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UMI
VIRTUAL BIO-INSTRUMENTATION:
INTEGRATING BIOMEDICAL
EXPERIMENTATION WITH SYSTEMS-
LEVEL MODELING AND ANALYSIS

By

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A THESIS SUBMITTED
IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE

DOCTOR OF PHILOSOPHY

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December, 1999
VIRTUAL BIO-INSTRUMENTATION:
INTEGRATING BIOMEDICAL EXPERIMENTATION WITH
SYSTEMS-LEVEL MODELING AND ANALYSIS

JON B. OLANSEN

Abstract

This dissertation is a treatise on the merging of biomedical experimentation with modern data acquisition and analysis as an integrated teaching and research platform. Virtual (i.e. computer-based) instrumentation forms the foundation for this platform development. Original virtual instruments (VIs) have been developed as a standardized means of acquiring, analyzing, and displaying data relevant to two significant areas of biological research, namely cardiovascular hemodynamics and pulmonary mechanics. Combination of these areas leads to investigations of interactive cardiopulmonary dynamics.

The VIs depicted herein incorporate the development of advanced mathematical models as a tool for increasing our comprehension of normal and abnormal function of the cardiovascular and pulmonary systems. The use of parameter estimation schemes makes the results of these studies relevant to individual subjects being tested. These innovative applications create a robust, user-friendly environment that enables the models developed to be used as instructional tools or as a basis for the pursuit of other significant research objectives. Additionally, these VIs are all modular in nature, enabling them to be used in a variety of settings with only minor modifications.
ACKNOWLEDGEMENTS

I would like to express my gratitude to my co-advisors, Dr. Fathi Ghorbel and Dr. John Clark, Jr. for their guidance throughout my tenure at Rice and the various research opportunities that they made available to me. I also want to note my sincere appreciation to Dr. Akhil Bidani, Dr. Alex Duarte and Mr. Harold Winnike of UTMB-Galveston as well as Dr. Claudia Robertson and Dr. Dirar Khoury of Baylor College of Medicine for their substantial support in providing clinical and laboratory access for this research.

I would like to acknowledge the support of numerous family and friends in this quest. Salvatore Ferrara and Sedra Spruell, as well as my parents, John and Jacquie Olansen, were instrumental in encouraging me to chase my dreams. My strongest inspiration came from Jennifer and Karl Pohl, who continually supported and motivated me even as Jennifer battled and eventually succumbed to leukemia. The inspiration I derived from their strength will remain with me for the rest of my life.

My deepest appreciation goes to my family. The continual support and undying love of my wife, Nancy, and my children, Kathy, Jon Jr., and Kristin, carried me through this endeavor. I am forever indebted to them for their sacrifices. With them as my family, I am truly blessed.
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CHAPTER I
INTRODUCTION

This thesis concerns the development of broad-based software tools that aid in the design and performance of biomedical experiments and associated mathematical modeling efforts. The systems are built upon a virtual instrumentation foundation, of which LabVIEW™ (National Instruments, Austin, TX), a powerful graphical programming environment, is the cornerstone. Each chapter deals with a specific application. It first presents pertinent background material (physiology, theoretical developments, and programming techniques employed in either data acquisition or model development), followed by a discussion of relevant results for the particular applications. Due to the modular nature of the LabVIEW software being used, many of the programs developed for one application may be readily adapted to other applications, avoiding undue development time.

1.1 Research Goals & Objectives

The primary objective of this research endeavor was the development of automated versions of biomedical experiments in two major areas of biology and medicine: the cardiovascular system and the pulmonary system. The automated systems developed
have both integrated data acquisition and system-level modeling aspects. The goal is simplified, accurate data acquisition, followed by rapid identification and parameterization of a model that is structurally consistent with the biological processes involved, and capable of rendering close fits to measured data. The value added in this approach is centered on the predictive capabilities of our models, as they are challenged to provide biophysically based explanations for phenomena measured in response to a variety of experimental or clinical manipulations of the biological system under study. We begin with a description of the data acquisition and modeling aspects of the LabVIEW environment.

1.2 Data Acquisition Fundamentals

This section provides a cursory overview of basic concepts fundamental to the establishment of generic experimental protocols. Two basic aspects of data acquisition (DAQ) are:

(1) the purpose of the data collection; and

(2) insight into the nature of the data being collected.

Basic Principles of Data Collection

The primary component of any data collection system is the device used to detect the phenomena in question. The wide variety of sensors available requires that the investigator have at least a rudimentary understanding of the principles upon which they operate and the accuracy of a particular type of device relative to a standard measurement technique employed in the field. Typically, a sensor will convert changes in its environment (e.g. temperature, gas concentration, etc.) to variations in voltage or current. Accurately reading and conditioning these converted signals is the task of the DAQ
system. Even if a separate commercial monitor is to be used to collect the data (as is often the case in the clinical laboratory), an understanding of the principles underlying the operation of such a unit greatly facilitates the interpretation of the resulting data. For example, it is necessary to consider how the input signals are digitized and then processed in their digital form. This requires a basic understanding of analog/digital (A/D) conversion techniques as well as basic analog to digital conversion (ADC) concepts such as resolution and least significant bit, and sampling frequency and its relation to the Nyquist criterion. These issues become even more prominent in the development of laboratory experiments that do not use the intermediate commercial components as described above.

Aside from the hardware components of DAQ, it is important to know about signal conditioning. A number of factors are important including:

1. calibration, and
2. appropriate signal conditioning.

Calibration requires that the measurement conform to a reference standard (e.g. known pressure, temperature, etc.). Many commercial components, including DAQ boards designed for personal computers, have self-calibration routines that may be sufficient if the investigator understands the methods and potential error sources involved. Stand-alone DAQ systems will require separate calibration procedures. Additionally, the signal can be conditioned by removing noise through various means including adequate buffering, amplification, and filtering. Here buffering refers to adequate isolation of the measurement device from the biological signal; that is, no loading of the biological source by the input stage of the measurement device. Applying adequate gain and
filtering are secondary to adequate buffering of the measurement device (i.e. the device itself does not interfere with the measurement.

*Understanding the Signal to be Acquired*

Armed with an understanding of the principles of data acquisition, the researcher should proceed to integrate this knowledge with a proper comprehension of the nature of the biological signal itself. For example, estimated peak values are necessary for the determination of appropriate amplification. Application of measurement techniques that minimize interference or measurement artifacts can enhance the signal to noise (S/N) ratio and hence the quality of the signal. This consideration could be as simple as modifying the location of a sensor. For example, when an esophageal balloon is used to estimate intrapleural pressure in the thorax, a very noisy signal is obtained if the balloon is placed close to the heart. This is called cardiogenic interference and it can be largely eliminated in many subjects with an appropriate repositioning of the balloon.

The investigator should use the above information to develop a complete test protocol that includes specification of the instruments to be used, as well as, the methodology whereby they are used. The protocol should yield a complete data set for the investigation at hand.

1.3 **Role of Virtual Instrumentation (LabVIEW)**

Developing a multidimensional data acquisition system requires a flexible programming environment such as C/C++ or BASIC. One program development application that combines such flexibility with a user-friendly graphical interface is LabVIEW™ (National Instruments, Austin, TX). LabVIEW was originally released in 1986 as a Macintosh-based DAQ system and was the first software application to apply
the 'G' programming language, which utilizes graphical and iconic scripting techniques. Since then, the National Instruments suite of 'G' based DAQ, Test, and Measurement applications, of which LabVIEW is one, has evolved into a standard in automated DAQ and test development. Most of these programs are available for Windows 95/NT, Macintosh, or Sun workstations.

Data Acquisition using LabVIEW

The flexibility of LabVIEW begins with underlying machine-level code that enables the software to communicate with a wide array of signal input sources. For example, a LabVIEW equipped computer (e.g. PC, Macintosh, Sun, etc.) can perform analog or digital data acquisition, processing, and instrument control over a GPIB (IEEE-488.2) interface. Built-in (or subsequently added) drivers enhance communication with an extensive range of standalone instruments. Digital DAQ can be accomplished via an RS-232 serial port or GPIB interface. Analog data (along with single TTL digital channels) can be obtained using any number of quality analog-to-digital (A/D) conversion boards developed by National Instruments (or other vendors). Recent advancements include the addition of an image acquisition board with a digital image processing toolkit extension for LabVIEW as well as the addition of specialized DSP boards for system control applications (originally developed by nuLogic of Boston, MA).

LabVIEW Application Development

LabVIEW applications are denoted as virtual instruments (VIs), due to their visual imitation of actual hardware instruments. Because of the graphical basis of LabVIEW development, all applications are developed with a ready-made graphical user interface (GUI). Additionally, the source code is developed graphically in a block diagram format.
Components of the block diagram can include any of the features of text-based programs such as FOR...NEXT or WHILE loops or conditional branching (IF...THEN) statements. Each of these can be represented by a graphical symbol, with the contents of each feature literally located within the appropriate symbol. Subroutines within the code appear as icons on the block diagram, with terminals for the passing of data/variables between the main code and the subroutine.

VIs are designed to be hierarchical and modular. LabVIEW is essentially a modular programming environment within which VIs are created. Complex programs are broken down into simpler tasks, each of which is coded in a VI. Icons representing these subroutines are incorporated into the block diagram of the higher level VIs, etc. until the top-level code is completed. This hierarchical structure permits easy modification of program elements, as well as the ability to use component VIs to develop a completely unrelated program.

Another benefit of the 'G' programming environment is the execution order. LabVIEW applications do not run line by line as standard text-based C/C++ or BASIC applications do. Rather, LabVIEW applications are data flow driven; that is, steps within the code do not execute until all of the required inputs are present. This semi-parallel execution scheme ensures that, for example, data processing does not occur until the desired data is read from the DAQ buffer.

It should be noted that LabVIEW, being graphics based, does require significant memory and computer power to operate efficiently. Newer Pentium or PowerPC computers, especially those with Advanced Graphics Port (AGP) capability, will have no problem running the latest versions of LabVIEW. Another issue to consider is the amount
of data to be collected. Collecting large amounts of data will require streaming the data to a hard disk or zip drive, whereas lesser amounts of data can be maintained in memory as the program is run.

*Signal Conditioning / Modeling Aspects*

Although LabVIEW is primarily considered a programming environment for acquiring signals, its capabilities extend far beyond that. LabVIEW 5.1 contains numerous function libraries, which serve to enhance data processing and display. These include various digital signal processing (DSP) algorithms such as Fast-Fourier Transform routines for frequency based analysis. Extensive statistical functions are also available from a moving average to peak detection to linear or polynomial curve fitting. A wide variety of digital filters are included as well. To meet specific needs, most of these features can be used by the investigator to design specific analysis routines to accompany data acquisition. These modifiable support libraries contribute to the development of a workstation environment approach to laboratory investigation, bringing analysis tools to the experiment itself.

1.4 **Laboratory Design**

This section is a short description of the laboratory workstation used for the experiments described in this thesis. The standard workstation includes a 333 MHz Pentium computer with a DAQ board (such as the 12-bit PCI-MIO-16E-4 developed by National Instruments). Secondarily, a mobile workstation is also available which includes a 266 MHz Pentium laptop computer with a PCMCIA DAQ card. A Signal Conditioning eXTensions for Instrumentation (SCXI) system, again developed by National Instruments (NI) is included to perform much of the signal conditioning required for either the fixed
or mobile platforms. The chassis houses an SCXI-1100 32-channel differential input multiplexer module, an SCXI-1120D high bandwidth 8-channel isolated input module and an SCXI-1180 feed-through panel. The 1100 and 1120D are used to condition input signals, whereas the 1180 allows for simultaneous output from the DAQ board (used as stimulator for the various preps). The 1100 and 1120D modules require some specific setup to be compatible with the data acquisition described in this thesis. The only physical setup required for the 1100 module is to set the filters as desired for the experiment at hand.

1.5 Organization of the Thesis

This introductory chapter has presented information regarding general goals, lab design, and layout and setup of a computer-based instrumentation laboratory workstation. The remainder of this thesis presents descriptions of advanced data collection and analysis techniques integrated within the virtual instrumentation environment. We consider three separate areas that each include data acquisition, system modeling and parameter estimation. Specifically, Chapter 2 is concerned with the study of cardiovascular hemodynamics in the dog. Chapter 3 applies virtual instrumentation in the study of pulmonary mechanics and lung tissue dynamics in the human subject, whereas Chapter 4 extends and integrates the concepts introduced in the previous chapters to study interactive cardiopulmonary dynamics. The results of the thesis are summarized in Chapter 5.
CHAPTER 2

CARDIOVASCULAR HEMODYNAMICS

Cardiovascular hemodynamics is an area that describes the pumping characteristics of the heart and the associated blood flows and pressures throughout the vasculature. The circulatory system serves to transport blood and distribute essential substances to body tissues and organs, and to remove by-products of metabolism. It also plays a role in homeostatic mechanisms, such as the regulation of body temperature, humoral communication throughout the body, and adjustments of supply of oxygen and nutrients in different physiological states. The cardiovascular system that serves these purposes consists of two pumps (the right and left ventricles) and a network of distributing and collecting conduits, which are bridged by a vast, extensive network of thin vessels, which permit rapid and efficient exchange of substances between the tissues and blood. Because the cardiovascular system plays an essential role in the functioning of the whole body, much research has been devoted to better understand its behavior under normal and pathophysiological conditions.

2.1 OBJECTIVES

Basic experiments in hemodynamics focus on left ventricular function, blood pressure and flow variations around the cardiovascular loop. In our studies, representative
measurements are taken from cannulated arteries and veins, as well as, from catheter-tipped pressure transducers placed within the ventricular chamber(s) of open chest canine preparations. Standard clinical hemodynamic indices such as stroke volume, cardiac output, and ejection fraction are also calculated to help bridge the gap between laboratory study and clinical understanding.

Advanced experiments in this field introduce modeling efforts with a modified Windkessel model of the closed-loop cardiovascular system. In particular, a closed-loop model of the cardiopulmonary circulation has been developed for the study of right-left heart interaction under physiologically normal and altered conditions. The core model provides insight into the effects of ventricular interaction and the pericardium on hemodynamics. The complete model contains a realistic model of (a) the interacting ventricular free walls and septum, (b) the atria, (c) pericardium, and (d) the systemic and pulmonary vascular loads. The current analysis extends previous work done by our group [7, 18] by applying the methodologies to individual data using parameter identification. Key model parameters are identified via comparison with canine hemodynamic data using a Levenberg-Marquardt algorithm.

The complete circulatory model, including septal and pericardial coupling, is a virtual testbed for assessing the global affects of localized mechanical or hemodynamic alterations. This closed-loop circulatory model is subsequently utilized to study the issues of both direct and series ventricular interaction, as well as the effect of the pericardium on cardiac performance. Additionally, alterations in model parameter values are used to predict the impact of disease and/or clinical interventions on steady-state hemodynamic performance.
2.2 Background

2.2.1 Physiological Basis

The electrical excitation of the heart results in a wave of contraction that spreads through the myocardium. The synchronous nature of this contraction results in the efficient pumping of blood through the pulmonic and systemic circulations. The circulatory system can be considered in terms of the cardiac pumps and their afterloads, which are the networks of blood-transporting vasculature. The heart consists of two pumps in series. The right pump propels blood through the lungs for exchange of oxygen and carbon dioxide (the pulmonal circulation). Figure 2-1 schematically depicts this closed-loop nature of the circulatory system [44], as well as, the arrangement of the various series and parallel circulations in specific organs. Taking the output from the right pump and the pulmonal vasculature, the left pump propels the oxygenated blood to all other organs of the body (the systemic circulation). The

![Diagram](image)

Figure 2-1. Schematic of closed-loop circulation.
deoxygenated blood is then transported through the venous system and eventually returned to the right pump, where the cycle begins anew.

The pressure afterload of the left pump (the left ventricle) is large relative to that of the right pump (the right ventricle). Approximately 20% of the total blood volume is stored in the lungs of the dog in the supine position, whereas the remainder may be considered stored in the systemic arterial system fed by the aorta. The left ventricle thus must be able to propel blood with enough energy to circulate through the relatively extensive systemic circulation. To maintain proper organ function, a continuous flow to the organs must be maintained in the face of disturbances (adequate organ perfusion). The ventricles, as the source, must maintain a reasonably constant mean flow output (cardiac output). During contraction (systole), the left ventricle generates enough pressure to exceed that in the aorta (~100 mmHg mean pressure) and propel blood into the systemic circulation. From the

Figure 2-2. Hemodynamic profile of systemic circulation.
aorta, blood moves through the systemic circulation with progressively greater decrease in pressure and velocity.

Figure 2-2 shows this progressive drop in blood pressure and flow velocity along the systemic circulation. Note that in Figure 2-2, the aorta and large arteries, which serve as major conduits for distributing blood to the regional circulations, have insignificant total cross-sectional area compared to the arterioles, capillaries, and venuoles, which comprise the dense network structures for organ perfusion. Since the capillaries consist of short tubes whose walls are very thin and since the flow rate is slow, conditions in the capillaries are ideally suited for the exchange of diffusible substances between blood and tissue. After circulating through the capillaries, blood returns to the heart, through the venous system, where the greatest portion of the circulating blood resides.

The Heart

The heart is a pump which provides the blood with energy to circulate through the body's vast and complex vascular network. As such, it is a primary component of the cardiovascular system. The anatomy of the heart and the mechanics of cardiac function are described in the following sections.

Anatomy. Figure 2-3 shows the anatomy of the heart [44]. The heart is divided into four chambers: the left and right atria (LA and RA, respectively) and ventricles (LV and RV, respectively). The atria are thin-walled, low-pressure chambers which function more as large reservoir conduits of blood for their respective ventricles, than as independent blood pumps. A compliant atrial (membranous) septum separates the atria, while a muscular interventricular septum separates the two ventricles. The interventricular septum, because of its anatomical relationship to the left and right
ventricles, plays an important role both in participating in ventricular contraction and mediating ventricular interaction.

There are two types of valves in the heart, the *atrioventricular valves* and the *semilunar valves*. The atrioventricular (AV) valve separates an atria and a ventricle. The valve between the right atrium and the right ventricle is made up of three cusps (*tricuspid valve*), whereas that between the left atrium and left ventricle has only two cusps (*mitral valve*). Attached to the free edges of these valves are fine, strong filaments (*chordae tendineae*), which prevent eversion of the valves during ventricular systole. A semilunar valve separates the ventricle from the great vessel attached. The *pulmonary valve* between the right ventricle and the pulmonary artery and the *aortic valve* between the left ventricle and the aorta, each have three cup-like cusps attached to the valve ring.
The structure of these valves prevents regurgitation of blood into the ventricles when a brief reversal of blood flow toward the ventricles occurs at the end of the reduced ejection phase of ventricular systole. To a good approximation, these valves can be considered unidirectional and pressure-operated. That is, these valves prevent regurgitation when the pressure in the source chamber is not sufficient to open the valve, and once open, these valves maintain blood flow in a single direction under the positive pressure gradient across the valve.

The entire heart is enclosed in the pericardium, which offers structural support for the heart and normally contains a small amount of lubricating fluid to minimize friction with the epicardial surface of the heart. The pericardium is an epithelialized fibrous sac and has little extensibility. As the result, it strongly resists a large and rapid over-distension of the cardiac chambers.

*Electrical Activity of the Heart.* In the heart, contraction of the atria (*atrial systole*) is followed by contraction of the ventricles (*ventricular systole*). The heartbeat originates in a specialized conduction system and spreads via this system to all parts of the myocardium. Figure 2-4 schematically shows the major structures that make up the heart's specialized conduction system [44].

The *sino-atrial node* (SA node), located at the junction of the superior vena cava and right atrium, is the normal cardiac pacemaker. The *internodal pathways*, which contain three bundles of atrial fibers containing Purkinje type fibers, connect the SA node to the *atrioventricular node* (AV node), which is located in the right posterior portion of the atrial septum. The AV node is continuous with the *bundle of His*, which branches into the *left bundle branch* (LBB) at the top of the ventricular septum and the *right bundle*
branch (RBB). The LBB divides into the anterior and posterior fascicles. These branches and fascicles run subendocardially down either side of the ventricular septum and come into contact with the Purkinje system, whose fibers spread throughout the ventricular myocardium.

The normal heart beat initiates at the SA node. Depolarization initiated in the SA node spreads radially through the atria, then converges on the AV node. During atrial depolarization, which completes in about 0.1 second, the atria contract. After a delay (AV nodal delay) of about 0.1 second, excitation spreads to the ventricles. From the top of the ventricular septum, the depolarization wave spreads in the rapidly conducting Purkinje fibers to all parts of the ventricles. Depolarization of the ventricular muscle first starts at the left side of the septum and then moves to the right across the mid-portion of the septum.
The wave of depolarization then spreads down the septum to the apex of the heart. It returns along the ventricular walls to the AV groove, from the endocardial (inner) to the epicardial (outer) surface of the ventricles. The last portions of the heart to be depolarized are the posterobasal portion of the left ventricle, the pulmonary conus, and the uppermost portion of the ventricular septum. The whole sequence of depolarization of the myocardium form the basis of the coordinated contraction of the ventricles. This coordinated contraction can be disrupted by a variety of means such as pacing [1].

![Heart Diagram]

**Figure 2-5. Schematic of mechanical activity in cardiac cycle.**

*Mechanical Events of the Heart.* Figures 2-5 and 2-6 summarize the sequence of mechanical events of the heart [44]. As shown in Figure 2-5, during late diastole, the ventricles fill as blood flows through the open mitral and tricuspid valves between the atria and ventricles, while the aortic and pulmonary valves are closed. After the P wave of the ECG, atrial systole (Phase 1 in Figure 2-6) begins, and the atria contract to propel additional blood into the ventricles. Ventricular volume at the end of diastole (ED) is called *end-diastolic volume* (EDV) and is dependent on the diastolic properties of the ventricle, as well as, hemodynamics of the input from the contracting atrium. The EDV represents the *preload* to the ventricle.
The R wave of the ECG marks the start of the ventricular systole and Phases 2 and 3 in Figure 2-6. At the start of ventricular systole, the mitral and tricuspid valves close, in addition to the already closed aortic and pulmonary valves. This creates isovolumic conditions in the ventricles, as there is neither inflow nor outflow. The

Figure 2-6. Phases of the cardiac cycle.
ventricles contract during this phase of isovolumic contraction (Phase 2 in Figure 2-6), and the ventricular pressures increase rapidly until the pressures in the ventricles exceed those in the aorta (80 mmHg) and pulmonary artery (10 mmHg). When the pressure-operated aortic and pulmonary valves open, ventricular ejection (Phase 3 in Figure 2-6) begins.

Ejection is rapid at first, slowing down as systole progresses. During ejection, ventricular pressures can reach to about 120 mmHg for left ventricle and 25 mmHg for the right. At the end of ejection, the aortic and pulmonary valves close, and the residual ventricular volumes at the end of systole (ES) are called end-systolic volumes (ESV). The stroke volume (SV) is then the volume ejected by the ventricle, or the difference between EDV and ESV. The cardiac output (CO) is then computed as the product of the stroke volume and the heart rate, in L/min. Upon valve closure, the ventricles enter the phase of isovolumic relaxation, during which the ventricular pressures decline rapidly (Phase 4 in Figure 2-6). When the ventricular pressures fall below those in the atria, the AV valves (mitral and tricuspid) open and the ventricles begin to fill. During diastolic filling, the ventricles are passive, subject to the compliant properties of the myocardial walls and the restraining effect of the pericardium. Passive filling continues until the next atrial systole, at which time the cardiac cycle begins anew.

**Pressure-Volume Analysis of Ventricular Function.** In the pressure-volume (P-V) plane, the complete cardiac cycle is shown as a loop, with different phases of the cardiac cycle as indicated in Figure 2-7. Note that the ventricle responds to different demands under different physiologic states (rest and exercise), and this change in the pump property of the ventricle manifests in different P-V loops. During exercise, the ventricle
does more work to meet the additional demands imposed by greater physical activity, and this is indicated by a P-V loop with greater P-V area [44]. In addition to using P-V area as a measure of work done by the ventricle, the P-V plane analysis is useful to indicate the contractile (*inotropic*) state of the ventricle, as represented by the study by Suga et al [16].

### 2.2.2 Theoretical Basis

This section presents the development of a closed-loop model for the study of ventricular interaction and pericardial mechanics on hemodynamics throughout the circulatory loop. This endeavor integrates three distinct areas of modeling: arterial circulation, closed-loop circulation, and heart mechanics (particularly ventricular mechanics). A comprehensive survey of mathematical models of the circulatory system [2] has shown that, while characterizing the same biological system, these models vary significantly in their complexity, modeling assumptions and objectives. Circulatory models range from simple resistive-compliant Windkessel models for the study of the interaction between the left ventricle and its systemic arterial afterload [3, 4], to very
complex distributed network representations of the systemic vascular tree [5] used for more detailed studies of the hemodynamics of the arterial system. Several lumped-parameter models of intermediate complexity have been developed to characterize the complete “closed” circulatory loop [6, 7, 8, 9, 10, 11, 12] and have been employed in studies of a wide variety of physiological phenomena, ranging from the circulatory response to gravitational acceleration [10] to the effects of intrathoracic pressure variations [11, 12]. Heart pump models range from simple spring-dashpot models [13, 14] to elastance models of ventricular function [15, 16], to finite element models of ventricular mechanics [17]. As a practical matter, elastance models are relatively simple in structure and can characterize the pump properties of the atria and ventricles quite well.

