
<tr>
<td>12</td>
<td>42</td>
<td>SVC</td>
<td>3.9228</td>
<td>14.0300</td>
<td>0.0140</td>
<td>0.0230</td>
<td>5.4000</td>
</tr>
<tr>
<td>13</td>
<td>51</td>
<td>SVC</td>
<td>6.3301</td>
<td>23.4800</td>
<td>0.0180</td>
<td>0.0140</td>
<td>9.0300</td>
</tr>
<tr>
<td>14</td>
<td>52</td>
<td>SVC</td>
<td>4.9387</td>
<td>13.3700</td>
<td>0.0140</td>
<td>0.0230</td>
<td>5.1400</td>
</tr>
<tr>
<td>15</td>
<td>55</td>
<td>SVC</td>
<td>3.9228</td>
<td>21.0450</td>
<td>0.0140</td>
<td>0.0345</td>
<td>5.4000</td>
</tr>
<tr>
<td>16</td>
<td>54</td>
<td>SVC</td>
<td>9.8066</td>
<td>30.4400</td>
<td>0.0210</td>
<td>0.0100</td>
<td>11.7100</td>
</tr>
<tr>
<td>17</td>
<td>46</td>
<td>SVC</td>
<td>117.0969</td>
<td>393.7000</td>
<td>0.2100</td>
<td>0.0009</td>
<td>151.4000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R (mm Hg.s.mL⁻¹)</td>
<td>L (mm Hg.s².mL⁻¹)</td>
<td>C (mL.mmHg⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>-----------------</td>
<td>------------------</td>
<td>--------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>45</td>
<td>25.6962</td>
<td>19.6900</td>
<td>0.0180</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0140</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>19</td>
<td>10.2272</td>
<td>17.0300</td>
<td>0.0180</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0140</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>16</td>
<td>6.0418</td>
<td>25.8800</td>
<td>0.0190</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0130</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>48</td>
<td>5.1769</td>
<td>21.8500</td>
<td>0.0170</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0150</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>40</td>
<td>2.2777</td>
<td>23.6000</td>
<td>0.0170</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0150</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>47</td>
<td>2.2777</td>
<td>23.6000</td>
<td>0.0170</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0150</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>39</td>
<td>5.1769</td>
<td>21.8500</td>
<td>0.0170</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0150</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>6</td>
<td>6.0418</td>
<td>25.8800</td>
<td>0.0190</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0130</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>8</td>
<td>10.2272</td>
<td>17.0300</td>
<td>0.0180</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0140</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>44</td>
<td>25.6962</td>
<td>39.3800</td>
<td>0.0180</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0140</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>43</td>
<td>117.0969</td>
<td>393.7000</td>
<td>0.2100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0009</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Units: R (mm Hg.s.mL⁻¹); L (mm Hg.s².mL⁻¹); C (mL.mmHg⁻¹)*
References


recorded changes of thoracic aortic blood flow in man in response to leg exercise

hemodynamics quantified in vivo at rest and during cycling exercise using
magnetic resonance imaging. American Journal of Physiology-Heart and Circulatory
Physiology, 284(4), H1161-H1167.

Measurement of normal renal artery blood flow: cine phase-contrast MR imaging
vs clearance of p-aminohippurate. AJR. American journal of roentgenology, 161(5),
995-1002.

flow in patients with arteriosclerosis obliterans. American Journal of Roentgenology,
125, 437-441.

Measurement of volume flow in the human common femoral artery using a duplex
ultrasound system. Ultrasound in medicine & biology, 12(10), 777-784.

evaluation of Fontan pathway flow dynamics by multidimensional phase-velocity
magnetic resonance imaging. Circulation, 98(25), 2873-2882.

69. Nichols, W., O’Rourke, M., & Vlachopoulos, C. (Eds.). (2011). McDonald’s blood flow
in arteries: theoretical, experimental and clinical principles. CRC press.

Arterial stiffness, wave reflections, and the risk of coronary artery

71. Alastruey, J., Khir, A. W., Matthys, K. S., Segers, P., Sherwin, S. J., Verdonck, P. R., ... &
assessment of 1-D visco-elastic simulations against in vitro measurements. Journal
of biomechanics, 44(12), 2250-2258.


73. Kim, H. J., Vignon-Clementel, I. E., Coogan, J. S., Figueroa, C. A., Jansen, K. E., & Taylor,