In addressing the question of modeling ventricular interaction in vivo, the development of an adequate closed-loop model of the circulation is a prime requisite. That is, in the intact circulation, changes in the output of one ventricle eventually affect the input to the other ventricle. All closed-loop circulatory models developed to date can emulate this series interaction between the ventricles and their vascular afterloads. However, in addition to this series interaction, ample experimental evidence points to another significant form of interaction called direct ventricular interaction [18, 19, 20, 21, 22, 23, 24, 25], where the state of one ventricle can affect the function of the other via the compliant interventricular septum (SPT). Through this direct form of interaction, the systolic and diastolic properties of both ventricles are interrelated. In addition, direct ventricular interaction is enhanced by the presence of the relatively stiff pericardium, and these two factors can have important consequences on the overall performance of the
heart, as well as the circulatory system as a whole. Few models of the circulation treat either direct ventricular interaction [9, 26] or the influence of the pericardium [27].

Direct ventricular interaction is addressed in some models of the closed-loop circulation [9, 26] via the use of “interaction gains” to model the modulation of ventricular pressures. However, these models do not include an explicit dynamic description of the contracting septum, and therefore cannot predict the hemodynamic consequences of the temporal (phasic) interaction between the contracting free walls and the septum. Moreover, these same models do not address the role of the pericardium in modulating ventricular interaction, and overall cardiac performance. In the present study, we: (1) connect mathematical models of the pulmonary and systemic circulations as physiologic afterloads to the dynamic models of the ventricles of the heart; (2) include mathematical models of the passive and active behavior of the atria; and (3) enclose the atria and coupled ventricles in a pericardium. These extensions are based on work previously developed by our group [7, 18].

2.3 Model Development

The integrated cardiovascular model considers two major components, cardiac mechanics and circulatory hemodynamics. The structures chosen to develop this lumped-parameter model were adopted with regard to the following considerations: 1) the ventricular model should be capable of describing the continuous direct interaction of the right and left ventricles via the interventricular septum; 2) the atrial models should adequately describe both the passive and active (contractile) behavior of each atrium (the atria are considered separate uncoupled compartments); 3) the heart model should include a description of the pericardial influence on the cardiac mechanics associated with all
four chambers; 4) the resistive, compliant, inertial system used to describe the hemodynamics of both the systemic and pulmonary vasculature should be appropriately apportioned with regard to blood volume, reflect appropriate mean pressure levels, and present an appropriate hydraulic input impedance to the ejecting ventricles; and 5) the complete model should be versatile and easily applied to a variety of simulated hemodynamic conditions (normal and pathophysiological).

2.3.1 Heart Model

Ventricular Description. The general form of the ventricular model is based on the work of Chung, et al. [7] on the isolated ventricle. The basic premise upon which the model is built is that the ventricles can be modeled as a three-walled system, the right ventricular (RV) and left ventricular (LV) free walls and the coupling septal wall. This creates three functional volumes as depicted in Figure 2-8A. The total chamber volumes are related to the functional volumes according to the relationship:

\[
V_{LV} = V_{LVF} + V_{SPT} \quad \text{(1a)}
\]

\[
V_{RV} = V_{RVF} - V_{SPT} \quad \text{(1b)}
\]

A septal volume of zero indicates a flat septum; the chamber volumes are then equal to the free wall volumes. \(V_{SPT} > 0\) represents septal movement into the RV, whereas \(V_{SPT} < 0\) indicates leftward septal motion. This characterization of functional volumes is intended to signify septal wall motion only, and does not affect the total chamber volumes unless accompanied by imbalanced input and output blood flows.

The ventricular walls are characterized by time-varying elastance functions that relate instantaneous pressure and volume. These elastance functions produce a smooth transition from a nonlinear end-diastolic pressure-volume curve (EDPVR) to a linear end-
systolic pressure-volume relationship (ESPVR), both of which have been established in [7]. Time-varying activation functions $e_v(t)$, which are representative of normalized elastance curves, are used to develop the elastances. For the ventricles and the septum, a series of four Gaussian curves of the form

$$e_v(t) = \sum_{i=1}^{4} A_i e^{-\left(\frac{t-C_i}{B_i}\right)^2}$$

(2)

has been adopted where $A_i$, $B_i$, and $C_i$ correspond to the magnitude, width, and delay of the individual curves. The parameters $A_i$, $B_i$, and $C_i$ are defined in Appendix B. A more complete description of the model equations can be found in [7].

Atrial Description. The ventricular model described above was extended to include a dynamic description of the atria. For this model, the atrial septum is assumed to
be rigid, i.e. the atria are uncoupled and have no direct mechanical influence on each other or the ventricles. The atrial free walls are characterized by a time-varying elastance in a fashion similar to the ventricles. In this case, however, the EDPVR and ESPVR have been developed to produce reasonable outputs that correspond to the work of Lau, et al [28] as well as to the data we have collected. Figure 2-9 depicts the curves used to describe the nonlinear EDPVR, which are of the form:

$$P_{ED,i}(V_i) = P_0,i e^{\lambda(V_i - V_{0,i})}$$

(3a)

where $\lambda$, $P_{0,i}$, and $V_{0,i}$ are constant parameters chosen to yield reasonable pressure-volume behavior for the atria ($i = \text{left or right}$). The ESPVR is also shown, and is given as:

$$P_{ES,i}(V_i) = E_{ES,i}(V_i - V_{D,i})$$

(3b)

where $E_{ES}$ is the maximal elastance at end systole. The activation function for the atrial free walls is a single Gaussian curve of the form in Equation 2, which is temporally offset

![Figure 2-9. Pressure-volume relationships of the left and right atria, with and without the pericardium.](image)
from the ventricular activation in accordance with the data collected. The parameters $A$, $B$, and $C$ for the atria are also defined in Appendix B.

**Heart Model Dynamics.** A schematic diagram showing the components of the heart model is depicted in Figure 2-8B. Pressure (force) balances across the appropriate walls, in addition to mass balances between the heart chambers, are used to derive the dynamic interaction of the heart chambers, the septum, and the pericardium. The pressure balances can be summarized as follows:

\[
P_i = P_{IF} + P_{PERI} \tag{4a}
\]

\[
P_{SPT} \equiv P_{LV} - P_{RV} \equiv P_{LVF} - P_{RVF} \tag{4b}
\]

where $P_i$ represents the pressure in the left ventricle ($LV$), right ventricle ($RV$), left atrium ($LA$), or right atrium ($RA$), $P_{IF}$ is the free wall pressure of the respective heart chamber, $P_{PERI}$ is the fluid pressure in the pericardium, and $P_{SPT}$ is the pressure across the ventricular septum. While the atria are modeled as active free walls within the pericardium, the atrial septum is considered rigid for model simplification purposes. The heart chambers are enclosed within an elastic pericardium under open chest conditions (i.e. intrathoracic pressure variations are neglected; $P_{PERI}$ is referenced to atmosphere).

The mass balances are developed based on the principles of conservation of mass and the continuity equation and result in a series of dynamic flow equations describing the changes in chamber volumes as a function of time:

\[
\dot{V}_{LV} = \frac{dV_{LV}}{dt} = Q_{MT} - Q_{AO} \tag{5a}
\]

\[
\dot{V}_{RV} = \frac{dV_{RV}}{dt} = Q_{TC} - Q_{PM} \tag{5b}
\]
\[ \dot{V}_{LA} \equiv \frac{dV_{LA}}{dt} = Q_{LA} - Q_{MT} \]  
\[ \dot{V}_{RA} \equiv \frac{dV_{RA}}{dt} = Q_{RA} - Q_{TC} \]  

where \( Q_{MT}, Q_{AO}, Q_{TC}, \) and \( Q_{PM} \) are flows through the mitral, aortic, tricuspid and pulmonary valves, respectively, and \( Q_{LA} \) and \( Q_{RA} \) are the flows into the left and right atria.

The flows are derived using the generic formula:

\[ Q_i = \frac{\Delta P_i}{R_i} \]  

where \( \Delta P_i \) is the forward pressure gradient across the flow resistance \( (R_i) \) encountered at each heart valve and the atrial inlets.

The pericardium is characterized by an exponential pressure-volume relationship of the form

\[ P_{PERI}(V_{TOT}) = P_{0,PERI} \left\{ e^{\lambda(V_{int} - V_{0,PERI})} \right\} - 1 \]  

where \( \lambda, P_{0,PERI}, \) and \( V_{0,PERI} \) are constant parameters chosen to yield reasonable pressure-volume behavior for the pericardium. \( V_{TOT} \) is the volume contained within the pericardium, which includes the chamber volumes and the fluid volume of the pericardium. Myocardial and coronary blood volumes are neglected for this study.

2.3.2 Circulatory Model

The systemic and pulmonary circulations are modeled as physiologic afterloads to the dynamic model of the coupled ventricles located, along with the atria, within the pericardium. Previous studies [10, 29] have characterized the circulatory loop as a series of hydraulic compliant elements. We also utilize this approach and characterize the circulatory hemodynamics in terms of an apportioned resistive, compliant and inertial
A hydraulic equivalent circuit model of the circulatory loop is depicted in Figure 2-10.

Each segment of the circulatory loop is modeled via a set of equations describing the relationships between the pressure \( (P_i, \text{mmHg}) \), volume \( (V_i, \text{ml}) \), and flow \( (Q_i, \text{ml/sec}) \) associated with that segment. The equations governing each hydraulic segment are listed below and they contain a number of parameters that describe each segment's resistance \( (R_i, \text{mmHg*sec/ml}) \), inertance \( (L_i, \text{mmHg*sec^2/ml}) \), and compliance \( (C_i, \text{ml/mmHg}) \). The relationships used to characterize each hydraulic element are:

\[
P_i = P_{TM,i}(V_i) + R_{T,i} \dot{V}_i + P_{EX,i} \tag{7a}
\]

\[
P_{TM,i} = \frac{1}{C_i}(V_i - V_{0,i}) \tag{7b}
\]

\[
\dot{Q}_i = \frac{P_{i+1} - P_i - Q_i R_i}{L_i} \tag{7c}
\]

\[
\dot{V}_i = Q_i - Q_{i+1} \tag{7d}
\]

where \( i \) indicates the specific element (e.g. \( AO_P \) for proximal aorta (aortic arch), \( VC \) for vena cava). Some segments of the circulatory loop contain only resistive and compliant elements because, as the diameter of the blood vessels diminishes around the circulatory loop (namely, the arterioles, capillaries, and venules), the volumetric flow likewise declines, reducing the significance of the inertance \( (L_i) \) parameter characterizing the blood column. Neglecting this term for the appropriate elements reduces Equations 7c and 7d to a single ordinary differential equation.

In the derivation above, the natural state variables are the volumes of each compliant element \( (V_i) \). However, the linear pressure-volume relationship about a given operating volume, given in Equation 7b, allows a transformation of variables. Thus, the
transmural pressure ($P_{TM,i}$), the pressure across the segment wall, is classified as a state variable. This leads to the following alternative equations:

$$\frac{dV_i}{dP_{TM,i}} = C_i \quad (7e)$$

$$\dot{P}_{TM,i} = \frac{dP_{TM,i}}{dt} = \frac{1}{C_i} (Q_i - Q_{i-1}) \quad (7f)$$

In this case, the pressure within a given segment ($P_i$) can be determined using Equation 7a. We assume experimental conditions consistent with the open-chest animal preparation, hence the external pressure ($P_{EX,i}$) is atmospheric.

Figure 2-10. Hydraulic equivalent schematic of the closed loop circulatory model. Model parameters are listed in Table 2-1 and Appendix B.
2.4 EXPERIMENTAL MEASUREMENTS

Pressure measurements from selected sites in the circulatory loop were obtained from open-chest canine preparations in the Center for Experimental Cardiac Electrophysiology, Baylor College of Medicine, Houston, Texas. These anatomic sites include the left ventricle, aortic arch, descending aorta, and femoral arteries. Additional records were obtained from the inferior vena cava, the right atrium, and right ventricle. The pressure recordings from four sites were typically acquired simultaneously, and the ECG was recorded as an independent timing reference.

Pressures were obtained using solid state catheter-tip transducers from Millar Instruments (Houston, TX). Positioning of the transducers within the heart chambers or vessels was verified via X-Ray imaging prior to initiating acquisition. The analog recordings were digitally sampled at a rate of 500 Hz, which was sufficient to capture all significant frequency content of the acquired waveform. Data acquisition was accomplished using mobile PC platform consisting of a National Instruments AI-16E-4 PCMCIA DAQCard and a 266 MHz laptop. Analog signal conditioning was incorporated via an SCXI-1120 module (National Instruments) in order to amplify the incoming signals (ECG x1000; Pressure x10).

The acquisition was controlled via virtual instruments (VI's) designed and developed within the LabVIEW™ programming environment, as well as, through use of the turnkey program BioBench™. (LabVIEW and BioBench are both products of National Instruments, Austin, TX.) The data collection virtual instruments enabled: 1) the raw data to be converted to engineering units (mmHg) using previously established calibration curves; 2) continuous real-time display of the acquired data for quality
control; and 3) storage of acquired, calibrated data for post-processing. A sample of the data acquired is shown in Figure 2-11A.

![Canine Hemodynamics - Experimental Data](image1.png)

![Canine Hemodynamics - Model Output Data](image2.png)

Figure 2-11. A) Typical canine cardiovascular pressure data collected during open-chest experiments. B) Typical model output pressure data produced under similar simulated conditions as the data displayed in panel A (e.g. equivalent heart rate, open chest, intact pericardium). $LV =$ left ventricle, $RV =$ right ventricle, $AO =$ aorta, $SA =$ systemic arteries, $VC =$ inferior vena cava, $RA =$ right atrium.

2.5 Computational Aspects

The model equations were initiated at the time of end-diastole with the atrioventricular valves open and the semilunar valves closed. Initial conditions employed for the 32 state variables, some of which were adopted from previous studies [7, 18], are defined in this mode. The model parameters were divided into static and adjustable sets, with the adjustable parameters determined using the parameter estimation algorithm described below. Nominal parameter values were selected to produce physiologically realistic values, such as cardiac output (CO), and hemodynamic waveforms for a typical 25-kg dog. Pulmonary shunt flow was set at 2% of the mean pulmonary blood flow [30], whereas mean coronary and cerebral flows were set at 5% and 15% of cardiac output,
respectively [31, 32]. The model equations were programmed in the “C” programming language and solved using a variable step-size Runge-Kutta-Merson algorithm with a maximum time step size of $2 \times 10^{-3}$ sec and an error tolerance of $1 \times 10^{-6}$.

2.5.1 Parameter Estimation and Sensitivity Analysis

A nominal set of parameters was first obtained that provided acceptable fits to a variety of indices such as cardiac output (CO), left and right ventricular ejection fractions, mean blood pressures and blood volume distributions around the circulatory loop, and ventricular and arterial pulse pressure waveforms. Model output pressures from a typical control case are depicted in Figure 2-11A, corresponding to the pressures obtained experimentally, and shown in Figure 2-11A. Comparison of Figures 2-11A and 2-11B establishes that the model output is in general agreement with typical in vivo data.

With the baseline hemodynamics established in the control case described above, use was made of parameter sensitivity analysis [97, 98] and a parameter estimation scheme [96] to achieve better agreement with experimental data. Examinations of the magnitude and time course of the relative sensitivity functions associated with all of the circulatory hemodynamic parameters (i.e. resistances, compliances, and inertances) were evaluated for the purpose of ranking the degree of sensitivity of the set (as described in Appendix A). This analysis revealed that the most sensitive parameters were $R_{TAO}$, $C_{AOP}$, and $L_{AOP}$ of the systemic circulation and $R_{TPA}$, $C_{PAP}$, and $L_{PA}$ of the pulmonary circulation. The resistance parameters $R_{SAD}$ and $R_{SC}$ are also quite sensitive, as they are largely responsible for establishing the mean aortic and systemic arterial pressures that are directly compared to the data.
Based on the dynamic sensitivity analysis, the model parameters classified as most sensitive are included in the nonlinear least-squares parameter estimation algorithm. This step significantly enhances convergence of the algorithm by constraining parameter variations to those that can bring about the greatest change in the system variables. The nature of the closed-loop circulation allowed initial estimation of the parameters to be performed on each circulation (i.e. systemic and pulmonic) separately followed by an integrated fine-tuning. This primarily enabled the ventricular systolic profiles and hemodynamic means to be established prior to identifying the parameters responsible for the oscillatory perturbations in the pressure waveforms. Figure 2-12 depicts the user interface for operation of the parameter estimation algorithm with typical results. These results show good agreement for specified pressures around the cardiovascular loop. A

Figure 2-12. Front panel of CardioPV parameter estimation routine depicting typical results of identification analysis. Parameters are defined in Table 2-1 and Appendix B. MSE is the mean square error of all compared data sets. Hemodynamic MSE disregards errors in pressures within heart chambers.
summary of parameter values determined for each of the experiments conducted is given in Table 2-1. These techniques are described in greater detail in Appendix A.

<table>
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<th>Parameter</th>
<th>Description</th>
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<th>Identified Values</th>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>$C_{PA}$</td>
<td>Compliance: pulmonary arterioles</td>
<td>0.1500</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.1571</td>
<td>0.0007</td>
</tr>
<tr>
<td>$L_{AOP}$</td>
<td>Inertance: proximal aorta</td>
<td>0.0034</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0056</td>
<td>0.0234</td>
</tr>
<tr>
<td>$L_{AOD}$</td>
<td>Inertance: distal aorta</td>
<td>0.0295</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0282</td>
<td>0.0506</td>
</tr>
<tr>
<td>$L_{PA}$</td>
<td>Inertance: pulmonary artery</td>
<td>0.0006</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0004</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Table 2-1. Key parameter values identified via the described parameter estimation routine for three separate canine experiments. Units for resistance terms are $mmHg*sec/ml$; for compliance terms are $ml/mmHg$; and for inertance terms are $mmHg*sec^2/ml$.

It should also be noted that heart rate is a significant factor in determining the circulatory hemodynamics. As such, the heart rate established from each data set was utilized in determining the adjustable parameters. Since the heart rate varies with respiratory, baroreceptor and other influences, only small data intervals incorporating three to four beats of roughly equal RR intervals (i.e. the interval of time between the peaks of the R wave in the ECG) were used at one time in the identification scheme. The effects of varying heart rate on the circulatory hemodynamics are discussed later.
By producing physiologically realistic outputs, this model allows the study of ventricular interaction through the septum (direct), as well as, via the circulatory loop (series) under simulated in vivo conditions. Once model parameters were identified, simulations were conducted to examine a number of additional problems that are often referenced in the literature. The results of these simulations are discussed below.

2.5.2 *CardioPV* Program Development

The *CardioPV* program, developed using the LabVIEW programming environment, is a compilation of original virtual instruments (VIs) designed both as the user and data interface to the model operation. Sophisticated graphical displays highlight the user interface while the *CardioPV* software can accept data from numerous sources, including direct acquisition via a data acquisition (DAQ) card for online operation. The model "C" code described above is integrated into the *CardioPV* program as an external call from LabVIEW. *CardioPV* also provides a continuous graphical feedback of the model operation, enhancing user understanding of the model performance as well as aiding any debugging efforts that may be required.

The computational flow diagram shown in Figure 2-13 depicts the various stages that are included within the software package. Data can be acquired directly allowing the software analysis to be utilized during an ongoing experiment. Data can also be read from a number of previously recorded file types. In these cases, the model is run with the average heart rate (HR) determined from the data, and will run for the same elapsed time as included in the data segment for comparison purposes. When data is linked in the program, the option to directly compare model output using the aforementioned parameter estimation and sensitivity analysis routines becomes available. This capability
greatly enhances the functionality of the model. The model can also be run without reference to experimental data by supplying a user specified HR and simulation elapsed time.

The screen panel shown in Figure 2-12 provides the user with multiple options to completely control the parameter estimation process, if so desired. Yet, its default configuration is sufficient to enable novice users to typically obtain satisfactory results. The sensitivity analysis is conducted in the background and can be reviewed during performance of the parameter estimation routine.

Once acceptable parameter values are obtained, simulations can be continuously conducted for any of the alterations or pathophysiology described in this paper. In these cases, all model parameter values are held constant except for those changes necessary to simulate the desired intervention. The model will run continuously until it reaches a steady-state output, at which time mean pressure, volume and flow data around the loop, as well as a variety of cardiac indices such as cardiac output (CO) and ejection fraction (EF), are calculated. These features allowed easy manipulation of model parameters, which helped to provide a quick, convenient, and thorough analysis of ventricular interaction, pericardial influence, and normal hemodynamics as well as the simulation of a wide variety of pathophysiological conditions or clinical interventions.
Figure 2-13. Computational Flow Diagram of the *CardioPV* software package.
2.6 RESULTS

To demonstrate the utility of a closed-loop circulatory model, which includes the description of ventricular interaction and pericardial influence, several simulation studies were undertaken. These include the hemodynamic consequences of physiological manipulations of circulatory or ventricular parameters, as well as simulation of certain pathophysiological states. Simulations of known pathophysiological cases are helpful both in validating the model formulation and identifying possible model limitations. For all simulations, only the model parameters pertinent to a particular protocol were adjusted, while the remaining parameters were fixed at values shown in Appendix B.

2.6.1 Baseline Hemodynamics

The model equations and associated parameter values given in Table 2-1 and Appendix B describe the nominal behavior of the canine cardiovascular system. That is, the simulation output resembles the waveforms typically observed in a normal 25-kg dog [31, 32, 33]. This simulation is referred to as the "control case", in which the model includes an active septum, an intact pericardium and the parameter set identified for dog 1 via the estimation routine discussed in Appendix A.

Figure 2-14 demonstrates that the model is capable of producing realistic waveforms of many hemodynamic variables of interest in the circulation. For example, simulation results for the left heart and systemic afterload include pressures in the left atrium (LA), left ventricle (LV), proximal and distal sections of the aorta (AO_p and AO_D), small arteries (SA), arterioles (SA_D), and the capillaries (SC), as well as the less pulsatile pressures in the veins (SV, systemic veins; and VC, vena cava) (Figure 2-14A). For the right heart and its pulmonary afterload (Figure 2-14B), the model generates
Figure 2-14. Typical temporal profiles of model output pressure data. A) Systemic circulation results. B) Pulmonic circulation results plus pericardial pressure. \(LV\) = left ventricle, \(AOP\) = aorta (proximal), \(AOD\) = aorta (distal), \(SA\) = systemic arteries, \(SAD\) = systemic arterioles, \(SC\) = systemic capillaries, \(VC\) = inferior vena cava, \(LA\) = left atrium, \(RV\) = right ventricle, \(PAP\) = pulmonary artery (proximal), \(PAD\) = pulmonary artery (distal), \(PA\) = pulmonic arterioles, \(PC\) = pulmonic capillaries, \(PV\) = pulmonic veins, \(RA\) = right atrium, \(PERI\) = pericardium.

Pressure waveforms in the right atrium (RA) and ventricle (RV), large and small pulmonary arteries (\(PA_p\) and \(PA_d\)), pulmonary arterioles (PA), pulmonary capillaries (PV), and the pulmonary veins (PV) adjoining the left atrium. In addition to pressures, the model generates the temporal profiles of volumes associated with each compartment (not shown). Mean pressures and volumes around the circulatory loop are shown in Table 2-2. The cardiac output, pressure gradient along the circulatory loop, and overall blood volume distribution are in agreement with commonly accepted values [32, 33, 31]. Note that the systemic circulation is the high-pressure system (due to left ventricular pumping) in contrast to the low-pressure pulmonary circulation. The blood volume is distributed such that the majority of the blood volume resides in the veins [32, 31].
<table>
<thead>
<tr>
<th>Compartment</th>
<th>Description</th>
<th>Pressure</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>AO&lt;sub&gt;p&lt;/sub&gt;</td>
<td>Aorta (proximal)</td>
<td>111.3</td>
<td>20.3</td>
</tr>
<tr>
<td>AO&lt;sub&gt;d&lt;/sub&gt;</td>
<td>Aorta (distal)</td>
<td>111.0</td>
<td>46.2</td>
</tr>
<tr>
<td>SA&lt;sub&gt;p&lt;/sub&gt;</td>
<td>Small Systemic Arteries</td>
<td>110.2</td>
<td>75.2</td>
</tr>
<tr>
<td>SA&lt;sub&gt;d&lt;/sub&gt;</td>
<td>Systemic Arterioles</td>
<td>56.8</td>
<td>58.3</td>
</tr>
<tr>
<td>SC</td>
<td>Systemic Capillaries</td>
<td>16.2</td>
<td>89.0</td>
</tr>
<tr>
<td>SV</td>
<td>Systemic Veins</td>
<td>6.1</td>
<td>1038.8</td>
</tr>
<tr>
<td>VC</td>
<td>Vena Cava</td>
<td>6.1</td>
<td>93.6</td>
</tr>
<tr>
<td>RA</td>
<td>Right Atrium</td>
<td>3.9</td>
<td>15.7</td>
</tr>
<tr>
<td>PA&lt;sub&gt;p&lt;/sub&gt;</td>
<td>Pulmonary Artery (proximal)</td>
<td>14.6</td>
<td>4.8</td>
</tr>
<tr>
<td>PA&lt;sub&gt;d&lt;/sub&gt;</td>
<td>Pulmonary Artery (distal)</td>
<td>13.6</td>
<td>24.9</td>
</tr>
<tr>
<td>PA</td>
<td>Pulmonary Arterioles</td>
<td>12.6</td>
<td>24.6</td>
</tr>
<tr>
<td>PC</td>
<td>Pulmonary Capillaries</td>
<td>10.0</td>
<td>63.0</td>
</tr>
<tr>
<td>PV</td>
<td>Pulmonary Veins</td>
<td>8.3</td>
<td>75.2</td>
</tr>
<tr>
<td>LA</td>
<td>Left Atrium</td>
<td>6.0</td>
<td>17.5</td>
</tr>
</tbody>
</table>

Table 2-2. Model output under control conditions: Mean pressures and volumes at various compartments throughout the closed-loop circulation. The units for pressure and volume are mmHg and ml, respectively.

### 2.6.2 Direct Ventricular Interaction

The contributions of one ventricle to the performance of the other are examined within the complete circulatory model. By convention, an increase in the septal volume ($V_{sep}$) indicates movement of the septal wall into the right ventricle, while leftward motion is represented by a decrease in $V_{sep}$. Typical M-mode echocardiographic observations [7, 34, 35] demonstrate that the normal systolic septum initially moves toward the LV free wall. Although the positive transseptal pressure ($P_{sep}$) gradient favors a rightward (paradoxic) motion of the passive septum, the activated septum continues to move against the gradient until the end of ejection. During the relaxation phase, the septum becomes more compliant and, thus, more responsive to instantaneous $P_{sep}$. In diastole, the septum is completely passive.
Following Chung et al [7], we examine three characterizations for the septum: a) a rigid, nondeformable, septum where only the free walls contribute to ventricular pumping; b) a passive septum where the septum merely couples the ventricles without contributing to ventricular pumping, and c) an active septum (control case), which combines the passive P-V relationship for diastole and an activation for systole \( e_s(t) \). Equation 2]. In all three cases, the P-V characterization and activation of the left and right free walls are considered identical and functioning within an intact pericardium. Additionally, the temporal profile of septal activation is identical to those for the free walls. The results of these simulations agree with findings previously discussed in Chung, et al [7] and are summarized in Table 2-3.

<table>
<thead>
<tr>
<th>Index</th>
<th>Control</th>
<th>Rigid Septum</th>
<th>Passive Septum</th>
<th>Pericardiectomy</th>
<th>Cardiac Tamponade</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>130.4</td>
<td>130.4</td>
<td>130.4</td>
<td>130.4</td>
<td>130.4</td>
</tr>
<tr>
<td>CO</td>
<td>1.72</td>
<td>1.72</td>
<td>1.69</td>
<td>2.20</td>
<td>1.07</td>
</tr>
<tr>
<td>SV</td>
<td>13.2</td>
<td>13.2</td>
<td>13.0</td>
<td>16.9</td>
<td>8.2</td>
</tr>
<tr>
<td>Mean ( P_{AO} )</td>
<td>111.3</td>
<td>111.0</td>
<td>109.1</td>
<td>138.6</td>
<td>73.8</td>
</tr>
<tr>
<td>Mean ( P_{PA} )</td>
<td>14.6</td>
<td>14.3</td>
<td>15.1</td>
<td>15.7</td>
<td>13.5</td>
</tr>
<tr>
<td>Mean ( P_{LA} )</td>
<td>6.0</td>
<td>5.8</td>
<td>6.7</td>
<td>4.8</td>
<td>8.2</td>
</tr>
<tr>
<td>Mean ( P_{RA} )</td>
<td>3.9</td>
<td>3.9</td>
<td>3.9</td>
<td>1.4</td>
<td>7.1</td>
</tr>
<tr>
<td>LVESP</td>
<td>126.0</td>
<td>124.1</td>
<td>121.9</td>
<td>156.8</td>
<td>83.5</td>
</tr>
<tr>
<td>RVESP</td>
<td>26.1</td>
<td>21.2</td>
<td>22.07</td>
<td>24.2</td>
<td>17.8</td>
</tr>
<tr>
<td>LVEDV</td>
<td>35.3</td>
<td>34.5</td>
<td>41.1</td>
<td>43.0</td>
<td>25.9</td>
</tr>
<tr>
<td>RVEDV</td>
<td>22.4</td>
<td>24.1</td>
<td>17.3</td>
<td>28.3</td>
<td>14.2</td>
</tr>
</tbody>
</table>

Table 2-3. Resultant cardiac indices produced by simulating: a) the control case (active septum with pericardium); b) rigid septum; c) passive septum; d) active septum without the pericardium intact; and e) cardiac tamponade (induced via infusion of 38 ml of saline solution.

A rigid, non-contractile septum decouples the ventricles such that the mechanics of each ventricular chamber are equivalent to those of the free walls. Thus, the rigid
septum does not provide any contractile effort and is unresponsive to $P_{SPT}$, yielding a constant $V_{SPT}$. While the active septum included in the control case mimics echocardiographic data as described previously and enhances LV function, the results listed in Table 2-3 suggest incorporating a rigid septum in the model has only a minor (<2%) effect on typical mean hemodynamic variables.

The passive septum is characterized by a time-invariant, passive P-V relationship (similar to the nonlinear diastolic P-V relationship in Equation 3a). When the passive septal characterization is employed, the positive $P_{SPT}$ causes an abnormal paradoxical movement of the septum towards the RV free wall, which is ultimately limited by the nonlinear nature of the passive septal V-P relationship. The passive septal model qualitatively mimics the paradoxic systolic motion observed in some patients during systole [34]. In contrast to the rigid septum studies, the influence of a passive septum on circulatory hemodynamics is expectedly more significant. This is most obviously documented by the end diastolic volumes of the left and right ventricles, which change by +28.8% and −36.1%, respectively, corresponding to the paradoxic rightward septal motion described earlier. This results in a concomitant rise in pulmonic arterial pressures, a decrease in systemic arterial pressures, and a cardiac output diminished by >3%.

2.6.3 Pericardial Influence

The importance of the pericardium in modulating cardiac performance has been well-established [18, 36]. This influence can be demonstrated in the CardioPV program via three pericardial variations: a) intact pericardium (control case); b) pericardiectomy; and c) cardiac tamponade (simulated by infusion of 38 ml of saline in the pericardial space). A pressure-volume (P-V) loop analysis of these simulations is depicted in Figure
2-15. In all cases, the shift in septal position throughout the cardiac cycle appears negligible, whereas the restriction on left and right free wall motion varies. This also applies to the atria wherein the interatrial septum is assumed rigid (decoupling the atria) and their free walls move to accommodate filling and contraction.

Removal of the pericardium eliminates a significant constraint on the filling capabilities of the heart chambers. In other words, the effective compliance of the atrial

Figure 2-15. Pressure-volume analysis of all four heart chambers under control conditions, pericardectomy, and cardiac tamponade (38 ml in pericardial space).
and ventricular free walls increases during diastole, thus increasing the EDV of each chamber (Figure 2-15), while simultaneously reducing the EDP. The increased EDV subsequently yields a more forceful systolic contraction as evidenced by a greater change in pressure from ED to ES. This also applies to the atria wherein the absolute pressures are lower, but the systolic pressure increase is greater without the pericardium. Conversely, during cardiac tamponade, the free walls of the atria and ventricles are significantly constrained, resulting in limited filling capability and an attendant reduction in the volumes of all four heart chambers.

Note that the PV diagram also lends itself to other assessments of cardiac function as well as model performance. The results depicted in Figure 2-15, and subsequent PV diagrams, are obtained after the model has achieved steady-state operation. In the absence of external influences, such as respiration, steady-state operation should yield the same stroke volume for all four chambers under the same experimental conditions. This is true for the ventricular data depicted in Figure 2-15. The right atrial SV also complies, however, the SV of the LA appears small in comparison. This is explained via the differences in the compliant nature of each atrium. Figure 2-9 showed the compliance curves of the atria used in this study. These curves were established to produce realistic atrial pressure waveforms as compared to the dog data collected. Typical $P_{RA}$ data shows a relatively small pressure increase during diastolic filling, whereas $P_{LA}$ increases substantially prior to mitral valve opening. From this we conclude that the LA is less compliant than the RA - a characteristic that is enhanced by the presence of the pericardium. Therefore, $P_{LA}$ rises as the LA fills with blood. When the mitral valve opens, there is a relatively large pressure difference between the LA and LV, resulting in a
greater blood flow through the mitral valve than the flow entering the atrium. Thus, atrial volume and pressure begin to decrease, even though the heart cycle is still in diastole. Atrial systole then causes the atrial pressure to rise and completes the ventricular filling.

Two other notes regarding the LA plot are relevant to these discussions. First, the apparent tail-like nature of the LA P-V plot is again a result of the above stroke volume discussion. As the pressure and volume decrease after mitral valve opening, hysteresis is evident in the intact pericardium cases. This is because the pericardium couples all the heart chambers. During early diastole, the total blood volume in the heart is low and the effect of the pericardium is reduced. In late diastole, however, the restrictive effect of the pericardium is more pronounced and thus, as $V_{LA}$ decreases, $P_{LA}$ does also but at a different rate than that by which it increased. This is confirmed as well by viewing the pericardiectomy PV loop which has no hysteresis. Secondly, due to the rapid increase in $P_{LV}$ during early systole and the relative timing of atrial and ventricular contractions, mitral valve closure occurs prior to completion of atrial systole. This yields a drop in pressure (on the low volume of left side of the PV loop in Figure 2-15) associated with an increasing volume, which is not intuitive. This phenomenon occurs in both atria, but is more evident in the LA.

Various physiological indices produced from these simulations of pericardiectomy and cardiac tamponade are summarized in Table 2-3. After pericardiectomy, there is a significant 23.5% increase in cardiac output (CO) and a 20.5% increase in mean aortic pressure. These increases echo the experimental results observed by Stokland, et al [37] and Hoit, et al [38], though to a greater extent. The reduction in atrial pressures reinforces the suggestion that opening the pericardium leads to an
increase in atrial compliance. During cardiac tamponade, the simulation produced a 27.1% reduction in cardiac output in comparison to the 33% reduction observed by Savitt et al [39] for a case of similar severity. The simulation also predicted a 21.4% reduction in left ventricular end-diastolic volume (LVEDF), which is reasonable, given a 13% reduction observed in the same study. Although the pericardium enhances direct ventricular interaction via the septum, the results of our simulation suggest that the intact pericardium exerts a moderate restrictive effect on overall cardiac performance, and that pericardial effusion enhances this constraint, adversely affecting cardiac performance and resulting in cardiac tamponade.

2.6.4 Filling and Afterload Effects

This combined model of cardiac mechanics and closed-loop circulation provides an opportunity to study altered preload and afterload effects on cardiac function. Specifically, these effects are examined by considering the following physiologic abnormalities: a) a significant increase in the input impedance (defined below) of the descending aorta; b) a significant increase in the input impedance of the pulmonary artery; c) significant occlusion of the vena cava (6% of control flow); and d) significant occlusion of the distal pulmonary arteries (6% of control flow). The effects of these cases on cardiac function are depicted in Figures 2-17 and 2-18 and summarized in Tables 2-4 and 2-5.

For our studies, alterations in ventricular afterload extended beyond simple increases in the zero frequency impedance or peripheral resistance. Rather, resistance increases were coupled with decreases in the compliance of proximal vascular components, thereby more realistically simulating a restrictive arterial system [40]. This
is best documented by studying the input impedance characteristics of the arterial system in question (e.g. systemic or pulmonic). The input impedance ($Z_{IN}$) seen by the ejection ventricle is defined as the spectral ratio of pressure to flow at the output of the ventricle (aortic and pulmonic roots).

We considered impedance at the aortic root ($Z_{IN,A}$) and the pulmonic root ($Z_{IN,A}$).

![Figure 2-16. Input impedance analysis of proximal aorta and pulmonary artery under control conditions, increased systemic afterload and increased pulmonic afterload. The units for the impedance modulus and phase are mmHg*sec/ml and degrees, respectively.](image)
sites in determining the afterloads presented here. Figure 2-16 shows the input impedance modulus and phase for the control, increased systemic and increased pulmonic afterloads, respectively. These impedance functions are in general agreement with the typical values and waveforms documented in [40]. Note that alterations in the impedance of one vascular system have very little effect on the other, further validating the piecewise parameter estimation scheme employed earlier.

Changes in preload or afterload have concurrent effects on the pressures and volumes of the heart chambers. Specifically, increasing the systemic afterload (i.e. the input impedance, \( Z_{in,A} \)) decreased the cardiac output (CO) by 19.8% while directly elevating the LV end-diastolic volume (LVEDV). This resulted in a significantly increased LV end-systolic pressure (LVESP). Consequently, the mean aortic pressures are raised by more than 50% (Figure 2-17 and Table 2-4).

<table>
<thead>
<tr>
<th>Index</th>
<th>Control</th>
<th>( \uparrow Z_{in,A} )</th>
<th>( \uparrow Z_{in,P} )</th>
<th>VC Occlusion</th>
<th>PA Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>130.4</td>
<td>130.4</td>
<td>130.4</td>
<td>130.4</td>
<td>130.4</td>
</tr>
<tr>
<td>CO</td>
<td>1.72</td>
<td>1.38</td>
<td>1.60</td>
<td>0.26</td>
<td>0.85</td>
</tr>
<tr>
<td>SV</td>
<td>13.2</td>
<td>10.6</td>
<td>12.25</td>
<td>2.0</td>
<td>6.6</td>
</tr>
<tr>
<td>Mean P(_{AO})</td>
<td>111.3</td>
<td>175.3</td>
<td>103.7</td>
<td>29.0</td>
<td>59.7</td>
</tr>
<tr>
<td>Mean P(_{PA})</td>
<td>14.6</td>
<td>13.0</td>
<td>17.4</td>
<td>1.3</td>
<td>56.8</td>
</tr>
<tr>
<td>P(_{LA})</td>
<td>6.0</td>
<td>6.2</td>
<td>6.0</td>
<td>0.0</td>
<td>6.1</td>
</tr>
<tr>
<td>P(_{RA})</td>
<td>3.9</td>
<td>3.7</td>
<td>4.2</td>
<td>-0.3</td>
<td>5.6</td>
</tr>
<tr>
<td>LVESP</td>
<td>126.0</td>
<td>191.8</td>
<td>117.5</td>
<td>33.4</td>
<td>68.0</td>
</tr>
<tr>
<td>RVESP</td>
<td>26.1</td>
<td>18.8</td>
<td>28.2</td>
<td>2.7</td>
<td>64.9</td>
</tr>
<tr>
<td>LVEDV</td>
<td>35.3</td>
<td>40.7</td>
<td>33.7</td>
<td>15.0</td>
<td>22.6</td>
</tr>
<tr>
<td>RVEDV</td>
<td>22.4</td>
<td>16.9</td>
<td>26.3</td>
<td>3.0</td>
<td>44.4</td>
</tr>
</tbody>
</table>

Table 2-4. Resultant cardiac indices produced by simulating: a) the control case (nominal hemodynamic parameters as given in Appendix B; b) moderate systemic afterload increase; c) moderate pulmonic afterload increase; d) severe vena caval occlusion; and e) severe pulmonary arteriole occlusion.
A similar percentage increase in the pulmonary afterload, $Z_{IN,P}$, decreases CO by a smaller amount (7.0%) and increases the pulmonary arterial pressures. The RV pressure increases in response to the higher load (by 33.6%), whereas the LV pressure decreases by 6.7% due to reduced inflow from the pulmonary circulation. The reduced LVESP corresponds to a reduction in mean aortic pressures of nearly 7%. The influence of the atria can also be seen in Figure 2-17. Specifically, the results show that in the cases

Figure 2-17. Pressure-volume analysis of all four heart chambers under control conditions, increased pulmonary afterload, and increased systemic afterload.
presented here, alterations in the systemic afterload have a much greater effect on the ventricular preload than do similar pulmonary changes. This is consistent with the reduced impact pulmonary afterload changes had on ventricular mechanics as discussed earlier.

When the afterload is severely elevated, as is simulated during the pulmonary artery occlusion, abnormal motion of the free walls and septum becomes apparent. Figure 2-18 shows that when the right ventricle encounters a large increase in its input impedance, its free wall exhibits pronounced expansion, accompanied by a shift in the septal position toward the left ventricle. Both PA and VC occlusion reduce LV volume as demonstrated in Figure 2-18 and documented in Table 2-4. VC occlusion also reduces RV volume due to limited inflow of blood. However, the RV volume is increased by PA occlusion, as blood accumulates in the chamber due to severe pulmonary restriction. Consequently, during PA occlusion, the right free wall expands outward, and the septum shows an abrupt, anteriorly-directed motion in early systole, followed by a leftward shift in its end-diastolic position. The reduction in RV output adversely affects the left ventricular input, causing a reduction in LV filling, and a consequent reduction in LVESP. Conversely, with vena caval occlusion, the systemic venous system becomes engorged, with the cardiac output eventually limited to the flow that is able to pass through the occlusion. This study provides a dynamic analog in general agreement to the static study performed by Amoore, et al [41].
2.6.5 Effects of Ventricular Interaction with Increased Afterloads

Hemodynamic loading not only affects the pressure and volume of the loaded ventricle, but also the state of the adjacent ventricle. Both direct and series ventricular interactions mediate these changes, shifting the loaded ventricle's P-V loop, as well as that of the adjacent ventricle. Up to 20% of the shifts in EDV of both ventricles can be attributed to changes in septal volume, $V_{SEPT}$, due to the compliant nature of the septum.
during diastole. Systolic septal interaction is less prevalent due to the active contraction of the septum itself. The combined effect of direct and series interaction is evident in Figure 2-17, where the smaller RV P-V loop occurs concomitantly with the larger P-V loop of the LV when the systemic afterload is increased, and vice versa, when the pulmonary afterload is increased. Note that, with the increased $Z_{IN,A}$, the left ventricular end-diastolic volume (LVEDV) increases by 13.5%, whereas the RVEDV decreases by nearly 25%. An increased pulmonary load brings a similar increase (17.2%) in RVEDV, accompanied by a smaller reduction (5.8%) in LVEDV. Also, due to the series interaction of the closed-loop circulation, the increased systemic afterload causes a concurrent increase in the LV preload pressure (i.e., $P_{LA}$) in the steady state, yielding an even greater increase in LVESP than would otherwise be noted.

This analysis can be extended further to address more involved ventricular interaction scenarios along the lines of the work done by Santamore, et al. [9]. Specifically, the Cardiov software can be used to address the influence of ventricular interaction in conjunction with high systemic or pulmonic afterloads. However, in this case, a dynamic assessment can be made, expanding on the two-point static analysis done earlier by Santamore, et al. [9]. Table 2-5 lists the results of simulations conducted with the interventricular septum characterized as active, rigid, or passive per previous descriptions, and with either a high systemic or pulmonic afterload, yielding six cases.
Table 2-5. Resultant cardiac indices produced by simulating: a) the control case (nominal hemodynamic parameters as given in Appendix B; b) moderate systemic and pulmonic afterload increases, respectively, with an active septum; c) moderate systemic and pulmonic afterload increases, respectively, with a rigid septum (i.e. decoupled ventricles); d) moderate systemic and pulmonic afterload increases, respectively, with a passive septum.

Figure 2-19 depicts a P-V loop assessment of direct ventricular interaction with a high systemic afterload, which is representative of typical results in this study. These results are in accord with those shown in [9]. We note that active interventricular coupling does limit the influence of high afterloads as compared to the decoupled (or rigid septum) case. This is also evident by comparing the cardiac output and stroke volume indices of the active and rigid septum cases, and referencing them to the control case. A passive septum, on the other hand, exacerbates the effect of high afterloads by allowing the left ventricle to be engorged at the expense of the right ventricle. In other words, the LVEDV increases significantly, while the RVEDV experiences a substantial decrease. This leads to a decreased effective contractility of the LV, resulting in a reduced stroke volume in the steady state.
Figure 2-19. Pressure-volume analysis of all four heart chambers depicting the septal influence on hemodynamics with an increased systemic afterload.

2.6.6 Ventricular Activation Timing Effects

Altering the activation sequence of the septum and the ventricular free walls of the heart model can simulate the ventricular dynamics and the abnormal septal motion observed during a variety of clinical conditions, such as intermittent right ventricular pacing, left bundle branch (LBB) block, and type B Wolff-Parkinson-White conduction. Figure 2-20 shows the results of simulation where the septum and the left free wall are
delayed by 20 and 60 msec, respectively, to simulate the conditions of delayed left ventricular activation, as in the case of Left Bundle Branch (LBB) block [42]. In Figure 2-20, delaying activation of the left free wall alters the temporal profiles of the left ventricular pressure and left free wall motion, as well as, the motion of the septum. Before LBB block, the simulated ventricles contract simultaneously, the pressure gradient across the septum (P_{SPT}) is positive (i.e. P_{LV} > P_{RV}), and the septum and ventricular free

![Figure 2-20. Temporal profiles of ventricular pressures and wall motions under control conditions, and left bundle branch (LBB) block.](image-url)
walls exhibit normal motion. During LBB block, development of left ventricular pressure is delayed (dashed lines in Figure 2-20), and the filling of the left ventricle is prolonged, resulting in a slightly higher end-diastolic volume (1.4 ml increase). During the pre-ejection (isovolumic) phase of the ventricles under LBB block, the transseptal pressure gradient transiently reverses ($P_{LV} < P_{RV}$) [43] and causes an abrupt abnormal leftward motion of the septum, accompanied by appropriate motion of the free walls to maintain constant ventricular volumes. When left ventricular pressure finally exceeds right ventricular pressure, and the transseptal pressure gradient is once again positive, the septum moves rightward, followed by normal septal motion during systolic ejection. This abrupt leftward (posterior) motion of the septum and the return (anterior, rightward), followed by a normal leftward motion during ejection, characterizes abnormal septal motion during delayed left ventricular activation, and can vary depending on the pacing site (right ventricular outflow tract or apex) [43].

Although the septum exhibits abnormal motion during LBB block, results obtained by simulating LBB block within the closed-loop model suggest that there is no significant hemodynamic compromise (Table 2-6). The cardiac output (CO) during simulated LBB block increases by 2.4% from baseline value (1.7 L/min). The change in mean arterial pressure is small, from 109.5 mmHg during control to 112.3 mmHg, representing a 2.6% reduction. In the pulmonary circulation, only a 2.3% reduction in mean pulmonary arterial pressure is observed. These results are comparable to those obtained by Yaku et al [42] to assess the effects of free wall ischemia and LBB block on systolic ventricular interaction in dog hearts. Despite disruption of coordinated
contraction by LBB block, both with and without the pericardium, they observed no significant hemodynamic changes in right ventricular stroke volume and stroke work.

<table>
<thead>
<tr>
<th>Index</th>
<th>Control</th>
<th>LBB Block</th>
<th>Tachycardia</th>
<th>Bradycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>130.4</td>
<td>130.4</td>
<td>160</td>
<td>60</td>
</tr>
<tr>
<td>CO</td>
<td>1.72</td>
<td>1.76</td>
<td>1.81</td>
<td>1.12</td>
</tr>
<tr>
<td>SV</td>
<td>13.2</td>
<td>13.5</td>
<td>11.3</td>
<td>18.6</td>
</tr>
<tr>
<td>Mean $P_{AO}$</td>
<td>111.3</td>
<td>113.8</td>
<td>116.6</td>
<td>75.5</td>
</tr>
<tr>
<td>Mean $P_{PA}$</td>
<td>14.6</td>
<td>14.1</td>
<td>15.1</td>
<td>12.4</td>
</tr>
<tr>
<td>$P_{LA}$</td>
<td>6.0</td>
<td>5.3</td>
<td>6.1</td>
<td>6.9</td>
</tr>
<tr>
<td>$P_{RA}$</td>
<td>3.9</td>
<td>3.8</td>
<td>3.6</td>
<td>5.6</td>
</tr>
<tr>
<td>LVED SP</td>
<td>126.0</td>
<td>130.3</td>
<td>130.1</td>
<td>94.9</td>
</tr>
<tr>
<td>RV ESP</td>
<td>26.1</td>
<td>22.1</td>
<td>20.3</td>
<td>24.5</td>
</tr>
<tr>
<td>LVEDV</td>
<td>35.3</td>
<td>37.7</td>
<td>34.4</td>
<td>37.4</td>
</tr>
<tr>
<td>RVEDV</td>
<td>22.4</td>
<td>22.4</td>
<td>20.0</td>
<td>30.3</td>
</tr>
</tbody>
</table>

Table 2-6. Resultant cardiac indices produced by simulating: a) the control case (nominal hemodynamic parameters as given in Appendix B; b) left bundle branch (LBB) block; c) an increased heart rate (tachycardia, 160 BPM); and d) a decreased heart rate (bradycardia, 60 BPM).

2.6.7 Heart Rate Effects

For all of the previous results, heart rate was maintained equal to that of the data used in identifying the model parameters. However, it is apparent from Table 2-6 and Figure 2-21 that heart rate plays an important role in establishing the hemodynamic state of the circulatory loop. Consistent with the findings of Suga. et al [16], ventricular elastance is not a strong function of heart rate (HR). We assume that for HR in the range $60 \leq HR \leq 160$ BPM, the strength and duration of contraction of each of the heart chambers is constant. However, the diastolic duration is assumed to vary with heart rate. This leads to the results listed in Table 2-6. When the heart rate is increased in tachycardia, there is insufficient time for the heart chambers to completely relax and fill
Figure 2-21. Pressure-volume analysis of all four heart chambers under control conditions, increased heart rate (tachycardia), and decreased heart rate (bradycardia).

with blood. This is indicated by 4.0% and 10.9% drops in LVEDV and RVEDV, respectively. As a result, the stroke volume, SV, decreases by 14.5%. However, due to the increased HR, cardiac output (CO) actually increases by more than 5%.

Conversely, in bradycardia, the preload is substantially increased as the end diastolic volumes rise (LVEDV: 4.3%; RVEDV: 34.9%). The difference in EDV between the left and right ventricles reveals the more compliant nature of the right heart during
diastole. As a result, peak systolic pressures increase in the right ventricle while decreasing in the left (Figure 2-21). While the stroke volume increases due the elongated filling time, the cardiac output (CO) is significantly reduced (34.9%).

2.7 DISCUSSION

In this study, we present a mathematical model of the canine circulation that emulates the functional behavior of the closed-loop circulation including dynamic ventricular interaction and the influence of pericardial mechanics. Secondarily, we discuss the incorporation of the model into a flexible, user-friendly software package. The combination provides the user with a powerful tool for rapidly assessing model performance and applying these techniques to individual experiment subjects.

The comprehensive closed-loop model describes the dynamics of the pressures and volumes in the circulation by lumping the major groups of blood vessels (arteries, capillaries, and veins) as individual compliances and by characterizing the cardiac pumps (atria and ventricles) as time-varying elastances. Cascading these compliant elements, the model is used to describe the pressure and volume dynamics in various points along the circulatory loop: the left atrium and ventricle; the aorta (proximal and distal); the systemic arterioles, capillaries, and veins; the vena cava; the right atrium and ventricle; the pulmonary arteries, capillaries, and veins. Similar lumped circulatory models have been developed [5, 6, 7, 9, 9, 10, 11, 26], each of which is capable of addressing series ventricular interaction. Direct ventricular interaction, characterized via a two-point static description, has been addressed in some models of the closed-loop circulation [9, 26] via the use of "interaction gains", in an effort to modulate ventricular pressures. However,
our model also includes the important continuous dynamics of direct ventricular interaction and pericardial influence [7].

Under control conditions, our model provides: (a) good fits to pressure waveform data; (b) predictions of mean blood pressure and blood volume distribution throughout the circulation; (c) good agreement with physiologic indices such as cardiac output and ejection fraction for a typical 25-kg dog; and (d) predictions of septal and free wall motion of the ventricles. By integrating physiologic afterloads (systemic and pulmonary) with the model of ventricular interaction via septum and pericardial influence, the complete model is useful in simulating a variety of interventions.

Applications of the model in the context of both direct and series ventricular interaction include simulation of the cardiovascular and hemodynamic response to altered heart mechanics or circulatory parameters. The heart mechanics or dynamics alterations included: (a) septal abnormalities (rigid or passive septum); (b) pericardial abnormalities (pericardium removed or pericardial effusion leading to cardiac tamponade); (c) altered activation timing within the heart (including heart rate variations and pathophysiologies such as left bundle branch block). In all of these cases, the CardioPV software provided a comprehensive, quantitative representation of the effects of each abnormal condition.

In reviewing these results in Figures 2-15, 20, and 21, and Tables 2-3 and 6, it is apparent that:

a) The active septal designation affords the most efficient pumping characterization of the heart. While the statistical variance of standard cardiac indices such as cardiac output (CO) is not large between the active and rigid septum designations, the active description is more physiologically realistic
and has been shown to agree well with echocardiographic septal motion data [7]. The passive septal designation results in substantially diminished pumping efficiency.

b) Pericardial mechanics have a dramatic influence on the capabilities of the heart pump. The heart chambers are constrained by the pericardium and, as such, have a limited diastolic filling capacity. Pericardieotomy removes this constraint resulting in a significantly increased CO, while pericardial effusion (leading to cardiac tamponade) yields a more severe constraint, significantly reducing the effectiveness of the heart pump. Employing a closed thoracic space with dynamic pleural pressures can further modulate these effects.

c) Heart rate has a significant effect on cardiac performance. It is imperative that HR is controlled when studying the influence of any other parameter on cardiac performance. While easy to accomplish in the model, this would require denervation (vagotomy) or administration of propranolol during the experiment to maintain relatively constant HR. For our purposes, model HR was made to equal the experimental HR, as discussed previously.

The current study also provides an analysis of preloads and afterloads to the heart model induced by alterations in circulatory hemodynamic parameters. In these cases, CardioPV analysis was able to provide dynamic descriptions of both series and direct ventricular interaction in the presence of altered circulatory loading. Figures 2-17, 2-18, and Tables 2-4 and 2-6, document the models' performance in this area, which was shown to be analogous to previous works [9]. These results provide a baseline for further
examination of various altered states, from the impact of hemorrhage to the effectiveness of implanted flow assist devices.
In this chapter, we develop relations that explicitly identify a nonlinear model of respiratory mechanics. The model partitions airways resistance into three components (upper, middle and small), includes a collapsible airways segment, a viscoelastic element describing lung tissue dynamics and a static chest wall compliance. Model predictions are validated against laboratory data collected from volunteer subjects and using the esophageal catheter balloon technique. As such, the data acquisition focus shifts from the animal experiments discussed previously to the collection of data from human subjects. Testing discussed herein does not imply the development of new experimental methods or equipment attempted on human subjects. Rather, the intent is to utilize data from conventional clinical testing procedures to identify parameters associated with our pulmonary system model. These established procedures have Institutional Review Board (IRB) approval and our modeling efforts constitute a secondary use of clinical data.

3.1 Objectives

The objectives of these experiments are to bring the flexibility and other advantages of Virtual Bio-Instrumentation to bear on clinical research endeavors,
specifically in the area of pulmonary mechanics. Clinical pulmonary function testing is an established means of characterizing respiratory mechanics to screen for pulmonary disorders. Study of the physiological mechanisms underlying abnormalities in pulmonary function requires a measurement/data acquisition system that supplements commercially available pulmonary function equipment.

3.2 BACKGROUND

3.2.1 Physiological Basis

The primary function of the respiratory system is to arterialize the blood, providing \( O_2 \) and removing \( CO_2 \) for the body tissues. Essentially this is accomplished by a three-part system: 1) ventilation; 2) gas exchange; and 3) perfusion. This chapter focuses on ventilation. The ventilatory system is a complex network of inhomogeneous airway structures which transport air into and out of the alveolar sacs where gas exchange occurs. Movement of the air is governed by the transairway pressure gradient created by the respiratory muscles of the chest wall, including the diaphragm. The resistance offered by the airways further modulates this airflow.

The airway divides 23 times between the trachea and the alveolar sacs within the lungs. The first 16 stages form a continuously narrowing series of conduits (bronchi) through which air flows. The remaining generations contain the bronchioles, alveolar ducts, and alveoli within which gas exchange occurs. These divisions increase the total cross-sectional area of the airways from 2.5 \( cm^2 \) in the trachea to 11,800 \( cm^2 \) in the alveoli [44]. The chest wall and the lungs are elastic structures with a thin layer of fluid in the pleural space between them. Contraction of the inspiratory muscles, particularly the
diaphragm, increases the intrathoracic volume, thereby reducing the intrapleural pressure from its typical end-expiration value of \(-2.5 \text{ mmHg}\) to about \(-6 \text{ mmHg}\). This causes the lungs to expand, reducing the pressure in the airways and causing air to flow into the lungs. After inspiration, the lung recoil force pulls the chest wall back towards equilibrium, where the recoil pressures of the lung and chest wall are balanced. This increases the pressure in the airways and air is forced out of the lungs.

The standard respiratory rate for a normal, resting human is \(6 - 8 \text{ L/min}\). This amount of air is exchanged in a series of breaths (12 - 15 \text{ breaths/min}) during which approximately 0.5 \(L\) of air is inspired and expired per breath. The amount of air that is inspired or expired in a single, resting breath is termed the \textit{tidal volume} (see Figure 3-1). The volume of air remaining in the lungs at the end of a normal, passive expiration is the \textit{functional residual capacity} (FRC). A maximal inspiratory effort will increase the amount of air inspired. The additional volume above tidal volume is the \textit{inspiratory reserve volume} (IRV). \textit{Expiratory reserve volume} (ERV) is the volume of air expired by active effort beyond the passive expiration. The amount of air left in the lungs after a maximal expiratory effort is the \textit{residual volume} (RV).
3.2.2 Theoretical Basis

In this chapter, we focus on the means of collecting pulmonary function data, and using that data to verify the development of theoretical models. Specifically, the particular model addressed here first deals with a study of the viscoelastic properties of lung tissue and is then incorporated into a more comprehensive nonlinear model of pulmonary mechanics.

Pulmonary Function Testing. Pulmonary function testing (PFT) is a routine, non-invasive clinical procedure conducted to assess the functional state of a patient's respiratory system [45, 46, 47]. A typical PFT includes spirometry, during which flow at the mouth is measured via a pneumotachometer, yielding a measure of changes in lung volume during a forced vital capacity maneuver. Combined with either plethysmography or helium dilution, through which absolute lung volumes can be estimated, a quantitative assessment of absolute lung volume can be conducted over the full vital capacity range. In this way, PFT results provide quantitative indices of airway/lung mechanics, such as total lung capacity (TLC), functional residual capacity (FRC), residual lung volume (RV), the volume of air forcefully expired in 1 sec (FEV$_1$), and many others. This standard repertoire of tests evaluates an individual's lung performance, and compares that information to population-specific standards. Pulmonary function tests are usually conducted to either: 1) screen for disease; 2) provide periodic checkup for chronic respiratory disease patients; 3) assess acute changes in patients with respiratory diseases; or 4) provide post-treatment follow-up. The testing can potentially be expanded to include blood gas or expired gas measurements in order to assess the effectiveness of gas exchange within the lungs.
**Lung Tissue Viscoelastance.** The mechanical properties of lung tissue are described by the relationship between transpulmonary pressure (alveolar pressure minus pleural pressure) and the volume of air contained in the alveoli (lung volume). This relationship is nonlinear and reveals both elastic and nonelastic behavior. In particular, under dynamic conditions, the pressure-volume (P-V) curve exhibits *hysteresis*, whereby the inspiratory and expiratory paths do not coincide (inspiration involves higher pressures than expiration). The area enclosed by the hysteretic loop equals the energy dissipated during each breathing cycle. This suggests the existence of a nonelastic component in the tissue, commonly referred to as the lung tissue resistance. Similarly, dynamic compliance quantifies the elasticity of the material and is measured as the slope of the line connecting the extrema of the hysteretic loop. Under static conditions, the loop collapses onto a single, nonlinear P-V curve, the slope of which equals the static compliance of the lung tissue. Lung tissue also exhibits *stress adaptation* [48], i.e. the pressure differential across it changes value over time under constant volume conditions. Equivalently, the volume changes even after the pressure has been fixed, a phenomenon termed *creep* [49]. It has been suggested that stress adaptation in the tissue can be attributed to the same mechanism responsible for the hysteretic loop observed under dynamic conditions [50]. The properties described above are characteristic of viscoelastic behavior.

Experimental studies [48, 51, 52, 53, 54], mostly on anesthetized animals, show that the dynamic behavior of lung tissue exhibits the following properties: i) dynamic compliance decreases as the frequency increases; ii) tissue resistance drops with increasing frequency; and iii) the static P-V curve is nonlinear and local incremental compliance varies with volume.
The linear viscoelastic solid, or Kelvin body, consisting of a compliance in series with a parallel combination of another compliance and resistance (often called the Maxwell body), is capable of simulating many aspects of tissue behavior, including the dependence of tissue resistance and compliance upon the frequency of breathing. Jonson et al. [55] employed this model in mimicking data collected from healthy anesthetized humans ventilated in the linear range of total respiratory system behavior (lung tissue plus chest wall). Svantesson et al. [56] proposed a variation of the Kelvin body that employs nonlinear viscoelastic components, and demonstrated that this model was able to predict respiratory system mechanics in ventilated rabbits.

Other modeling schemes have been introduced in the literature, as well. Among them is the work of Hildebrandt [53] who proposed a composite model of linear viscoelastic and plastoelastic elements. The latter are required to account for the static hysteresis that some experimenters have discovered in lung tissue (i.e., P-V hysteresis under zero flow conditions). The need to address respiratory mechanics properties in nonlinear ranges and higher frequencies has guided research to more advanced modeling efforts. These include distributions of Kelvin bodies [57], viscoelastic and plastoelastic elements [58], nonlinear viscoelasticity (implemented with a Volterra series) [59], and coupled dissipative and elastic processes (hysteresivity) [60].

Variations of the Kelvin body have been employed in the past to characterize lung tissue properties in ventilated dogs [61], but most studies have employed this model to simulate the total respiratory system (lung and chest wall) in anesthetized humans [55], ventilated rabbits [56], anesthetized dogs [62] and cats [63].
Unlike these works, this study confines the application of the model to the simulation of human lung tissue dynamics only. As discussed later, transpulmonary pressure data is collected in naturally breathing human subjects, and, thus, the lung tissue is isolated from its neighboring structures. Then, the data is used to run the model (experimentally generated driving waveform), identify its parameters, and make comparisons, both for dynamic and frequency dependent variables. This study establishes that this simple model fits experimental data well, both over the nonlinear range of breathing volumes, and also over a range of breathing frequencies. This model is subsequently used as part of a larger model of the respiratory system that includes characterizations for airway, thorax and diaphragm dynamics.

Pulmonary Mechanics. Similar to the numerous modeling endeavors undertaken to describe the cardiovascular system, a wide variety of modeling efforts have been applied to the study of pulmonary mechanics, dynamics, and gas exchange. For the present study, we consider only the modeling of airway mechanics. Previously, detailed distributed models of airway mechanics have been developed to describe pressures and flows in each airway generation [64, 65, 66, 67]. The complexities of these models enable them to mimic both tidal breathing and a variety of maneuvers, such as the forced vital capacity (FVC) maneuver. However, the complexities also make it difficult to estimate the distributed parameters of the model from data routinely collected in a PFT. Conversely, lumped parameter models, which are adequate to describe airway dynamics, yet sufficiently simple to be useful for clinical applications, have also been developed [68, 69, 70, 71]. Lumped models of this type have been applied to the study of various breathing maneuvers, from tidal breathing to panting to the FVC maneuver.
Our objective is to gain better insight into normal respiratory function for potential applications in clinical settings. One common clinical reason for studying pulmonary mechanics is the assessment of work of breathing (WOB). WOB measurement finds application in the assessment of respiratory failure and in ventilatory management, as an indicator of the metabolic energy of breathing. Recently, with the advent of new ventilatory modes for the critically ill patient, assessment of breathing effort has received revived interest among clinicians. The application of this model to the estimation of the WOB and respiration energetics is discussed in Athanasiades, 1999 [72].

3.3 MODEL DEVELOPMENT

The pulmonary mechanics model includes nonlinear characterizations of airway resistance, chest wall compliance and lung tissue viscoelasticity. The model features separate resistive coefficients for the upper, middle and small airways; a compliant characterization of partially supported airways; a modified Kelvin body that describes the dynamic compliance of lung tissue; and a static compliance for the chest wall.

The mathematical models employed here are based on our respiratory model developed in [73]. A physical representation of the full model, depicting its individual components, appears in Figure 3-2a, along with its pneumatic analog in Figure 3-2b. To allow for a complete accounting of the work associated with breathing and for a better response to maneuvers of variable frequency, the following modifications are introduced to the original model:
i) a nonlinear compliance $C_{CW}$ is used to represent the combined elastic behavior of the chest wall and diaphragm, such that the energy stored in these structures can be accounted for;

ii) as a result of this modification, the signal driving the model is no longer pleural pressure $P_{PL}$, but rather the pressure $P_{MUS}$, which describes the net equivalent effect of respiratory muscle activity; $P_{MUS}$ is directly influenced by the respiratory controller in the brain and its waveform is easily reproduced in simulated maneuvers; and

iii) a viscoelastic structure (Kelvin body) replaces the original pressure-volume characterization of lung tissue. The modifications are treated in more detail below.

Figure 3-2. A) Physical model of respiratory system; B) Pneumatic analog of pulmonary mechanics model.
Model functions and parameters for all subjects are summarized in Tables 2 and 3, respectively. Parameter values of the full nonlinear model have been tuned to match experimental records of volume and flow in the FVC maneuver, as it is rich enough to excite most system dynamics. In general, parameter values comply with specifications given in [73]. In addition, they remain unchanged for all simulated maneuvers in a single subject.

3.3.1 Lung Tissue Viscoelastance

A pneumatic representation of the lung tissue model appears as the shaded portion in Figure 3-3. It employs a combination of a nonlinear compliance $C_L$, of volume $V_A$ (lung volume), in series with a linear compliance $C_{VE}$, of volume $V_{VE}$, and linear resistance, $R_{VE}$. The compliance, $C_L$, describes the relationship between $V_A$ and the pressure drop across the tissue wall, under static conditions.

Experimental evidence shows that this pressure-volume relationship is nonlinear [48, 51]; it is modeled here as a logarithmic function of volume, according to the formula:

![Figure 3-3. Pneumatic representation of pulmonary mechanics model. Shaded region describes lung tissue viscoelastance.](image)

\[ P_a - P_t = a + b \cdot \ln \left( \frac{TLC - RV}{V_A - RV} - 1.0 \right) \]  \hspace{1cm} (8)

where \( a \) and \( b \) are constants, \( TLC \) is the total lung capacity of each subject, and \( RV \) is the residual volume. Due to the nonlinearity in the formula, the value of \( C_L \) is not constant (as is \( C_{VE} \)), but rather varies with volume:

\[ C_i(V_A) = \frac{dV_A}{d(P_a - P_t)} \]  \hspace{1cm} (9)

Logarithmic expressions such as this have been used previously to characterize elastic structures of the lung [73].

The total pressure drop across the shaded elements of Figure 3-3 is the dynamic elastic recoil of lung tissue, \( P_{EL} \), accounting for both the elastic forces, and the forces introduced by any nonelastic behavior. We use our measurements of \( P_{EL} \) as the independent forcing function in our simulations. This allows us to isolate the lung tissue structure from the total respiratory system, effectively separating lung tissue from the adjoining airways and chest wall. Figure 3-3 shows a pneumatic representation of the total respiratory system, which includes characterizations for the airways and chest wall, in addition to lung tissue. The model successfully predicts lung volume and flow waveforms in dynamic maneuvers that include tidal breathing, panting and forced vital capacity efforts (simulations generated with a similar model appear in [73]). We have used this model to simulate our measurement procedure, as explained later. It is presented here to more clearly identify the modeled lung tissue structure in the context of a full lung/airways model.

The volumes \( V_A \) and \( V_{VE} \), associated with the compliant elements of the lung tissue model, are the two independent variables that completely describe the dynamic
behavior of the pneumatic network shown in the shaded portion of Figure 3-3. The
differential equations describing the motion of the system can be derived from the
balance of pressures along the branches of the network; they are:

\[
\begin{bmatrix}
1 + \frac{bC_{ve}(TLC - RV)}{(V_A - TLC)(V_A - RV)} & 0 & 1
\end{bmatrix}
\begin{bmatrix}
\dot{V}_A \\
\dot{V}_{VE}
\end{bmatrix}
+ \begin{bmatrix}
\frac{1}{(R_{ve}C_{ve})V_{VE}} \\
\frac{1}{(R_{ve}C_{ve})V_{VE}}
\end{bmatrix}
= \begin{bmatrix}
\dot{P}_{el} \\
0
\end{bmatrix}
\tag{10}
\]

Linearized Lung Tissue Model Analysis

Analytical tools applicable to linear systems can be applied to the foregoing
model development as done previously by our group [79]. The linear analysis enables us
to: a) identify the significance of individual model elements in simulating the viscoelastic
properties of lung tissue; b) introduce commonly employed concepts (such as impedance)
and relate them to the current model; and c) relate analytical expressions and their
dependencies to experimental data. In the following, we assume small volume
excursions, as during normal breathing. It is then possible to linearize the compliance \(C_L\).
i.e., take a constant value for \(C_L\), which is valid at the midtidal volume, \(V_{A\,mt}\), of each
maneuver.

Total lung tissue impedance for the shaded elements of Figure 3-3 is defined in
the complex frequency domain, \(s\), as:

\[
Z(s) = \frac{P_{el}(s)}{sV_A(s)}
\tag{11}
\]

which can be broken down into the component impedances of the model elements:

\[
\begin{align*}
Z_1 & = \frac{1}{sC_L} \\
Z_2 & = R_{ve} \\
Z_3 & = \frac{1}{sC_{ve}}
\end{align*}
\tag{12}
\]
Applying these elements yields:

\[ Z(s) = Z_1(s) + \frac{Z_2(s)Z_3(s)}{Z_2(s) + Z_3(s)} = \frac{1}{sC_L} + \frac{R_{ve}}{sR_{ve}C_{ve} + 1} \]  

(13)

Assuming that system oscillates at a frequency \( w \) about the mid-tidal volume, such that:

\[ V_A = V_0 \sin(\omega t) + V_{A,mt} \]  

(14)

where \( V_0 \) is one half the tidal volume, \( V_{A,mt} \) is the mid-tidal volume and \( t \) is time. The real and imaginary parts of \( Z \) can now be identified as functions of frequency by substituting \( s = j\omega \) in Equation 13 and rearranging:

\[ Z(w) = \frac{R_{ve}}{w^2R_{ve}^2C_{ve}^2 + 1} - j \left( \frac{1}{wC_L} + \frac{wR_{ve}^2C_{ve}}{w^2R_{ve}^2C_{ve}^2 + 1} \right) \]

(15)

\[ = R(w) - j[X_1(w) + X_2(w)] \]

Here the real (resistive) part of \( Z \) is defined as \( R(w) \); the imaginary or reactive part consists of two terms, \( X_1 \) and \( X_2 \), which correspond to the compliance \( C_L \) and the Maxwell combination \( (R_{ve} - C_{ve}) \), respectively.

From Equations (11) and (15), \( P_{el} \) can be written as:

\[ P_{el} = \left[ \frac{R_{ve}}{w^2R_{ve}^2C_{ve}^2 + 1} - j \left( \frac{1}{wC_L} + \frac{wR_{ve}^2C_{ve}}{w^2R_{ve}^2C_{ve}^2 + 1} \right) \right] \cdot j\omega V_A \]

(16)

which can be rearranged to reveal the equivalent (effective) compliance, \( C(w) \), and resistance, \( R(w) \), of the model in a fashion similar to an analysis that appears in [61]:

\[ P_{el} = \frac{1}{C(w)}V_A + R(w)j\omega V_A \]

(17)

Comparing Equations (16) and (17) yields the following expressions:

\[ \frac{1}{C(w)} = \frac{1}{C_L} + \frac{w^2R_{ve}^2C_{ve}}{w^2R_{ve}^2C_{ve}^2 + 1} \]

(18)
\[ R(w) = \frac{R_{ve}}{w^2 R_{ve}^2 C_{ve}^2 + 1} \quad (19) \]

Effective resistance \( R(w) \) has already been identified as the real part of impedance (see Equation (15)), whereas the effective compliance \( C(w) \) equals \( [wX(w)]^{-1} \), where \( X = X_1 + X_2 \). The value of \( C(w) \) equals the dynamic compliance of lung tissue, as defined previously, for the linear range of volumes. \( R(w) \) and \( C(w) \) are obviously functions of frequency (they decay in a sigmoidal manner with respect to frequency, as verified later).

In the limiting case, when \( w \to 0 \), \( C(w) = C_L \) and \( R(w) = R_{ve} \); as \( w \to \infty \), \( C(w) = (C_L C_{ve})/(C_L + C_{ve}) \), which is the series combination of the two compliances, and \( R(w) = 0 \).

### 3.3.2 Chest Wall

In our previous studies [73], the chest wall was assumed rigid and the lungs were driven by the pleural pressure waveform measured via the esophageal balloon technique. Since elastic forces developed in the chest wall and diaphragm expend part of the effort during breathing, we have reformulated our model to include a lumped characterization of the thoracic wall and diaphragm. They are modeled as a series combination of an independent pressure source, \( P_{MUS} \), serving as the dynamic force driving the model, and a passive compliant element, \( C_{CW} \), as shown in Figure 3-3. The volume of air contained in \( C_{CW} \) is the chest wall volume, \( V_{CW} \), and the pressure across it is the chest wall elastic recoil, \( P_{CW} \). This is equal to the difference between the total pressure across the chest wall, pleural pressure \( P_{PL} \), and the pressure developed due to the respiratory muscles:

\[ P_{PL} = P_{CW} - P_{MUS} \quad (20) \]
$P_{CW}$ is commonly approximated by a sigmoidal curve [29] that is linear in the range of quiet breathing and saturating at higher and lower volumes. We mimic this relationship with a logarithmic expression:

$$P_{CW} = A_{CW} - B_{CW} \cdot \ln\left(\frac{TLC - RV}{V_{CW} - RV} - 0.999\right)$$

(21)

where $A_{CW}$ and $B_{CW}$ are constants. Numerical values are chosen so that chest wall compliance, $C_{CW} = dP_{CW} / dV_{CW}$, is approximately 0.2 l/cmH$_2$O in the linear range (volumes of 2.5 to 3 liters), for the subject tested. During tidal breathing the chest wall has mostly outward recoil.

3.3.3 Airways

Functional relationships and parameter values modeling the airways are adopted directly from Liu et. al. [73], except for the resistive characterization of the peripheral airways which now bear a nonlinear relationship with volume only:

$$R_S = A_S \cdot e^{K_S(V_{A}-RV)/(V^*-RV)} + B_S$$

(22)

where $A_S$, $B_S$, $K_S$, and $V^*$ are constants. The corresponding characterization of [73] incorporated an effort dependent term, aimed to achieve the limitation of flow during the expiratory portion of the forced vital capacity maneuver. We replace that mechanism by restricting the airways elastic recoil $P_C$ to positive values only: the airways can now sustain distension, but not compression.

According to Equation 22, the value of $R_S$ increases exponentially as lung volume $V_A$ decreases. The formula aims to capture the dependence of small airway resistance on lung volume. As the lung inflates, small airways imbedded into the lung parenchyma are stretched open, allowing free passage of airflow (low resistance). At low lung volumes,
these airways are constricted, offering large resistance to flow. The value of \( R_C \) is inversely proportional to the square of the volume in the airways \( V_C \). The same principle applies here: as the airways become narrower (lower volume) they offer higher resistance to flow, and vice versa. The characterization of \( R_C \) was originally developed in [68] and [70].

3.3.4 Full Model of Respiratory Mechanics

The equations governing the motion of the system are developed using a Lagrangian analysis [74]. The dynamic behavior of the system is described completely by generalized coordinates whose number is equal to the number of energy storage elements minus the number of constraints [74]. In the absence of inertial elements, kinetic energy is zero and potential energy is stored in the four compliant compartments. Due to the kinematic constraint \( V_{CW} = V_A + V_C + V_D \), however, only three independent generalized coordinates are realized, namely, \( q_1 = V_C \), \( q_2 = V_A \) and \( q_3 = V_{VE} \), depicted in the mechanical representation of the model in Figure 3-4 (\( V_D \) is the volume of the dead space).
Lagrange's equation [74] applicable to each generalized coordinate \( q_i \) is then given as:

\[
\frac{\partial E_{\text{pot}}}{\partial q_i} = Q_{NC_i}, \quad \text{for } i = 1, 2, 3. \tag{23}
\]

where \( E_{\text{pot}} \) is the potential energy of the system and \( Q_{NC_i} \) the sum of all nonconservative, generalized forces that correspond to the coordinate \( q_i \). They include the externally applied muscle pressure \( P_{\text{MUS}} \) and the pressure drop \( P_{\text{DISS}} \) across resistive elements in Figure 3-4. In the case of viscous damping,

\[
P_{\text{DISS}} = -R\dot{q} \tag{24}
\]

where \( R \) is the resistive coefficient that corresponds to the time derivative of coordinate \( q \) (the minus sign indicates that the force acts in a direction opposite to that of the velocity).

In the context of Lagrangian dynamics the total virtual work for this system (not to be confused with work of breathing) can be easily calculated [74] and is given as:

\[
\delta W = \left[ P_{\text{MUS}} - (R_u + R_c)(\dot{V}_c + \dot{V}_A) \right] \delta V_c \\
+ \left[ P_{\text{MUS}} - (R_u + R_c)(\dot{V}_c + \dot{V}_A) - R_s \dot{V}_A - R_{ve} (\dot{V}_A - \dot{V}_{ve}) \right] \delta V_A \\
+ \left[ R_{ve} (\dot{V}_A - \dot{V}_{ve}) \right] \delta V_{ve} \tag{25}
\]

where \( \delta V_c, \delta V_A \) and \( \delta V_{ve} \) are virtual displacements. The nonconservative forces for each generalized coordinate are then given by the terms multiplying the corresponding virtual displacement, or:

\[
Q_{NC_i} = P_{\text{MUS}} - (R_u + R_c)(\dot{V}_c + \dot{V}_A) \tag{26}
\]

\[
Q_{NC_i} = P_{\text{MUS}} - (R_u + R_c)(\dot{V}_c + \dot{V}_A) - R_s \dot{V}_A - R_{ve} (\dot{V}_A - \dot{V}_{ve}) \tag{27}
\]

\[
Q_{NC_i} = R_{ve} (\dot{V}_A - \dot{V}_{ve}) \tag{28}
\]
Potential energy is given by the formula

$$E_{POT} = -\int_{q_{ref}}^{q} P dq$$  \hspace{1cm} (29)$$

where $P$ is the generalized elastic force, in this case the pressure drop across a compliant element. The integral is evaluated from the current coordinate value $q$ to a reference (fixed) value $q_{ref}$. The elastic forces that correspond to coordinates $V_C$, $V_A$ and $V_{VE}$ are pressures $(P_C + P_{CW})$, $(P_L + P_{CW})$ and $P_{VE}$, respectively. The total potential energy is

$$E_{POT} = \int_0^{V_C} (P_C + P_{CW}) dV_C + \int_0^{V_A} (P_L + P_{CW}) dV_A + \int_0^{V_{VE}} (P_{VE}) dV_{VE}$$  \hspace{1cm} (30)$$

Note that the minus sign of the general equation is canceled by the reversal of the integration limits in Equation (21). Also, due to the conservative nature of the elastic forces, reference positions are arbitrarily set to zero.

Substituting Equations (18), (19) and (21) into Lagrange's formula and rearranging yields the equations of motion. In matrix form the equations are:

$$\begin{bmatrix}
R_U + R_C & R_U + R_C & 0 \\
R_U + R_C & R_U + R_C + R_s + R_{VE} & -R_{VE} \\
0 & -R_{VE} & R_{VE}
\end{bmatrix}
\begin{bmatrix}
\dot{V}_C \\
\dot{V}_A \\
\dot{V}_{VE}
\end{bmatrix}
+
\begin{bmatrix}
P_C + P_{CW} \\
P_L + P_{CW} \\
P_{VE}
\end{bmatrix}
= \begin{bmatrix}
P_{MUS} \\
0
\end{bmatrix}$$  \hspace{1cm} (31)$$

The temporal variation of the generalized coordinates $V_C$, $V_A$ and $V_{VE}$ is described by three coupled, nonlinear, ordinary differential equations. $P_{MUS}$ is the independent, time-varying input function resulting from a particular breathing pattern. The first term on the left side of Equation (22) represents the dissipative forces introduced by the four resistances in the model while the second term on the left side of the equation represents the elastic forces that characterize the compliant elements. The term on the right side of Equation (22) represents the applied force.
3.4 **Experimental Measurements**

Instrumentation and methodologies developed for the measurement of pulmonary mechanics relied on simultaneous pleural pressure and lung volume recordings. The former is approximated by esophageal pressure, measured with a nasogastric catheter balloon [75]. Volume is measured either with spirography or by integrating volumetric flow from a pneumotachograph. In clinical practice, the two variables (pressure and volume) are directed to a computerized monitor and plotted against each other. In this manner, work is estimated by calculating the area enclosed in the pleural pressure loop [76].

3.4.1 **Pulmonary Function Experiments**

The desired measurements, namely pleural pressure, airflow at the mouth, and expired gas concentrations (particularly O\textsubscript{2} and CO\textsubscript{2}), were obtained utilizing minimally invasive measurement techniques as listed in Table 3-1. Specifically, a Sensor Medics 2800 Body Plethysmograph and associated pneumotachometer were used to establish baseline subject measurements of volume and airflow, respectively. In routine PFT, only
airflow at the mouth and lung volume are utilized in the assessment of lung function. This study includes pleural pressure and expired gas (O\textsubscript{2} and CO\textsubscript{2}) concentrations in an attempt to extend the capabilities of lung function assessment. Pleural pressure was measured using a latex balloon appropriately positioned in the esophagus [75] and connected to a pressure transducer in the plethysmographic system. A Datex Capnomac Ultima, using side-stream gas analysis, provided continuous measurements of expired O\textsubscript{2} and CO\textsubscript{2} concentrations.

Discrete sampling of all analog signals was accomplished using a Macintosh Quadra 800 personal computer outfitted with a National Instruments NB-MIO-16X multifunction DAQ board, and an AMUX-64T multiplexer terminal board. The ensuing digital data was processed, displayed and stored using original code developed within the LabVIEW programming environment. A schematic of the typical experimental/DAQ system setup is shown in Figure 3-5. The data acquisition system was based on that developed by Olansen et al. [77].

<table>
<thead>
<tr>
<th>System Driving Input</th>
<th>Physiological Signal</th>
<th>Measurement Apparatus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural Pressure (cm H\textsubscript{2}O)</td>
<td>Esophageal Pressure</td>
<td>Naso-gastric Esophageal Balloon/ Pressure Transducer</td>
</tr>
<tr>
<td><strong>Airway Mechanics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow (L/sec)</td>
<td>Airflow at the Mouth</td>
<td>Differential Pressure Pneumotachometer</td>
</tr>
<tr>
<td>Lung Volume (L)</td>
<td>Integrated Airflow</td>
<td></td>
</tr>
<tr>
<td><strong>Gas Exchange</strong></td>
<td>Expired O\textsubscript{2}, CO\textsubscript{2} (%)</td>
<td>Datex Capnomac Gas Analyzer</td>
</tr>
<tr>
<td>Expired O\textsubscript{2}, CO\textsubscript{2} (%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3-1. Pulmonary Function Testing data collection components.
3.4.2 Lung Tissue Viscoelastance Experiments

Measurements of airflow at the mouth and elastic recoil pressure were obtained from three volunteer human male subjects using the described earlier. All subjects were healthy with no current or significant history of respiratory ailments. Elastic recoil data were obtained during inspiration and expiration over the entire volume capacity of spontaneously breathing subjects. To this end, the esophageal pressure was continuously referenced to mouth pressure to enable a direct recoil pressure measurement when the airflow was zero [75]. By instituting a shuttering technique, as shown in Figure 3-6, the airflow at the mouth could be repetitively halted, enabling mouth pressure to equalize with alveolar pressure. Thus, the actual measurement recorded was that of pleural (esophageal) pressure, $P_{PL}$, minus alveolar pressure, $P_{A}$, which equates to the elastic recoil pressure, $P_{EL}$.

Each experimental episode started with a minimum of four tidal breaths, followed by a complete inhalation to total lung capacity (TLC) and relaxed exhalation to functional residual capacity (FRC). Some episodes included forced exhalation to residual volume (RV). During these large volume excursions, a shuttering mechanism in the flow passageway was manually activated and deactivated in rapid succession (23 Hz). In this manner, a significant number of data points could be obtained over the entire vital capacity range.

Data were also gathered on the frequency dependent behavior of lung tissue. Subjects executed a panting maneuver at different frequencies near FRC. During this procedure, flow shuttering was not performed, since it would alter the true frequency of breathing. Instead, only pleural pressure data and volume were collected. Pleural pressure
equals the elastic recoil pressure at both end-inspiration and endexpiration (in the absence of flow, pressure drop in the airways is zero). The endpoint data thus collected can be utilized to calculate the dynamic compliance of tissue. It is defined as the ratio of tidal volume to the change in pressure measured, at the respective breathing frequency [78]. After each testing episode, the subject rested for a period of time that ensured full recovery of baseline levels of pO\textsubscript{2} and pCO\textsubscript{2}.

**Measurement Issues.** As discussed earlier, dynamic compliance is clinically measured as the slope of the line connecting the volume extrema of the hysteretic pressure-volume loop [78]. This line is not to be confused with the major axis of the
hysteretic ellipse. The angle \( q \) formed between the major axis of the ellipse and the abscissa is given by the expression:

\[
\theta = 0.5 \tan^{-1} \frac{2/C(\omega)}{1 - (1/C(\omega))^2 - \omega^2 R(\omega)^2}
\]  \( (32) \)

The slope suggested by \( \theta \) (i.e. the tangent of \( \theta \)) is close in value to \( C(\omega) \), especially at higher frequencies, for which the ellipse is greatly inclined, and at lower values, when the slope is nearly equal to \( 1/C_L \). Yet, the apparent inclination of the elliptical loop (as indicated by \( \theta \)) does not always coincide with the actual measure of compliance, \( C(\omega) \).

An additional point should be made concerning the accuracy of the flow shuttering technique in equalizing mouth to alveolar pressure. A separate simulation, not included here, was employed to predict the error introduced in the measurement of elastic recoil by any compliance in the airways. As the airways are not totally rigid, a secondary flow may exist even when the shutter is closed. The simulation is based on the model of Figure 3-3, where compliance \( C_C \) represents the elasticity in the airways. Its branch will shunt flow away from the airway path (resistances \( R_U, R_C \) and \( R_S \)), even under closed shutter conditions. Pressure measured at the mouth will differ from the actual alveolar pressure \( P_A \) by an amount equal to the flow in the shunt multiplied by the resistive coefficient \( R_S \). The simulation reveals that during slow breathing this error lies in the range of \( \pm 0.025 \text{ cmH}_2\text{O} \), which is negligible.
3.5 **Computational Aspects**

3.5.1 **Model Operation**

The model equations were initiated at the time of end-expiration with no flow at the mouth. Measured physiological data of the pleural pressure, $P_{PL}$, or the dynamic elastic recoil, $P_{EL}$, are the input waveform used to run the appropriate model ($P_{PL}$ for the full model, and $P_{EL}$ for the reduced viscoelastance model). The model equations were programmed in the “C” programming language and solved using a variable step-size Runge-Kutta-Merson algorithm with a maximum time step size of $2 \times 10^{-3}$ sec and an error tolerance of $1 \times 10^{-6}$.

3.5.2 **Lung DAQ VI Development**

This section describes the development of a flexible data acquisition system that can routinely collect research-quality pulmonary function data in a clinical setting. LabVIEW was used to generate virtual instruments that controlled an automated data acquisition system, enabling the simultaneous collection of a variety of data signals. The digitized data was subsequently processed to either yield near real-time displays of clinically significant information or be stored for further post-processing off-line.

The target population for this pulmonary function application was the pulmonary physicians, respiratory therapists, and other clinical personnel directly involved in the routine collection of PFT data. Hence, the graphical user interface (GUI) designed within LabVIEW enabled tests to be conducted by personnel unfamiliar with LabVIEW. As a consequence, research-quality PFT experiments could be routinely conducted in a clinical (hospital) setting, without requiring an in-depth knowledge of ‘G’ programming.
The principal DAQ procedures for this pulmonary application are incorporated into a VI called the **Lung DAQ VI**. This VI controls the complete sequence of events necessary for data collection, from acquiring the digitized samples to processing the data, including near real-time displays and data storage for future applications. Prior to performing the main tasks of data collection, the program queries the user on system readiness via a series of dialog boxes. This process ensures that:

a) a thorough calibration has been performed;

b) the various instruments have been initialized; and

c) that any required baseline measurements have been taken.

If any of these steps are incomplete, the VI automatically invokes the appropriate software to complete the task. Upon completion of a test run, the user is able to view the full data set, determine if the test was successful, and save either the raw data, filtered data (5\textsuperscript{th} order, zero phase shift Butterworth), or both. The primary features of the **Lung DAQ VI** program are listed in Table 3-2.

Figure 3-7 is the front panel of the **Lung DAQ VI** created using LabVIEW. Components of the front panel include both input and output. The boxes at the top and left of the panel allow the investigator to input various static data points related to the test conditions or the subject being tested. These include particulars such as room temperature, humidity, subject height, weight and predetermined TLC, FRC, and RV pulmonary indices. Additional inputs consist of the virtual buttons, which are used to operate the system.
<table>
<thead>
<tr>
<th><strong>Acquisition</strong></th>
<th><strong>Processing</strong></th>
<th><strong>Display/Storage</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung DAQ</td>
<td>Integrate pneumotach data to obtain instantaneous change in lung volume. Allow input of known FRC or calculation of FRC using mouth pressure, box pressure, and Boyle’s law. Zero phase shift (dual-pass) Butterworth filter to lightly smooth the data.</td>
<td>Continuous display of all input channels and lung volume in real-time strip chart monitoring format. Continuous display of the clinically significant Flow-Volume Loop. Data is saved as tab-delimited ASCII spreadsheet file.</td>
</tr>
<tr>
<td>Calibration</td>
<td>Apply the calibration to the data as it is collected on-line so that only calibrated data is directly displayed or saved.</td>
<td>Test parameters, including calibration coefficients, and subject notes are saved after each test run for future reference.</td>
</tr>
</tbody>
</table>

Table 3-2. **Lung DAQ VI** and **Calibration VI** Primary Features.

The START DAQ and STOP DAQ buttons perform their prescribed functions, initializing acquisition of data from the First Input, First Output (FIFO) buffer on the NBMIO-16X DAQ card, and ending it, respectively. These allow for conducting multiple test runs in one session. The CLEAR PLOT button erases all previously acquired data (in that run), without having to reinitialize the DAQ drivers. The FINISH SESSION button terminates the program operation.
Figure 3-7. Front panel of the Lung DAQ VI.

The outputs on the Lung DAQ front panel include the continuous display of the raw data in the strip charts on the right of Figure 3-7, a running strip chart of instantaneous lung volume on the left, and the clinically significant flow-volume loop in the lower left. The data displayed in Figure 3-7 is typical research data collected during a forced vital capacity maneuver. The Lung DAQ VI is executed, as with all VIs, by mouse-clicking the opaque arrow in the upper left-hand corner of the toolbar. Responses to a series of dialog boxes then guide the user through the calibration procedure (discussed later) and establishment of baseline measurements (FRC, RV, and TLC). With a complete calibration and baseline values determined, if required, the system is
initialized and awaits a further input, the START DAQ button. With the click of a mouse on that button, the program begins to acquire, process, and display the data.

*Lung DAQ VI Source Code*

The source code necessary to implement the aforementioned VIs is developed graphically in a block diagram-programming format. Figure 3-8 portrays one of the main frames of the program code, within which the data is collected, analyzed, integrated and displayed. Numerous embedded structures can be observed within this frame, beginning with the outer frame itself. This one looks like a filmstrip; it is a sequencer, the third out of three. The items shown within this frame occur last in a sequence (i.e. the first two frames accounted for the calibration and FRC determination steps in the program.) Everything in this frame also acts within a while loop, which is only terminated with the execution of the FINISH SESSION button.

![Figure 3-8. Block diagram of the Lung DAQ VI.](image-url)
As stated earlier, the START DAQ button begins the acquisition by terminating the while loop on the left of Figure 3-8, and activating the inner filmstrip. Within this sequence, the DAQ board is initialized, and data collection begins. The dual while-loop formation allows for the CLEAR PLOT function described earlier. Within the inner loop, the sequence of events follows the circular acquisition/process/display flow depicted in Figure 3-9.

Figure 3-9. Lung DAQ VI circular acquisition routine.

This repetitive sequence continues until the STOP DAQ button is activated, at which time both while loops terminate and the next filmstrip frame is enabled. This next frame saves the data to the hard drive, if so desired. The data can be saved in either a raw (calibrated) data format or it can be lightly filtered by a dual-pass (zero phase shift)
Butterworth filter. A related text file is also saved with all static information that the operator entered on the front panel, as well as the calibration coefficients.

All of the manipulation and presentation of data is meaningless without proper calibration of the transducers being sampled. Figure 3-10 is the front panel of one of the calibration subroutines included in the current DAQ system. This calibration scheme is volume-referenced, which is typical of plethysmograph boxes. The other subroutine is a straight linear regression analysis based on several readings in the transducer's linear range of operation. The primary features of the Calibration VIs are listed in Table 3-2.

The volume referenced calibration can be performed on the pneumotachometer or the plethysmograph box pressure sensor, if required. This method replaces the use of a
flowmeter for calibrating airflow through the pneumotach. In other words, instead of referencing a given pneumotach output voltage to a known flow, the output is integrated to yield a volume and the result is referenced to a known volume. For calibration purposes, a 3L syringe is available with the plethysmograph (see Figure 3-5). The Volume Calibration VI reads the pneumotach signal, integrates it and compares it with the known volume change that comes from a full stroke of the syringe. The incoming data, and the resulting calibration curve, are displayed on the front panel. The calibration coefficients are saved for use in the Lung DAQ VI discussed previously. The Linear Calibration VI operates in a similar manner, but compares the sampled data directly to known source values and performs a simple linear regression analysis.

With the system in place as described, care must still be taken to ensure an accurate calibration. Drift of the pneumotach must be considered and eliminated. Calibration must be performed over the full range of expected outputs to ensure linear operation of the transducers. And, finally, calibration should be repeated at set intervals to accommodate transducer drift or shift with time.
Figure 3-11. Computational flow diagram for PulmonaryPV software package.
3.5.3 PulmonaryPV VI Development

The PulmonaryPV software package provides a sophisticated graphical user interface to the full airway mechanics model described in this chapter. The PulmonaryPV program, also developed using the LabVIEW programming environment, is a compilation of original virtual instruments (VIs) designed both as the user and data interface to the model operation. Sophisticated graphical displays highlight the user interface while the PulmonaryPV software can accept data from numerous sources, including direct acquisition via a data acquisition (DAQ) card for online operation. The model "C" code described above is integrated into the PulmonaryPV program as an external call from LabVIEW. PulmonaryPV also provides a continuous graphical feedback of the model operation, enhancing user understanding of the model performance as well as aiding any debugging efforts that may be required. Figure 3-11 schematically depicts the execution flow of the PulmonaryPV software package. Several features such as user selection of appropriate species or options for breathing patterns (e.g. tidal, ventilated, PEEP settings, etc.) were added to the program to demonstrate its adaptability.

3.5.4 Parameter Identification

Similar to the approach developed for the cardiovascular studies of Chapter 2, parameter estimation techniques are employed in the current settings to relate analytical results to experimental data. These efforts to coordinate model prediction with clinical research serve as a potent validation tool for the modeling efforts undertaken.

Lung Tissue Model

The equations of motion of the lung viscoelastance model (Eqs. 10) involve five parameters, namely, $b$, $R_{VE}$, $C_{VE}$, TLC and RV. The latter two are identified for each
subject from standard pulmonary function tests (Olansen et al., 1998). Parameter $b$
establishes, in the P-V plane, the slope of the static elastic recoil curve given by Equation 8. This parameter is initially identified such that the static recoil fits, in a least-squares sense, measured $P_{EL} - V_A$ data over the full range of lung volumes (collected with the shuttering technique described previously). After parameters $R_{VE}$ and $C_{VE}$ are identified (as explained below), the value of $b$ is further tuned (manually) such that model simulations of the dynamic $P_{EL} - V_A$ relationship match experimental data.

Employing the virtual instrumentation capabilities that are the focus of this thesis, the parameters $R_{VE}$ and $C_{VE}$ can be identified using a nonlinear Levenberg-Marquardt algorithm. This routine is described in detail in Appendix A. Typical results from this identification scheme are displayed in Figure 3-12.

![Figure 3-12. Front panel of the parameter estimation routine as applied to the analysis of viscoelastic properties of lung tissue.](image)
Parameter Sensitivity. The values of parameters $R_{VE}$ and $C_{VE}$ determine the shape of the $P_{EL}$ - $V_A$ loop in a manner described mathematically as the equation of a rotated ellipse [79]. Figure 3-13 plots the components of the equation while varying parameters $R_{VE}$ and $C_{VE}$ independently. Effective elastance, $1/C(\omega)$, initially a constant value at $1/C_L$, increases considerably as the value of $R_{VE}$ increases (panel A, solid line). It attains a constant value for large values of $R_{VE}$. The dependence upon $C_{VE}$ (panel B) is weak, with a modest initial increase that peaks at 0.23 L/cmH$_2$O. The term quantifying the extent of hysteresis [79], $\omega R(\omega)$ similarly

Figure 3-13. Sensitivity of the components of the lung tissue viscoelastic model to variations in the parameters $R_{VE}$ and $C_{VE}$. 
exhibits a peak at $R_{VE} = 36$ cmH$_2$O·sec/L (panel A, dashed line); it subsequently declines to a constant value. The term decays slowly as $C_{VE}$ increases (panel B).

**Full Pulmonary Dynamics Model**

When data is linked in the *PulmonaryPV* program, the option to directly compare model output using the parameter estimation and sensitivity analysis routines of Appendix A becomes available. This capability greatly enhances the functionality of the model. By estimating the values of the adjustable parameters for a specific subject via direct comparison with the subject's data records, the results of simulated pathophysiologies become directly applicable to that subject.

The screen panel shown in Figure 3-14 provides the user with multiple options to completely control the parameter estimation process, if so desired. Yet, its default configuration is sufficient to enable novice users to typically obtain satisfactory results.

![Figure 3-14. Front panel of *PulmonaryPV* parameter estimation routine depicting typical results of identification analysis. Parameters are defined in Appendix B. $MSE$ is the mean square error of all compared data sets.](image-url)
3.6 RESULTS

3.6.1 Lung Tissue Model

*Dynamic Elastic Recoil.* Figure 3-15 plots measurements of the dynamic elastic recoil of lung tissue $P_{EL}$ (filled and empty dots), against volume measurements for three human subjects performing a full capacity maneuver. The data exhibit measurable hysteresis in the range of volumes above functional residual capacity (FRC). In subject 1, at midtidal volume (4.47 liters), the inspiratory path pressure is approximately 3.5 cmH$_2$O higher than the expiratory path pressure (mitidial volume hysteresis, or MTH). A maximum hysteresis of 6.6 cmH$_2$O is observed at approximately 5.8 liters. Close to FRC the inspiratory and expiratory paths cannot be clearly separated. Volumes below FRC correspond to negative values of $P_{EL}$. There is noticeable variation among the three subjects, both in the extent of the volume excursion (subjects were instructed to perform full capacity maneuvers) and the slope of the hysteretic loops. Model predictions are also plotted in Figure 3-15, and show good agreement with the measurements, in both the general shape of the loop and the extent of hysteresis.
Figure 3-15. Experimental data and model predictions of lung elastic recoil pressure plotted versus alveolar volume.
Frequency Dependence. In Figure 3-16, pleural pressure measurements are plotted against volume data for two maneuvers at frequencies of 0.20 and 0.79 Hz. Although elastic recoil measurements are not collected for these maneuvers (see section on measurement), the effective compliance, $C(w)$, can be computed as the slope of the line connecting the volume extrema of each loop (as drawn in the figure). This line coincides with the line connecting the extrema of the elastic recoil loop (if it were measured), since at the points of zero flow, pleural pressure equals the elastic recoil pressure. As indicated by the difference in slope in the two loops of Figure 3-16, effective compliance decreases as the frequency of breathing increases. The model imitates this trend successfully. Figure 3-17 shows the dependence of effective tissue compliance...
upon frequency. Included in this diagram are experimental data (triangles) for the three subjects breathing at different frequencies. Compliance is measured as the slope of the line connecting the P-V loop extrema. Also plotted is the model generated effective compliance $C(\omega)$ (solid line), which matches experimental data well.

Figure 3-17. Experimental derived data and model predictions of effective compliance of lung tissue as a function of breathing frequency.
3.6.2 Full Pulmonary Dynamics Model

The complete airway mechanics model was modified from Liu, et al [73] and Athanasiades, et al [79] and incorporated into the PulmonaryPV software primarily as a precursor to the interactive modeling endeavor discussed in Chapter 4. Thus, the main results taken from this study are associated with identification of parameters that account for changes made to the model.

Parameter Estimation. A nominal set of parameters was first obtained that provided reasonable flows and volumes for given $P_{pl}$ variations. Model output pressures from a typical control case are depicted in Figure 3-18. Comparison of Figure 3-18 with classical textbook figures [78] establishes that the model output is in general agreement with typical in vivo data.

Figure 3-18. Front panel of PulmonaryPV VI depicting typical model output pressures. Parameters are defined in Appendix B.
With the baseline airway mechanics established in the control case described above, use was made of a Levenberg-Marquardt parameter estimation scheme [96] to achieve agreement with experimental data (see Appendix A). The forced vital capacity (FVC) maneuver was chosen for the identification analysis due to expected excitation of most dynamic modes of the respiratory system. Examinations of the magnitude and time course of the relative sensitivity functions associated with all of the airway mechanics parameters (i.e. resistances and compliances) were evaluated to rank the degree of sensitivity of the set (as described in Appendix A). A typical output of the initial sensitivity analysis for all adjustable parameters is included in Figure 3-19. The data in this figure is quite busy, but is intended to give the reader insight into the determination of sensitive parameters. From Figure 3-19, it is apparent that the parameters $PTM_{max}$ and $PLS$ are the most sensitive in an inversely proportional manner, particularly during large volume excursions. These parameters are included in the descriptions of the transmural pressures across the collapsible airways, $PTM$, and the lungs, $P_{EL}$, respectively. On the other hand, alterations in $RRSA$ and $V_{sur}$, which are component parameters of the small airway resistance, $R_s$, are directly proportional to changes in the lung volume and airway flow.

The current sensitivity analysis is also in agreement with the results of Liu [73] in that the sensitive parameters have a regional importance relative to the different phases of the breathing cycle. For example, $RC$ has a significant effect throughout the FVC maneuver, whereas $R_s$ is more evident at low lung volumes, and $R_{UAW}$ manifests its influence on the peak inspiratory and expiratory flow rates. Based on the sensitivity analysis, the most sensitive parameters are included in the nonlinear least-squares
Figure 3-19. Front panel of *PulmonaryPV* Sensitivity Analysis VI depicting initial sensitivity of all adjustable parameters for subject 1. Parameters are defined in Appendix B.

parameter estimation algorithm. This enhances convergence of the algorithm by constraining parameter variations to those that can bring about significant change in the state variables.

Figure 3-14 depicts the user interface for operation of the parameter estimation algorithm with typical results for subject 1. Results for another subject are evidenced in Figure 3-20. These results show good agreement for specified pressures around the cardiovascular loop. A summary of parameter values determined for each of the experiments conducted is given in Appendix B. These techniques are described in greater detail in Appendix A.
Figure 3-20. Front panel of *PulmonaryPV* parameter estimation VI depicting results for subject 2 in A) temporal format and B) Flow-volume loop format. Parameters are defined in Appendix B.
3.7 DISCUSSION

In this chapter, we presented a series of interrelated mathematical models of the pulmonary system that emulate the functional behavior of the airways and lungs, including lung tissue viscoelasticity. Secondarily, we discuss the incorporation of the model into a flexible, user-friendly software package. The combination provides the user with a powerful tool for rapidly assessing model performance and applying these techniques to individual experiment subjects.

3.7.1 Lung Tissue Model

*Dynamic Elastic Recoil*. Figure 3-15 shows good agreement between the model and experimental measurement for the hysteretic PV relationship between dynamic elastic recoil and lung volume. The average recorded "extent of hysteresis", $wR(w)$, was 3.57 cmH$_2$O for the three subjects at midtidal volume. Sharp et al. [48] conducted similar measurements on 18 healthy, anesthetized humans. We have read an average midtidal hysteresis of 2.3 cmH$_2$O from their measurements. An exact comparison is not possible, however, since measurements were made at different frequencies of breathing and different tidal volumes. The measurements appearing in [48] were collected at 0.0167 Hz, accounting for 5-second long flow interruptions at each volume step. As we have shown, frequency has an effect both on the extent of hysteresis and on the slope of the loop.

*Frequency Dependence*. Linearizing the static compliance term, $C_L$, enabled the analysis to extend further into the frequency dependent nature of the lung tissue. In particular, we derived the impedance of lung tissue as a function of frequency and of the constant parameters in the model. We subsequently related impedance to what we
defined as the effective compliance and resistance of lung tissue (allowing direct comparison between model generated data and measurements of dynamic compliance). Finally, we identified, through mathematical formulas, how these variables affect the shape and size of the elliptical pressure-volume characterization of tissue.

Figures 3-16 and 3-17 show the frequency dependence of the effective compliance $C(\omega)$. Figure 3-17 shows good agreement between measured and model-predicted effective compliance for three subjects. According to model predictions, compliance drops approximately 88% for subject 1 as breathing frequency is altered from a normal value of 0.2 Hz to a value of 3.56 Hz (77% for subject 2 and 79% for subject 3). Experiments on mechanically ventilated anesthetized cat lungs indicate smaller changes in compliance. Hantos et al. [80] report a change of approximately 37% for lung tissue compliance at the same frequency range. It was not possible to collect measurements on the frequency dependence of the effective resistance $R(\omega)$, and therefore we cannot verify the extent of the $P_{EL} - V_A$ hysteresis during maneuvers at different frequencies (see measurement section).

Further investigation is required to identify the behavior of tissue at low lung volumes (close to residual volume). Data indicate that the inspiratory and expiratory paths cross at a certain volume (see Figure 3-15). Elastic recoil pressures below this level are negative. It is not yet established whether this behavior is real or due to measurement error. The flow interruption technique employed here assumes a uniform distribution of pressure in the pleural cavity, which may not be true when the subject actively expires below FRC. Model predictions at low volume do not predict a "crossover" of the inspiratory and expiratory paths.
3.7.2 Automated Lung DAQ Software

Commercial pulmonary function systems are generally sufficient for the assessment of pulmonary mechanics associated with diseases such as emphysema, asthma, or fibrosis. While the accuracy of the outputs from these commercial systems meets industry standards, they generally do not retain the raw data used in performing the analyses, and typically use a proprietary calibration scheme that cannot be easily accessed or verified. In other words, a commercial system is virtually a black box. When conducting detailed research studies, the raw data, calibration approach/results, and details of the data processing are also typically required. A general-purpose data collection system is therefore more desirable from three standpoints:

1) the flexibility of such a system allows it to be adapted to a wide variety of studies with minimal of time or additional hardware;

2) the quality of data collection can be directly controlled through hands-on calibration and filtering processes;

3) the raw data remains available for any post-processing that may be desired.

*Flexibility of the DAQ System.* As stated previously, one of the prime motivating factors in the development of the current system was flexibility. This flexibility manifests itself in two different ways. The first is the adaptability of the source code itself. LabVIEW is essentially a modular programming environment wherein VIs can be created in a hierarchical and modular fashion. Complex programs are, as a result, broken down into simpler tasks, each of which is coded into a VI. Icons representing these subroutines are embedded into the block diagram of the higher level VIs, and so on, until
the top-level code is completed. This hierarchical structure permits easy modification of program elements, as well as the ability to reuse component VIs to develop completely unrelated programs.

The adaptability of the system described in this paper has already been demonstrated through other procedures at John Sealy Hospital. For example, it would be difficult at best to diagnose partial diaphragmatic paralysis using a special-purpose commercial system. Using the current DAQ system as a baseline, however, a quick study of suspected diaphragmatic paralysis was initiated, developed, and performed in less than six hours. The VIs described in this chapter served as the basis for the new program. In this partial paralysis case, a second esophageal pressure source had to be acquired. The data processing was modified to depict variations between the two esophageal pressures, recording the maximum and minimum differences. The existing VIs were adequate for obtaining and displaying the required data.

The other way in which this general-purpose DAQ system exhibits flexibility is in the portability of the system as a whole. To facilitate the routine collection of data from diseased subjects, a portable data acquisition system may be required. Because the DAQ components of the system (DAQ board, LabVIEW VIs) are contained in a PC/Mac, it is relatively simple to relocate the system to wherever it is needed. National Instruments also makes available high-quality PCMCIA DAQ cards that allow the use of a laptop, making the system truly portable. In particular, this type of system would enhance the data collection from subjects requiring mechanically assisted ventilation.

Adaptability of Acquired Data. A primary feature of the system presented here is the ability to utilize the collected raw data for numerous applications after the testing is
complete. The data can be stored in binary or ASCII files and even tab-delimited if so desired. This makes it accessible to spreadsheet or data analysis programs. Generation of a robust data acquisition scheme that includes minimization of quantization and aliasing effects and application of light pre-filtering to primary data, greatly enhances any attempts to post-process the data.

With the adaptability of the data collected comes the ability to find secondary uses for that data. The number of secondary uses is virtually unlimited and could include items such as an automated diagnosis sheet, or it could be used in the development/ manufacture of new clinical products. Alternatively, the pulmonary function data collected may be used in more basic research endeavors such as the mathematical modeling discussed extensively in this chapter.
CHAPTER 4
CARDIOPULMONARY INTERACTION

A current thrust in the modeling of biological systems is the development of large-scale integrative models that can help unravel complex interactions between different organ systems. Based on decades of research and analysis of isolated subsystems, computer modeling at the organ level is poised to take its place in quantitative computer-aided medical diagnosis. In Chapters 2 and 3, subsystem models of the uncontrolled circulation and pulmonary mechanics were studied. The current chapter pulls these subsystem models into a larger integrated, closed-chest cardiopulmonary model for two specific cases: the dog, and the normal human subject. In each case, we first mimic the normal cardiopulmonary physiology and then proceed to study specific organ system interactions (i.e. cardiopulmonary interactions).

4.1 OBJECTIVES

The purpose of this chapter is to expand on the cardiovascular and pulmonary modeling efforts (on different species) depicted in the previous two chapters, and integrate them into a single combined model of cardiopulmonary dynamics that can be applied to each species. That is, we develop a model that, when appropriately scaled, can
be applied to the closed-chest dog and human cardiopulmonary systems, using essentially
the same basic model structures discussed in Chapters 2 and 3. This integrated model
provides us with the opportunity to study the effects of interaction between the
cardiovascular and pulmonary systems in each case. In particular, we examine the
alterations in hemodynamics and cardiac mechanics caused by variations in breathing
patterns. Tidal breathing, the vital capacity maneuver, and intubated subjects supported
on a ventilator are the specific cases considered herein.

4.2 BACKGROUND

Several studies of the interaction of the human cardiovascular and pulmonary
systems have previously been reported in the literature. Typically, however, they focus
on a particular area of interest, rather than overall cardiopulmonary function. Examples of
these studies date back to the 1950's when Coleridge, et al [81] and Opdyke, et al [82]
studied respiratory effects on ventricular preload (i.e. left and right atrial pressures).
Since then, substantial effort has been applied to characterizing systemic afterloads under
the influence of respiration. This includes studies of the effects of intrathoracic pressure
on left ventricular function [83, 84, 85, 86] and the effects of positive end-expiratory
pressure (PEEP) on cardiovascular function in ventilated subjects [87, 88, 89, 90], as well
as work by Beyar, et al [11], who have studied interaction specifically in the performance
of cardiopulmonary resuscitation (CPR). The integrated model presented herein is
sufficiently comprehensive to enable us to study a variety of interactive phenomena,
including the ones delineated above.
4.3 **Human Cardiovascular Model Development**

Comparative physiology endeavors to associate various physiologic functions across species. Indeed, when we consider conducting animal experiments, the underlying intent is to transform any insight obtained so that it may enhance our understanding of human physiology. We have applied this concept in the current study by appropriately scaling the cardiovascular model developed in Chapter 2. Specifically, it is necessary to increase the volumes and flows around the loop to accommodate the larger fluid content of a normal, 70-kg man. Pressure variations about the mean are roughly the same, heart rate is divided by a factor of approximately 2. Gross adjustment of the full parameter set is necessary to bring the values of the parameter set into the appropriate range for humans. Parameters used to describe the nominal human subject are listed in Table 4-1 and Appendix B.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Typical Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_{SAD}$</td>
<td>Resistance: systemic arterioles</td>
<td>2.105</td>
</tr>
<tr>
<td>$R_{SC}$</td>
<td>Resistance: systemic capillaries</td>
<td>1.5477</td>
</tr>
<tr>
<td>$R_{PAD}$</td>
<td>Resistance: distal pulmonary artery</td>
<td>0.0147</td>
</tr>
<tr>
<td>$R_{TAP}$</td>
<td>Viscoelastic element: proximal aorta</td>
<td>0.0805</td>
</tr>
<tr>
<td>$R_{TPA}$</td>
<td>Viscoelastic element: pulmonary artery</td>
<td>0.0276</td>
</tr>
<tr>
<td>$C_{AOP}$</td>
<td>Compliance: proximal aorta</td>
<td>0.6493</td>
</tr>
<tr>
<td>$C_{AOD}$</td>
<td>Compliance: distal aorta</td>
<td>0.0932</td>
</tr>
<tr>
<td>$C_{SA}$</td>
<td>Compliance: large systemic arteries</td>
<td>0.0358</td>
</tr>
<tr>
<td>$C_{SAD}$</td>
<td>Compliance: systemic arterioles</td>
<td>0.0276</td>
</tr>
<tr>
<td>$C_{PAP}$</td>
<td>Compliance: proximal pulmonary artery</td>
<td>0.3943</td>
</tr>
<tr>
<td>$C_{PAD}$</td>
<td>Compliance: distal pulmonary artery</td>
<td>0.0202</td>
</tr>
<tr>
<td>$C_{PA}$</td>
<td>Compliance: pulmonary arterioles</td>
<td>0.1571</td>
</tr>
<tr>
<td>$L_{AOP}$</td>
<td>Inertance: proximal aorta</td>
<td>0.0056</td>
</tr>
<tr>
<td>$L_{AOD}$</td>
<td>Inertance: distal aorta</td>
<td>0.0282</td>
</tr>
<tr>
<td>$L_{PA}$</td>
<td>Inertance: pulmonary artery</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

Table 4-1. Typical *CardioPulm* control parameter values for both canine and human studies.
4.3.1 Typical Model Output for Human

Applying the parameter adjustments mentioned above yielded acceptable fits to a variety of indices, such as cardiac output (CO), left and right ventricular ejection fractions, mean blood pressures and blood volume distributions around the circulatory loop, that are documented as typical in the literature [32, 31]. Table 4-2 documents the mean hemodynamic pressure and volumes around the circulatory loop for both dog and human simulations. Using these new parameters the model computes hemodynamic waveforms in good agreement with previously published human data [32, 31]. Figure 4-1 depicts the typical model output as compared with standard textbook waveforms from [32]. Comparison of these figures establishes that the model output is in general agreement with typical human data, verifying the models' adaptation to mimic human cardiac function.

<table>
<thead>
<tr>
<th>Vascular Segment</th>
<th>Description</th>
<th>Canine Pressure</th>
<th>Canine Volume</th>
<th>Human Pressure</th>
<th>Human Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>AO_p</td>
<td>Aorta (prox)</td>
<td>111.3</td>
<td>20.3</td>
<td>104.5</td>
<td>49.1</td>
</tr>
<tr>
<td>AO_d</td>
<td>Aorta (distal)</td>
<td>111.0</td>
<td>46.2</td>
<td>103.6</td>
<td>135.2</td>
</tr>
<tr>
<td>SA_p</td>
<td>Small Systemic Arteries</td>
<td>110.2</td>
<td>75.2</td>
<td>95.1</td>
<td>224.5</td>
</tr>
<tr>
<td>SA_d</td>
<td>Systemic Arterioles</td>
<td>56.8</td>
<td>58.3</td>
<td>45.4</td>
<td>175.0</td>
</tr>
<tr>
<td>SC</td>
<td>Systemic Capillaries</td>
<td>16.2</td>
<td>89.0</td>
<td>14.6</td>
<td>264.4</td>
</tr>
<tr>
<td>SV</td>
<td>Systemic Veins</td>
<td>6.1</td>
<td>1038.8</td>
<td>5.8</td>
<td>3260.5</td>
</tr>
<tr>
<td>VC</td>
<td>Vena Cava</td>
<td>6.1</td>
<td>93.6</td>
<td>6.1</td>
<td>310.3</td>
</tr>
<tr>
<td>RA</td>
<td>Right Atrium</td>
<td>3.9</td>
<td>15.7</td>
<td>4.9</td>
<td>70.6</td>
</tr>
<tr>
<td>PA_p</td>
<td>Pulmonary Artery (prox)</td>
<td>14.6</td>
<td>4.8</td>
<td>18.9</td>
<td>18.9</td>
</tr>
<tr>
<td>PA_d</td>
<td>Pulmonary Artery (distal)</td>
<td>13.6</td>
<td>24.9</td>
<td>17.7</td>
<td>75.0</td>
</tr>
<tr>
<td>PA</td>
<td>Pulmonary Arterioles</td>
<td>12.6</td>
<td>24.6</td>
<td>12.2</td>
<td>74.7</td>
</tr>
<tr>
<td>PC</td>
<td>Pulmonary Capillaries</td>
<td>10.0</td>
<td>63.0</td>
<td>11.6</td>
<td>203.3</td>
</tr>
<tr>
<td>PV</td>
<td>Pulmonary Veins</td>
<td>8.3</td>
<td>75.2</td>
<td>11.3</td>
<td>230.4</td>
</tr>
<tr>
<td>LA</td>
<td>Left Atrium</td>
<td>6.0</td>
<td>17.5</td>
<td>7.0</td>
<td>88.0</td>
</tr>
</tbody>
</table>

Table 4-2. Model output under control conditions: Mean pressures and volumes at various compartments throughout the closed-loop circulation. The units for pressure and volume are mmHg and ml, respectively.
4.3.2 Deviation from Dog Model

Comparing the pressure data in Figure 4-1 with the canine data depicted in Chapter 2, it appears that there is little difference between the species. Indeed, for the most part, pressure profiles are strikingly consistent across the mammalian species [91]. Mean flow velocities are generally conserved as well among species, with only a slight dependence on body weight (see Li, p. 104, [91]). However, the blood volumes and flows associated with those same species vary substantially. For example, a typical 70-kg
man will have a heart rate of 60-75 beats/min and a respiratory rate of 12-15 breaths/min, with a cardiac output (CO) of approximately 5 L/min. This means the man must average a stroke volume (SV) of 66-83 ml per heartbeat. A 25 kg dog, on the other hand, could have a resting heartbeat of 120 BPM, a respiratory rate of 24 breaths/min, and a CO of 2 L/min, resulting in a average SV requirement of 16 ml per heartbeat. It is these differences that must be accounted for in the extrapolation of the model from one species to another.

4.4 INTEGRATION OF CARDIOVASCULAR AND PULMONARY MODELS

The Model Development sections of Chapters 2 and 3 delineate the details of the cardiovascular and pulmonary models being used in the current study. In this section we address modifications to those models that are required to properly integrate them.

An important change necessary to the process of combining these models is to anatomically close the chest of the animal (i.e. to consider the effects of intrathoracic, or pleural, pressure variations). Specifically, the pressures in the cardiac chambers, the aorta, vena cava, and pulmonary arteries and veins are all referenced to atmosphere in the open chest configuration, whereas the non-thoracic component pressures are referenced to a relatively constant tissue pressure. Thus, in Chapter 2, those pressures referenced to atmosphere are all considered absolute pressures since the absolute and transmural pressures are equivalent in the open chest case (i.e. \( P_{PL} = P_{Ref} = 0.0 \)). By closing the chest, however, as in the current assessment, the pleural pressure, \( P_{PL} \), is established and the transmural pressures in the thoracic cavity are measured relative to \( P_{PL} \). The pulmonary arterioles and capillaries are more influenced by alveolar pressure than pleural pressure
such that $P_{ALV}$ is added to the transmural $P_{PA}$ and $P_{PC}$ to obtain their absolute pressures.

The other prominent feature necessary to integrate the cardiovascular and pulmonary models is the nonlinear effect the variation in lung volume has on the resistance of blood flow through the pulmonary capillaries. As the lungs expand, the alveolar blood vessels are elongated and thinned, resulting in an increase in pulmonary vascular resistance, which we denote by the overall capillary resistance, $R_{PC}$. The relationship used herein to emulate this physiological phenomenon is:

$$R_{PC}(V_A) = R_{PC,0} \left( \frac{V_A}{V_{A,\max}} \right)^2$$  \hspace{1cm} (33)

where $R_{PC,0}$ is a constant characterizing the overall magnitude of $R_{PC}$ and $V_{A,\max}$ is the value of $V_A$ when $R_{PC}$ is dominated by $R_{PC,0}$.

4.5 Computational Aspects

The model equations were initiated at the time of end-expiration with no flow at the mouth and at end-diastole with the atrioventricular valves open and the semilunar valves closed. Measured physiological data of the pleural pressure, $P_{PL}$, (simulated data for use in canine studies) or a generated external pressure waveform data, $P_{EXT}$, are the input waveform used to run the appropriate model ($P_{PL}$ for the normal model, and $P_{EXT}$ for the ventilator version). Initial conditions employed for the 36 state variables are defined in this mode. Nominal parameter values were selected to produce physiologically realistic values, such as cardiac output (CO), and hemodynamic waveforms for a typical 25 kg dog. Pulmonary shunt flow was set at 2% of the mean pulmonary blood flow [30], while mean coronary and cerebral flows were set at 5% and 15% of cardiac output,
respectively [31, 32]. The model equations were programmed in the “C” programming language and solved using a variable step-size Runge-Kutta-Merson algorithm with a maximum time step size of $2 \times 10^{-3}$ sec and an error tolerance of $1 \times 10^{-6}$.

4.5.1 CardioPulm VI Development

The *CardioPulm* software package provides a sophisticated graphical user interface to the interactive cardiopulmonary model described in this chapter. The *CardioPV* software described in Chapter 2 and the *PulmonaryPV* software of Chapter 3 served as the basis for the development of *CardioPulm*. The *CardioPulm* program, also developed using the LabVIEW programming environment, is a compilation of original virtual instruments (VIs) designed both as the user and data interface to the model operation. Sophisticated graphical displays highlight the user interface while the *CardioPulm* software can accept data from numerous sources, including direct acquisition via a data acquisition (DAQ) card for online operation. The model "C" code described above is integrated into the *CardioPulm* program as an external call from LabVIEW. *CardioPulm* also provides a continuous graphical feedback of the model operation, enhancing user understanding of the model performance as well as aiding any debugging efforts that may be required. Figure 4-2 schematically depicts the execution flow of the *CardioPulm* software package.

In addition to combining the models included in the *CardioPV* and *PulmonaryPV* programs, several software modifications were necessary to create the *CardioPulm* program.
(1) Since combined cardiopulmonary data could not be directly obtained from human subjects in this study, the parameter estimation portions of the software were not needed in the interactive model.

(2) The study of specific cardiovascular pathophysiologies was removed from the combined model as this study required near-term steady-state hemodynamics, which are not available with the incorporation of pulmonary dynamics.

(3) Additional features such as user selection of appropriate species to options for breathing patterns (e.g. tidal, ventilated, PEEP settings, etc.) were added.
Figure 4-2. Computational flow diagram for \textit{CardioPulm} software package.
4.6 **INTEGRATED MODEL RESULTS**

To demonstrate the utility of an interactive cardiopulmonary model, which includes the descriptions of ventricular interaction, pericardial influence, airway mechanics, and intrathoracic pressure modulation, several simulation studies were undertaken. These include the hemodynamic consequences of intrathoracic pressure modulation via various breathing maneuvers or intubation settings. For all simulations, only the model parameters pertinent to a particular protocol were adjusted, whereas the remaining parameters were fixed at values shown in Appendix B.

4.7 **CANINE CARDIOPULMONARY INTERACTION**

4.7.1 **Baseline Hemodynamics**

The model equations and associated parameter values given in Appendix B describe the nominal behavior of the canine cardiopulmonary system. That is, the simulation output resembles the waveforms typically observed in a normal 25-kg dog. This simulation is referred to as the "control case", in which the model includes an active septum, an intact pericardium and the parameter set as established in Chapter 2 for dog 1. The difference in this case is that the dog's chest is closed and pleural pressure variations exhibit appreciable effects on the circulatory system performance (Figure 4-3).

Figure 4-3 demonstrates that the model is capable of producing realistic waveforms of many hemodynamic variables of interest in the airways and circulation. Similar to results depicted in Chapter 2, simulation results for the left heart and systemic afterload include: pressures in the left atrium (LA), left ventricle (LV), proximal and distal sections of the aorta (AO_p and AO_d), small arteries (SA), arterioles (SA_d), and...
capillaries (SC), as well as the less pulsatile pressures in the veins (SV, systemic veins; and VC, vena cava) (see Figure 4-3a). For the pulmonic circulation (Figure 4-3b), the model generates pressure waveforms in the right atrium (RA) and ventricle (RV), large and small pulmonary arteries (PAp and PAd), pulmonary arterioles (PA), pulmonary capillaries (PV), and the pulmonary veins (PV) adjoining the left atrium. Additionally, Figure 4-3c includes airway pressure waveforms such as pressure in the pleural space (PL), the lumped alveolar space (ALV), the transmural pressure across lumped collapsible airway segment (TM), the driving pressure of the respiratory muscles (MUS), the elastic recoil of the lung (EL), and the dead space in the upper airway (DEAD). The model also generates the temporal profiles of volumes associated with each compartment (Figure 4-4) in addition to the pressure profiles described above.

4.7.2 Tidal Breathing

Figures 4-3 and 4-4 show the results of cardiopulmonary interaction in tidal breathing. Respiratory effects on the systemic circulation are apparent by noting the oscillatory nature of the pressure peaks in the left heart and aorta. These are absolute pressures, thus directly altered by pleural pressure variations. However, transmural pressures show similar alterations due to variations in the blood volume of the individual segments. As expected, the impact on the pulmonary circulation is more significant as seen in Figure 4-3B. While the actual values of pressure changes in the pulmonary circulation are similar to the systemic, the percentage change is much more substantial.
Figure 4-3. *CardioPulm* model output pressures for integrated closed-chest canine model:
A) Systemic vasculature;
B) Pulmonic vasculature;
C) Pulmonary system. See text for nomenclature description.
Figure 4-4. *CardioPulm* model output volumes for integrated closed-chest canine model:
A) Systemic vasculature;
B) Pulmonic vasculature;
C) Pulmonary system. See text for nomenclature description.
Figure 4-4 shows the temporal variation of volume distribution through the pulmonary vasculature along with lung volume levels during dynamic inflation and deflation. It is apparent from these figures that the variations in $P_{PL}$ and $V_{ALV}$ associated with respiration do affect the preload of the heart pumps, most notably the right ventricle, increasing the RV stroke volume (SV) during inspiration. The concomitant increases in RV diastolic filling pressures combine with decreasing absolute pressures in the LV (Figure 4-3A) to minimize the rightward shift of the interventricular septum during inspiration. Decreased venous return from the pulmonary circuit also tends to reduce LV filling. Thus, even though the LV free wall does expand further due to decreasing $P_{PL}$, the reduced septal volume and decreased venous return offset this volume gain, effectively reducing the LV preload during inspiration. Alterations in LV afterload due to $P_{PL}$ changes are not as significant and are essentially masked by the preload effects, as evidenced by the reduction in the systolic pressures of the LV and aorta (Figure 4-3A). The additional right heart (RH) blood volume generated during inspiration is moved through the pulmonary circuit, leading to an increased LVSV several heartbeats later, during early expiration (Figure 4-4). It is apparent from this discourse that cardiac function during tidal breathing is primarily mediated by changes in ventricular preloads, most notably in the RV.

The effect of respiration on vascular volumes is also demonstrated as the blood volume of the larger vessels increases during inspiration while the arteriole and capillary volumes decrease. During normal tidal breathing, changes in alveolar pressure, $P_{ALV}$, are relatively minimal. Therefore, the effects of the nonlinear resistance in the pulmonary capillaries are not strongly evidenced during tidal breathing.
Typical steady-state results are included in Table 4-3. Mean transmural pressures and volumes around the circulatory loop do not vary significantly from those presented in Chapter 2, nor does the cardiac output, the pressure gradient along the circulatory loop, or the overall blood volume distribution. However, respiratory variations are clearly seen in both the systemic and pulmonary pressure waveforms (Figures 4-3A & B). Indices such as cardiac output (CO) can be calculated on a beat-by-beat basis, but are only meaningful if averaged over the period of tidal breathing. As mentioned previously, these results are typical for closed-chest dog preparations.

<table>
<thead>
<tr>
<th>Index</th>
<th>Open Chest</th>
<th>Tidal</th>
<th>Ventilated</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>130.4</td>
<td>130.4</td>
<td>130.4</td>
</tr>
<tr>
<td>CO</td>
<td>1.72</td>
<td>1.64</td>
<td>1.60</td>
</tr>
<tr>
<td>SV</td>
<td>13.2</td>
<td>12.6</td>
<td>12.25</td>
</tr>
<tr>
<td>Mean P_{AO}</td>
<td>111.3</td>
<td>105.9</td>
<td>103.7</td>
</tr>
<tr>
<td>Mean P_{PA}</td>
<td>14.6</td>
<td>17.5</td>
<td>17.4</td>
</tr>
<tr>
<td>P_{LA}</td>
<td>6.0</td>
<td>5.8</td>
<td>6.0</td>
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<tr>
<td>P_{RA}</td>
<td>3.9</td>
<td>4.1</td>
<td>4.2</td>
</tr>
<tr>
<td>LVEDP</td>
<td>126.0</td>
<td>117.9</td>
<td>117.5</td>
</tr>
<tr>
<td>RVESP</td>
<td>26.1</td>
<td>25.3</td>
<td>28.2</td>
</tr>
<tr>
<td>LVEDV</td>
<td>35.3</td>
<td>33.3</td>
<td>33.7</td>
</tr>
<tr>
<td>RVEDV</td>
<td>22.4</td>
<td>26.4</td>
<td>26.3</td>
</tr>
</tbody>
</table>

Table 4-3. Comparative canine cardiac indices for various pulmonary configurations.

### 4.7.3 Intubated Animal

Typical animal experiments require the animal to be anesthetized and ventilated. Our experiments were no exception. However, since the data described in Chapter 2 was from open-chest experiments, the effect of intubation was assumed negligible. Extrapolating the modeling effort to study the effects of ventilation therefore assumed the
parameter estimation and associated results from Chapters 2 and 3 were still applicable, with the additional factor of closing the chest wall. The airway mechanics model was slightly modified to be driven by an external pressure waveform, with the respiratory muscles assumed inactive (i.e. $P_{MUS} = 0.0$) thereby yielding a pleural pressure equal to the chest wall pressure (i.e. $P_{PL} = P_{CW}$).

Figure 4-5 depicts the hemodynamic and airway pressures under simulated intubation with no positive end-expiratory pressure (PEEP). In contrast to normal tidal breathing, during mechanical support ventilation both systemic and pulmonic pressures increase during inspiration and decrease again during expiration. Comparing Figures 4-3 and 4-5, there is also a noticeable increase in systolic pressure variance when mechanical ventilation is used due to transients caused by the rapid changes in respiratory state (i.e. inspiration vs. expiration) relative to the transitory behavior of tidal breathing. Additionally, $P_{ALV}$ increases significantly during forced inspiration, which has a pronounced effect on the pulmonary capillary resistance, $R_{PC}$, with a concomitant reduction in $V_{PC}$ of greater than 10%.

4.7.4 Respiratory Effects on Canine Cardiovascular Function

The effects of varying the pulmonary configuration on cardiac function are indicated in Table 4-3. From this data, it is evident that closing the chest alters the steady-state operations of the circulatory system. Under normal tidal breathing conditions, cardiac output (CO) is reduced by nearly 5% from the open chest condition due to the reduction in stroke volume. The negative pleural pressure induced by closing the chest yields a 17.9% increase in the mean RVEDV with a concomitant 5.7% decrease in mean LVEDV. Nearly half of the volume shift can be attributed to reduced septal deflection
during diastolic filling; a claim supported by the significantly reduced LVESP as compared to the RVESP. Additionally, LV preload, as indicated by the mean $P_{LA}$, is reduced compared with the increased RV preload, $P_{RA}$.

When mechanical ventilation is introduced, pulmonary impedance is increased cyclically with lung inflation, as evidenced by the increased RVESP. However, due to a less-negative pleural pressure, the pulmonary afterload increase is mitigated and the systemic afterload decreases as compared to the tidal results. While the EDV of either ventricle does not change significantly from the tidal case, end-systolic volumes (ESV) increase, leading to a reduction in stroke volume and a further 2.5% decrease in CO from the tidal breathing case. Further increases in ventilator pressures required to inflate the lungs would be expected to exacerbate the effects demonstrated here. The advent of increasing PEEP levels will be addressed later in the human cardiopulmonary study.
Figure 4-5. *CardioPulm* model output volumes for integrated canine model with mechanical ventilation:
A) Systemic vasculature;
B) Pulmonic vasculature;
C) Pulmonary system. See text for nomenclature description.
4.8 **Human Cardiopulmonary Interaction**

One of the advantages of modeling is demonstrated in extensions of the model to simulate scenarios for which data is not available. In this case, we do not have simultaneous cardiovascular and pulmonary data from human subjects. Using the cardiovascular parameters defined previously as appropriate to make the model applicable to human study, along with the human parameters identified for the pulmonary subjects in Chapter 3, the *CardioPulm* software can be adapted to study human cardiopulmonary interaction. This section documents the results of such a study using similar simulations as those undertaken in the canine study, with additional studies included to assess the effects of forced vital capacity maneuvers as well as variations in the positive end-expiratory pressure (PEEP) levels of intubated subjects.

4.8.1 **Baseline Hemodynamics**

The model equations and associated parameter values given in Table 4-1 and Appendix B describe the nominal behavior of the human cardiopulmonary system. Simulations conducted under these conditions are referred to as the "control case", in which the model includes an active septum, an intact pericardium, and is susceptible to intrathoracic pressure variations. As in the canine study earlier, Figures 4-6 and 4-7 demonstrate that the model is capable of producing realistic waveforms of many hemodynamic variables of interest in the airways and circulation. The same model outputs are available in this study as those previously described.
Figure 4-6. *CardioPulm* model output pressures for integrated human model during tidal breath:
A) Systemic vasculature;
B) Pulmonic vasculature;
C) Pulmonary system. See text for nomenclature description.
Figure 4-7. *CardioPulm* model output volumes for integrated human model during tidal breath:
A) Systemic vasculature;
B) Pulmonic vasculature;
C) Pulmonary system. See text for nomenclature description.
4.8.2 Tidal Breathing

Figures 4-6 and 4-7 highlight the results of cardiopulmonary interaction in tidal breathing for human subjects. The effects on the systemic and pulmonic circulations are again apparent by noting the oscillatory nature of the peak systolic and diastolic pressures, which are similar to the results obtained for the dog. Note that during inspiration, there is an increase in RVESP secondary to rising RVEDV, whereas decreasing LVEDV yields lower end-systolic pressures for the LV. This trend is reversed during expiration.

As discussed earlier in the canine study, pleural pressure variations affect the heart pump function predominantly due to changes RH volume during tidal respiration. These effects are again demonstrated in Figures 4-6 and 4-7. While the actual volumes and flows vary significantly from the dog to the human, the volumetric waveforms displayed in Figure 4-7 show that the temporal variation of volume distribution through the vasculature is quite similar between the species. Again the effect of inhalation on blood volumes of the larger, more compliant vessels (e.g. the vena cava) is evident from the figure. Typical steady-state results a variety of cardiac indices are included in Table 4-4. These tidal breathing results serve as the baseline for for the human cardiopulmonary study; the influence of altered respiratory maneuvers will be discussed in comparison with these results.
<table>
<thead>
<tr>
<th>Index</th>
<th>Tidal Breath</th>
<th>FVC Maneuver</th>
<th>Mechanical Ventilation (PEEP Level)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0 (cmH2O)</td>
</tr>
<tr>
<td>HR</td>
<td>70</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>CO</td>
<td>5.17</td>
<td>4.27</td>
<td>4.74</td>
</tr>
<tr>
<td>SV</td>
<td>73.9</td>
<td>61.2</td>
<td>67.8</td>
</tr>
<tr>
<td>Mean $P_{AO}$</td>
<td>104.5</td>
<td>55.5</td>
<td>95.8</td>
</tr>
<tr>
<td>Mean $P_{PA}$</td>
<td>18.9</td>
<td>10.5</td>
<td>16.9</td>
</tr>
<tr>
<td>$P_{LA}$</td>
<td>7.0</td>
<td>44.9</td>
<td>9.0</td>
</tr>
<tr>
<td>$P_{RA}$</td>
<td>4.9</td>
<td>44.5</td>
<td>7.3</td>
</tr>
<tr>
<td>LVESP</td>
<td>133.6</td>
<td>138.2</td>
<td>127.8</td>
</tr>
<tr>
<td>RVESP</td>
<td>40.4</td>
<td>73.9</td>
<td>40.0</td>
</tr>
<tr>
<td>LVEDV</td>
<td>130.9</td>
<td>108.9</td>
<td>122.9</td>
</tr>
<tr>
<td>RVEDV</td>
<td>127.9</td>
<td>97.6</td>
<td>116.4</td>
</tr>
</tbody>
</table>

Table 4-4. *CardioPulm* results of human cardiopulmonary function studies with various breathing maneuvers.

4.8.3 Vital Capacity Maneuver

As detailed in Chapter 3, the forced vital capacity (FVC) maneuver is an integral part of clinical pulmonary function testing. In simulating this cardiopulmonary interaction, experimental pleural pressure data collected from a volunteer subject, according to the protocol outlined in Chapter 3, is used to drive the model. The airway mechanics model has been previously fit to the data per Chapter 3, verifying the use of realistic pulmonary dynamics to assess the impact of an FVC maneuver on cardiovascular hemodynamics. The FVC maneuver depicted herein follows a protocol of complete expiration followed by a deep, rapid inspiration to full lung capacity (TLC), and then a forced expiration all the way back to the residual volume (RV) level.

Mean values for various cardiac indices are included in Table 4-4 for reference purposes. These reveal the expected drops in CO and SV as the flow leaving the ventricles is severely diminished during a prolonged forced exhalation. However, we are
primarily interested in the transient dynamics associated with FVC maneuvers, rather than mean or steady-state results. This transient behavior is best depicted graphically as in Figure 4-8. Note that the pressures included in Figure 4-8 are transmural pressures, which enhances the reader's visualization of the physiological phenomena, whereas the pressures in Table 4-4 are absolute pressures since it is the absolute pressures which dictate flows throughout the circulation.

Significant insight into the effects of an FVC maneuver on cardiac function can be garnered upon close examination of all panels in Figure 4-8. Several of these effects are discussed below.

1) The most striking observation is the reduction in blood volume in both the RV and LV during the forced expiration when $P_{PL}$ is substantially greater than zero. This positive pleural pressure has the effect of compressing the large, compliant vessels, as well as the heart itself, significantly increasing the ventricular afterloads while severely restricting inlet flow into both atria. Considering the mean absolute atrial pressures in Table 4-4, which indicate a considerable resistance to inflow, corroborates this assessment.

2) The reduction in peak systolic pressures in both the systemic and pulmonary circulations is associated with the ventricular volumes discussed above via the compliant nature of the components. In Chapter 2, it was shown that increased afterload, achieved via an increase in arterial impedance, typically causes an increase in peak systolic pressure. However, even though the input impedance of both circulations increases drastically during forced expiration, the
reduction in ventricular volume is a more dominant factor, thereby reducing the systolic pressures generated by each ventricle.

3) Note that it only takes 6 -7 heartbeats during a forced expiration to essentially cut off blood flow from the heart, even though the heart continues to pump. This result is in accordance with previous experimental studies [32] that demonstrated severe cardiac output reductions during forced respiratory maneuvers.

4) Deep inspiration has a rapid filling effect on both sides of the heart, though to a much greater extent on the right. This is evidenced by the significant increase in the end-diastolic volumes of both ventricles. This oscillatory behavior demonstrates the Starling mechanism, whereby the system overcompensates in an attempt to restore proper function around a nominal operating point.

5) There is a more significant effect of the nonlinear resistance, $R_{PC}$, in this scenario due to the substantial increase in lung volume upon inspiration. The larger lung volume causes $R_{PC}$ to increase, which, in conjunction with the increased RVSV results in the transient pooling of some blood within the pulmonary arteries and capillaries. Within 1 - 2 additional heartbeats, this excess blood has been redistributed through the circulation.
Figure 4-8. **CardioPulm** model output pressures and volumes for the integrated human model during a forced vital capacity (FVC) maneuver. Pleural pressure inputs from Subject 1 discussed in Chapter 3. A) Systemic vasculature pressures; B) Pulmonic vasculature pressures; C) Pulmonary system pressures; D) Systemic vasculature volumes; E) Pulmonic vasculature volumes; F) Pulmonary system volumes. See text for nomenclature description.
6) Comparing the systemic pressure variations between the first and second forced expiration, it is apparent that the more proximal components (i.e. the $P_{LV}$, $P_{AOP}$ and $P_{AOD}$) achieve significantly reduced peak systolic pressures during the latter expiration. This occurs even though the LVEDV is the same or greater during the initial phase of the second expiration than it was during the first. In contrast, the more distal components actually attain similar or higher peak systolic pressures. Though this is a complex scenario, the results can be attributed to the near stoppage of flow in the systemic venous system (particularly, the large systemic veins and the vena cava) as well as the variation in compliances and direct $P_{PL}$ effects between the proximal and distal components. Essentially, the sustained increased pressures in the systemic venous system cause the buildup of pressures all the way into the systemic arteries. The buildup encompasses several relatively stiff vasculature components. However, the aorta is quite compliant (estimated to be 10 times greater than peripheral systemic compliances [94, 95], a feature that is accounted for in the current model) and able to accommodate larger volumetric influx without significant pressure buildup. Additionally, the aortic volumes, $V_{AOP}$ and $V_{AOD}$, are significantly reduced during the second expiration. Thus, less pressure is necessary within the LV to open the aortic valve resulting in lower peak systolic pressures for the LV and aorta only.

4.8.4 The Intubated Subject

Using the control case and the FVC maneuver to indicate the quantitative and comprehensive capabilities of the integrated model, we move further to an area of study
that garners substantial interest in the medical community today. We are referring to the critical care of patients, patients in an intensive care unit (ICU), breathing only with the aid of a mechanical respirator. We present merely the backbone for conducting such studies and a single foray into the study of PEEP; extrapolations regarding ventilator input variations, impacts on gas exchange and other noble pursuits are left as future research endeavors. Applying the same modeling extensions developed in the canine study to the physiological assessment of ventilated human subjects creates a powerful tool that may be employed in the evaluation of ventilation methodologies and their impact on cardiac function.

Figure 4-9 depicts the hemodynamic and airway pressures under simulated intubation with no positive end-expiratory pressure (PEEP). The incorporation of mechanical ventilation transiently enhances left heart function while reducing the performance of the RV as indicated by SV; a result that is in direct contrast to the tidal breathing results shown in Figures 4-6 and 4-7. This contradiction is due to the positive pleural pressure attained during a supported inspiration versus a normal tidal breath. Positive $P_{PL}$ further restricts free wall expansion of the heart chambers (i.e. enhances the restrictive pericardial influence), which would tend to increase the diastolic filling pressures of the atria and ventricles, thereby reducing ventricular filling (i.e. EDV). Inspection of the transmural pressure curves in Figure 4-9 reveals a slight decrease in $P_{RA}$, indicative of reduced systemic venous return. This is in line with experimental findings [90]. However, transmural $P_{LA}$ remains relatively constant, indicating the less-compliant left heart does not respond as markedly to pressure fluctuations, another feature that has been demonstrated experimentally [87]. The lower $RVEDV$ during
inspiration translates into a reduced RVSV. After a couple of heartbeats, serial ventricular interaction causes the LVEDV and LVSV to reduce as well. The transient increase in LVSV observed at the onset of inspiration (Figure 4-9) is due to the effective reduction of the LV afterload induced by a positive $P_{PL}$.

The mean steady-state effects of mechanical ventilation on cardiac performance are compared with the tidal breathing results in Table 4-4. The use of a respirator decreases the EDV of both ventricles by 6% for the LV and 9% for the RV. As mentioned earlier, the increased pleural pressure effectively reduces the ventricular afterload, resulting in an 8.3% drop in mean $P_{AO}$ and a 10.6% drop in mean $P_{PA}$. The combination of influences around the cardiovascular loop combine to yield an 8.3% reduction in cardiac output (CO).

Simulations were also conducted with varying levels of PEEP applied (Table 4-4). From this data, it is apparent that increases in PEEP yield further decreases in ventricular filling volumes, EDV, documented as a 12.4% and 15.6 reduction for LVEDV and RVEDV respectively when a PEEP of 10 cmH$_2$O is applied. Peak systolic pressures attained in the left ventricle, LVESP, also decreased with increasing PEEP, whereas the mean RVESP slightly rose. PEEP application also increases pulmonary capillary resistance, $R_{PC}$, further restricting flow through the pulmonary vasculature. Compilation of these complex interactions leads to the conclusion that increased PEEP exacerbates the negative impacts positive pressure ventilation (PPV) has on cardiac function reducing CO by more than 15% when a PEEP of 10 cmH$_2$O is applied. These results are reasonable given that experimental observations using continuous PPV (CPPV) with a PEEP of 12 cmH$_2$O yielded a 26% reduction in CO on average [88].
Figure 4-9. *CardioPulm* model output pressures and volumes for the integrated human model during mechanical ventilation with no PEEP. A) Systemic vasculature pressures; B) Pulmonic vasculature pressures; C) Pulmonary system pressures; D) Systemic vasculature volumes; E) Pulmonic vasculature volumes; F) Pulmonary system volumes. See text for nomenclature description.
4.9 DISCUSSION

In this study, we present a mathematical model for the study of cardiopulmonary interaction that emulates the functional behavior of the closed-loop circulation including dynamic ventricular interaction and pericardial mechanics, under the influence of pulmonary dynamics. Secondarily, we discuss the incorporation of the model into a flexible, user-friendly software package. The combination provides the user with a powerful tool for rapidly assessing model performance and applying these techniques to data gathered routinely in the Pulmonary Function Laboratory.

The integrated model describes the hemodynamics of the circulation as well as airway mechanics through a combination of lumped compartments [i.e. the major groups of blood vessels (arteries, capillaries, and veins) or the major bronchiolar divisions (upper airway, collapsible airway, alveoli)]. The volume storage elements are characterized as individual compliances and the cardiac pumps (atria and ventricles) as time-varying elastances. The pulmonary and cardiovascular model components interact in the application of intrathoracic pressure on appropriate blood vessels and the heart as well through the nonlinear effect lung volume has on the flow of blood through the pulmonary capillaries. This further extends the capabilities of the models outlined in Chapters 2 and 3, and enables the study of ventricular interaction, pericardial influence, or cardiopulmonary interaction under open or closed chest conditions.

Under control conditions, our model provides (a) representative pressure waveform data for both the cardiovascular and pulmonary systems; (b) predictions of mean blood pressure and blood volume distribution throughout the circulation; (c) good agreement with physiologic indices such as cardiac output and ejection fraction for either
a typical 25-kg dog or a typical 70-kg human; and (d) predictions of septal and free wall motion of the ventricles. Clearly, the complete model is useful in simulating a variety of interventions.

While relevant experimental studies in the literature [26, 83, 84] focus on systemic performance, the use of an integrated cardiopulmonary model with a closed-loop circulation and dynamic septum enables the additional study pulmonic performance as well as the interaction between the right and left heart. The model output is also considerably more complete, in that simulation data is generated throughout the cardiopulmonary system, whereas experimental data is typically limited in scope. This abundance of data allows a variety of contributing factors to be assessed as we delve into the complexities of system interaction.

Previous experimental and modeling studies [26, 83, 84] have regularly cited the decrease in LV function (i.e. stroke volume) during inspiration and based the result on the interaction of two sometimes contradictory causes, namely:

1) the pleural pressure reduction causes a concomitant increase in the volume of the right heart, which has both direct and serial ventricular interaction consequences; and

2) the reduction in pleural pressure during inspiration reduces the absolute pressure in the left ventricle, thereby increasing LV afterload and reducing the outflow through the aortic valve.

Our results strongly echo the effect of RH volume variations resulting from $P_{PL}$ variations during tidal respiration. The results depicted in Figures 4-4 and 4-7 (for dog and human, respectively) clearly demonstrate that decreasing $P_{PL}$ during inspiration
yields an increased RVEDV, causing the RV to generate an increased RVESP as it ejects a larger stroke volume (SV). This is consistent with the results of prior studies as described earlier. With the relatively small changes in pleural pressure during tidal breathing, it is the increased RV volume that has the most significant impact on hemodynamics during tidal breathing. The effect of increased LV afterload ascribed to in these previous studies is not evident in the results developed herein. This effect is largely masked by the volumetric changes. Additional studies should be undertaken to decouple these effects and properly attribute their individual impacts.

Applications of the model directly involve the cardiovascular and hemodynamic response to various breathing states. These patterns include (a) normal tidal breathing; (b) forced vital capacity (FVC) maneuver; (c) tidal breathing under mechanical ventilation; and (d) mechanical ventilation with extrinsic PEEP. In all of these cases, the CardioPulm software provides a comprehensive, quantitative representation of the effects of each respiratory condition.
We have presented a variety of mathematical models and associated software development tools that provide a rich platform for pursuit of integrated cardiopulmonary research. While this development is an evolving effort, this thesis presents several original and important contributions to the study of cardiopulmonary dynamics.

5.1 Systems-Level Modeling

(1) A closed-loop model has been developed that integrates a dynamic heart model, including ventricular and pericardial coupling, with a lumped-parameter model of both the systemic and pulmonic circulations. The identified model produces realistic, continuous hemodynamic waveforms around the circulatory loop, as well as reasonable estimates of cardiac output and blood pressure gradients and volume distributions. The control case then serves as a basis for study of pathophysiological states and the impact of direct and series ventricular interaction.

(2) We have presented a mathematical model that simulates airway mechanics based on work done previously [73, 79], as well as a subset to complete
airway model that describes the dynamic behavior of lung tissue in spontaneously breathing human subjects over full capacity maneuvers, and brief maneuvers of variable frequency. Both model versions have been incorporated into the PulmonaryPV virtual instruments (VIs), providing a user-friendly graphical interface for operation of the model. This software also enables the use of the parameter estimation routines described in Appendix A as a useful adjunct to the study at hand.

(3) The models delineated in points (1) and (2) above have been integrated to further pursue the effects of cardiopulmonary interaction. Specifically, an assessment of hemodynamic fluctuations as a result of pulmonary system variations was accomplished. While the results presented herein do not include the study of pulmonary disease processes or the effects on gas exchange, the integrated model does provide a foundation upon which many of these potential research projects can be built.

5.2 PHYSIOLOGICAL ANALYSIS

(4) Simulations utilizing the closed-loop cardiovascular model have demonstrated various effects of septal contraction and pericardial mechanics in modulating ventricular pump function, as well as, the effects of changing afterloads on ventricular wall motions and pump function.

(5) The study of both series and direct ventricular interaction is accomplished in a dynamic fashion using the closed-loop model. This allows the assessment of variations in septal motion relative to hemodynamic variations under a variety of abnormal or pathophysiological conditions.
(6) Results of the lung tissue study show that the variation of the Kelvin body presented here can successfully predict normal lung tissue dynamics in humans over the full volume capacity and for different breathing frequencies. As such, the model may be used as a component part in models of lung/airway mechanics. Although abnormalities in lung tissue behavior have not been addressed here, the model can be adjusted to account for different pathologies.

(7) The integrated model brings the study closer to the clinical level, considering the complex interactions of the cardiopulmonary system. Application to both dogs and humans is warranted due to the availability of canine data and the aim of applying results to enhance the treatment of human subjects.

5.3 Virtual Instrumentation

(8) The CardioPV analysis program, which incorporates the complete cardiovascular model and the PulmonaryPV program, which contains the complete airway mechanics model, each apply system identification techniques to estimate the key model parameters, and serve as virtual testbeds for assessing the global effects of localized mechanical or hemodynamic alterations. Additionally, the CardioPalm software package builds on the capabilities of CardioPV and PulmonaryPV while incorporating the integrated cardiopulmonary model described above. This enables the assessment of various clinical interventions of the pulmonary system and their concomitant effects on cardiovascular hemodynamics. Given the demonstrated capabilities of the CardioPV, PulmonaryPV and CardioPalm
software packages, with the incorporated model developments, *virtual modeling* can serve as a useful adjunct in cardiopulmonary research.

(9) The development of flexible, portable systems that efficiently collect and analyze data has been documented throughout this thesis. The capability to readily incorporate data from numerous measuring devices in a clinical research study has significant ramifications. While commercial equipment is essential to ongoing clinical monitoring as well as limited clinical research, it is clear that more complex research protocols require a more flexible and robust solution. At present, DAQ systems such as those described in this thesis provide the necessary foundation upon which portable, adaptable, and comprehensive research applications can be built.

Thus, this thesis has demonstrated the potential for data acquisition, data analysis, and model development all within the framework of virtual instrumentation. With the flexibility and adaptability available through a research platform such as the ones described herein, comprehensive, integrated clinical and laboratory research efforts will continue to prosper.
APPENDIX A
PARAMETER ESTIMATION & SENSITIVITY ANALYSIS

A.1 PARAMETER ESTIMATION

A.1.1 CardioPV Application

A typical data set used for the estimation included the left ventricular ($P_{LV}$), aortic arch ($P_{AOP}$), systemic artery ($P_{SA}$; e.g. femoral artery), inferior vena cava ($P_{IVC}$), right atrial ($P_{RA}$), and right ventricular ($P_{RV}$) pressures. Identification of the nominal parameter set first focused on the systemic arterial system. Specifically, the adjustable parameter set was initially restricted to include only the resistances, compliances, and inertances used to characterize the systemic arterial system [compartments include: proximal aorta ($AO_P$), distal aorta ($AO_D$), systemic arteries (SA), systemic arterioles (SA_D) and systemic capillaries (SC)]. The pulmonic component parameters were then estimated independent of the systemic parameters. This process continued iteratively until a good nominal parameter set around the loop was defined. The resistances were then fixed at their estimated values to establish accurate mean pressures around the loop. The parameter estimation routine described below was then applied to the compliance and inertance elements of both circulations to complete the fine-tuning of the closed loop model.
A.1.2 PulmonaryPV Application

A typical data set used for the estimation included the flow at the mouth ($Q_M$) and the change in lung volume ($\Delta V_A$). Since $P_{pl}$ (either experimentally determined or simulated) was used to drive the model, it was not considered one of the data sets for estimation. Identification of the nominal parameter set began with the parameter set previously identified by our group [73]. However, due to model modifications discussed in Chapter 3, a new nominal parameter set was required. Specifically, the parameters associated with the tissue viscoelastance were identified separately as described in Chapter 3 and then added to the PulmonaryPV routine. The full model was then operated using an FVC maneuver input. This process continued iteratively until a good nominal parameter set for the FVC was defined. These results were then used for tidal breathing to ensure realistic pulmonary function. Then, using the data sets available, the parameter estimation routine described below was applied to the compliance and resistive elements of the airway to complete the fine-tuning of the model.

A.1.3 Identification Routine

Values for the adjustable parameters were obtained using a modified Levenberg-Marquardt algorithm [96], which is an iterative, nonlinear least-squares parameter identification scheme. Our nominal set yielded feasible solutions, which enhanced convergence of the estimation algorithm. The iterative estimation routine was terminated when the maximum relative change in the adjustable parameters did not exceed 0.1% on subsequent iterative cycles.
The scalar objective function $E(\alpha)$ employed in achieving good fits simultaneously to three pressure waveforms ($P_{LV}, P_{AOP}, P_{SA}$) was the square of weighted residuals in these pressures, i.e.

$$E(\alpha) = \frac{1}{2} e^T(\alpha) W e(\alpha) = \frac{1}{2} Q^T Q,$$

where

$$Q = \left( \sqrt{W} e \right)$$

(34a)

(34b)

and $e(\alpha)$ is the residual error vector. The elements of the positive definite diagonal matrix, $W$, are the individual weights assigned to each residual $r$ at time $t$, ($r = P_{LV}, P_{AOP}, P_{SA}$). The individual weights are imposed on specific portions of the time record in order to emphasize the fits in those regions. In both the CardioPV and PulmonaryPV programs, weight functions are readily adjustable to accommodate variations in data usage or other desired alterations. In the present study, however, the weighting elements are typically equal so that the entire data set is accommodated proportionately. Constraints on parameter values are also incorporated in the algorithm to ensure physiologically reasonable values. The identification problem is thus transformed into the estimation of the parameter vector ($\alpha$) that minimizes the scalar functional $E(\alpha)$ in a least-squares sense.

A.2 SENSITIVITY ANALYSIS

To accurately estimate the parameters of a given model, it is necessary to determine which of the parameters is most sensitive. We consider the closed circulatory model to be represented in terms of a set of ordinary differential equations (ODEs) of the form:
\[ \dot{x}(t) = f(x, \alpha) \] (35a)

where \( \alpha \) is an \( m \) dimensional vector representing the adjustable parameters of the model.

It is desired to know which of the parameters, \( \alpha_i, i = 1, 2, \ldots, m \), when changed, effects the greatest change in the state variables. To this end, a sensitivity function \cite{97, 98} can be defined for each adjustable parameter as:

\[ \xi^{(i)}(\alpha, t) = \frac{\partial x(t, \alpha_i)}{\partial \alpha_i} \] (35b)

where \( x \) is the solution vector and \( \alpha_i \) is the \( i \)th component of the adjustable parameter vector. \( \xi^{(i)}(t) \) represents the unique solution to the co-state or sensitivity equation:

\[ \xi^{(i)}(\alpha, t) = J_x^{\dot{s}} \xi^{(i)}(\alpha, t) + \frac{\partial f(x, \alpha)}{\partial \alpha_i} \] (35c)

where \( J_x^{\dot{s}} \) is a Jacobian matrix defined as

\[ J_x^{\dot{s}} = \left[ \frac{\partial f_i(x, \alpha)}{\partial x_j} \right]_{0} \quad \text{for } i, j = 1, 2, \ldots, n. \] (35d)

The \( \xi^{(i)} \) notation implies evaluation under nominal conditions for the parameter vector. These sensitivity functions provide first-order estimates of the effect of parameter variations on the state variables. Equations 35b-d can be solved numerically in conjunction with the original state equations, 35a, to obtain the trajectory sensitivity vectors. However, further inspection reveals that numerical solution is not required. The sensitivity functions \( \xi^{(i)}(\alpha, t) \) described above are equivalent to the column vectors of the Jacobian matrix, \( J_x^{\dot{s}} \) (Equation 35d) used in the parameter estimation algorithm. The \textit{CardioPV} and \textit{PulmonaryPV} programs take advantage of this duplication to make a comprehensive sensitivity analysis readily available during performance of the parameter
identification routine. The *sensitivity functions* plotted in figures in this thesis are actually *relative sensitivities* \( S \) defined [97] according to the expression

\[
S_{\alpha_k}^{S} = \left( \frac{\alpha_{\alpha_k}}{x_{i_0}(t)} \right) \frac{\partial x_i(t)}{\partial \alpha_k} \quad \text{for } i = 1, 2, ..., n; \, k = 1, 2, ..., m \quad (35c)
\]

where \( \alpha_{\alpha_k} \) is the nominal value of the parameter and \( x_{i_0}(t) \) is the nominal solution for the \( i \)th state variable. This allows the direct comparison of changes in a state variable as a result of modifications in various model parameters.
APPENDIX B

TYPICAL PARAMETER VALUES

Using the model equations described in the text, the mathematical model of the closed-loop cardiovascular and pulmonary systems can be simulated using the parameters listed in the following tables. A detailed description of the coupled ventricles model, as well as the parameters associated with that model, can be found in [7].

B.1 CANINE MODEL PARAMETERS

B.1.1 Cardiovascular Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>$i=1$</th>
<th>$i=2$</th>
<th>$i=3$</th>
<th>$i=4$</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_{vt}$</td>
<td>N/A</td>
<td>0.43</td>
<td>0.36</td>
<td>0.5</td>
<td>0.55</td>
<td>Gaussian curve magnitude</td>
</tr>
<tr>
<td>$B_{vt}$</td>
<td>sec</td>
<td>0.045</td>
<td>0.035</td>
<td>0.037</td>
<td>0.036</td>
<td>Gaussian curve width</td>
</tr>
<tr>
<td>$C_{vt}$</td>
<td>sec</td>
<td>0.175</td>
<td>0.23</td>
<td>0.275</td>
<td>0.3</td>
<td>Gaussian curve delay</td>
</tr>
<tr>
<td>$A_a$</td>
<td>N/A</td>
<td>0.9</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Gaussian curve magnitude</td>
</tr>
<tr>
<td>$B_a$</td>
<td>sec</td>
<td>0.018</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Gaussian curve width</td>
</tr>
<tr>
<td>$C_a$</td>
<td>sec</td>
<td>0.065</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Gaussian curve delay</td>
</tr>
</tbody>
</table>

Table B-1. Parameters used to define the Gaussian characterization of ventricular and atrial elastance in the canine cardiovascular model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>$LAF$</th>
<th>$RAF$</th>
<th>$PCD$</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{ES}$</td>
<td>mmHg/ml</td>
<td>1.1</td>
<td>1.0</td>
<td>N/A</td>
<td>Systolic maximal elastance</td>
</tr>
<tr>
<td>$V_D$</td>
<td>ml</td>
<td>5.0</td>
<td>5.0</td>
<td>N/A</td>
<td>Systolic volume intercept</td>
</tr>
<tr>
<td>$P_O$</td>
<td>mmHg</td>
<td>0.5</td>
<td>0.35</td>
<td>1.0</td>
<td>Diastolic scale parameter</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>ml$^{-1}$</td>
<td>0.05</td>
<td>0.05</td>
<td>0.03</td>
<td>Diastolic exponential parameter</td>
</tr>
<tr>
<td>$V_O$</td>
<td>ml</td>
<td>5.0</td>
<td>5.0</td>
<td>45.0</td>
<td>Diastolic volume offset</td>
</tr>
</tbody>
</table>

Table B-2. Parameters used to characterize the pressure-volume relationship of the atria and pericardium in the canine cardiovascular model.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>R\textsubscript{M}</td>
<td>Resistance: mitral valve</td>
<td>0.0225</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>R\textsubscript{AOP}</td>
<td>Resistance: proximal aorta</td>
<td>0.0544</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>R\textsubscript{COR}</td>
<td>Resistance: coronary circulation</td>
<td>89.9</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>R\textsubscript{CRB}</td>
<td>Resistance: cerebral circulation</td>
<td>29.97</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>R\textsubscript{AOD}</td>
<td>Resistance: distal aorta</td>
<td>0.0093</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>R\textsubscript{SA}</td>
<td>Resistance: large systemic arteries</td>
<td>0.0577</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>R\textsubscript{SV}</td>
<td>Resistance: systemic veins</td>
<td>0.42</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>R\textsubscript{VC}</td>
<td>Resistance: vena cava</td>
<td>0.005</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>R\textsubscript{RA}</td>
<td>Resistance: right atrium</td>
<td>0.08</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>R\textsubscript{TC}</td>
<td>Resistance: tricuspid valve</td>
<td>0.035</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>R\textsubscript{PAP}</td>
<td>Resistance: proximal pulmonary artery</td>
<td>0.011</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>R\textsubscript{PA}</td>
<td>Resistance: pulmonary arterioles</td>
<td>0.043</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>R\textsubscript{PS}</td>
<td>Resistance: pulmonary shunt</td>
<td>11.3</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>R\textsubscript{PC}</td>
<td>Resistance: pulmonary capillaries</td>
<td>0.09</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>R\textsubscript{PV}</td>
<td>Resistance: pulmonary veins</td>
<td>0.06</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>R\textsubscript{LA}</td>
<td>Resistance: left atrium</td>
<td>0.08</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>R\textsubscript{TAD}</td>
<td>Viscoelastic element: distal aorta</td>
<td>0.0285</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>C\textsubscript{SC}</td>
<td>Compliance: systemic capillaries</td>
<td>0.0577</td>
<td>ml/mmHg</td>
</tr>
<tr>
<td>C\textsubscript{SV}</td>
<td>Compliance: systemic veins</td>
<td>0.42</td>
<td>ml/mmHg</td>
</tr>
<tr>
<td>C\textsubscript{VC}</td>
<td>Compliance: vena cava</td>
<td>0.005</td>
<td>ml/mmHg</td>
</tr>
<tr>
<td>C\textsubscript{PC}</td>
<td>Compliance: pulmonary capillaries</td>
<td>0.0577</td>
<td>ml/mmHg</td>
</tr>
<tr>
<td>C\textsubscript{PV}</td>
<td>Compliance: pulmonary veins</td>
<td>0.42</td>
<td>ml/mmHg</td>
</tr>
</tbody>
</table>

Table B-3. Fixed Parameters used to characterize the resistive and compliant elements of the canine cardiovascular model.

### B.2 Human Model Parameters

#### B.2.1 Cardiovascular Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>(i=1)</th>
<th>(i=2)</th>
<th>(i=3)</th>
<th>(i=4)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A\textsubscript{v,i}</td>
<td>N/A</td>
<td>0.37</td>
<td>0.36</td>
<td>0.5</td>
<td>0.56</td>
<td>Gaussian curve magnitude</td>
</tr>
<tr>
<td>B\textsubscript{v,i}</td>
<td>sec</td>
<td>0.045</td>
<td>0.035</td>
<td>0.037</td>
<td>0.036</td>
<td>Gaussian curve width</td>
</tr>
<tr>
<td>C\textsubscript{v,i}</td>
<td>sec</td>
<td>0.175</td>
<td>0.23</td>
<td>0.275</td>
<td>0.3</td>
<td>Gaussian curve delay</td>
</tr>
<tr>
<td>A\textsubscript{a}</td>
<td>N/A</td>
<td>0.9</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Gaussian curve magnitude</td>
</tr>
<tr>
<td>B\textsubscript{a}</td>
<td>sec</td>
<td>0.018</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Gaussian curve width</td>
</tr>
<tr>
<td>C\textsubscript{a}</td>
<td>sec</td>
<td>0.065</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Gaussian curve delay</td>
</tr>
</tbody>
</table>

Table B-4. Parameters used to define the Gaussian characterization of ventricular and atrial elastance in the human cardiovascular model.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>LAF</th>
<th>RAF</th>
<th>PCD</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{ES}$</td>
<td>mmHg/ml</td>
<td>0.4</td>
<td>0.4</td>
<td>N/A</td>
<td>Systolic maximal elastance</td>
</tr>
<tr>
<td>$V_D$</td>
<td>ml</td>
<td>35.0</td>
<td>35.0</td>
<td>N/A</td>
<td>Systolic volume intercept</td>
</tr>
<tr>
<td>$P_O$</td>
<td>mmHg</td>
<td>0.5</td>
<td>0.22</td>
<td>1.0</td>
<td>Diastolic scale parameter</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>ml$^{-1}$</td>
<td>0.038</td>
<td>0.06</td>
<td>0.009</td>
<td>Diastolic exponential parameter</td>
</tr>
<tr>
<td>$V_O$</td>
<td>ml</td>
<td>35.0</td>
<td>35.0</td>
<td>135.0</td>
<td>Diastolic volume offset</td>
</tr>
</tbody>
</table>

Table B-5. Parameters used to characterize the pressure-volume relationship of the atria and pericardium in the human cardiovascular model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_M$</td>
<td>Resistance: mitral valve</td>
<td>0.0095</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{AOP}$</td>
<td>Resistance: proximal aorta</td>
<td>0.0084</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{COR}$</td>
<td>Resistance: coronary circulation</td>
<td>35.900</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{CRB}$</td>
<td>Resistance: cerebral circulation</td>
<td>12.000</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{AOD}$</td>
<td>Resistance: distal aorta</td>
<td>0.0090</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{SA}$</td>
<td>Resistance: large systemic arteries</td>
<td>0.0230</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{SV}$</td>
<td>Resistance: systemic veins</td>
<td>0.1300</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{VC}$</td>
<td>Resistance: vena cava</td>
<td>0.0020</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{RA}$</td>
<td>Resistance: right atrium</td>
<td>0.0320</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{TC}$</td>
<td>Resistance: tricuspid valve</td>
<td>0.0150</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{PAP}$</td>
<td>Resistance: proximal pulmonary artery</td>
<td>0.0040</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{PA}$</td>
<td>Resistance: pulmonary arterioles</td>
<td>0.0172</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{PS}$</td>
<td>Resistance: pulmonary shunt</td>
<td>4.5200</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{PC.0}$</td>
<td>Resistance: pulmonary capillaries</td>
<td>6.7000</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{PV}$</td>
<td>Resistance: pulmonary veins</td>
<td>0.0140</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{LA}$</td>
<td>Resistance: left atrium</td>
<td>0.0420</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{TAOD}$</td>
<td>Viscoelastic element: distal aorta</td>
<td>0.0125</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$C_{SC}$</td>
<td>Compliance: systemic capillaries</td>
<td>0.4000</td>
<td>ml/mmHg</td>
</tr>
<tr>
<td>$C_{SV}$</td>
<td>Compliance: systemic veins</td>
<td>15.000</td>
<td>ml/mmHg</td>
</tr>
<tr>
<td>$C_{VC}$</td>
<td>Compliance: vena cava</td>
<td>3.5000</td>
<td>ml/mmHg</td>
</tr>
<tr>
<td>$C_{PC}$</td>
<td>Compliance: pulmonary capillaries</td>
<td>1.2000</td>
<td>ml/mmHg</td>
</tr>
<tr>
<td>$C_{PV}$</td>
<td>Compliance: pulmonary veins</td>
<td>0.4000</td>
<td>ml/mmHg</td>
</tr>
</tbody>
</table>

Table B-6. Fixed Parameters used to characterize the resistive and compliant elements of the human cardiovascular model.
### B.2.2 Pulmonary Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{TM_{max}}$</td>
<td>Max transmural pressure</td>
<td>33.106</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$V_{C_{max}}$</td>
<td>Max volume: collapsible segment</td>
<td>0.1863</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$V_{C_{term}}$</td>
<td>Collapsible seg. P decay parameter</td>
<td>0.0451</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{VE}$</td>
<td>Viscoelastic Resistance: lung tissue</td>
<td>0.7841</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$C_{VE}$</td>
<td>Viscoelastic Compliance: lung tissue</td>
<td>0.0150</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{RSA}$</td>
<td>Resistance: large systemic arteries</td>
<td>-9.965</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{SM_{i}}$</td>
<td>Small a/w resistance param: inspiration</td>
<td>1.8498</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{SM_{c}}$</td>
<td>Small a/w resistance param: expiration</td>
<td>49.599</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{SC_{min}}$</td>
<td>Small a/w resistance param</td>
<td>0.2000</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$R_{SC_{max}}$</td>
<td>Small a/w resistance param</td>
<td>1.0845</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$V_{crit}$</td>
<td>Small a/w resistance param</td>
<td>0.8000</td>
<td>ml/mmHg</td>
</tr>
<tr>
<td>$V_{star}$</td>
<td>Small a/w resistance param</td>
<td>3.9202</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$P_{PLA}$</td>
<td>Lung elastic recoil parameter</td>
<td>0.1753</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$P_{PL_{off}}$</td>
<td>Lung elastic recoil parameter</td>
<td>-0.532</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$P_{LS}$</td>
<td>Lung elastic recoil parameter</td>
<td>0.9908</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$K_{1}$</td>
<td>Resistance parameter</td>
<td>0.3802</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$K_{2}$</td>
<td>Resistance parameter</td>
<td>0.4816</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>$K_{3}$</td>
<td>Resistance parameter</td>
<td>0.3638</td>
<td>mmHg*sec/ml</td>
</tr>
<tr>
<td>TLC</td>
<td>Total lung capacity (subject dependent)</td>
<td>5.1900</td>
<td>L</td>
</tr>
<tr>
<td>RV</td>
<td>Residual volume (subject dependent)</td>
<td>1.3600</td>
<td>L</td>
</tr>
</tbody>
</table>

Table B-7. Adjustable parameters used to characterize the resistive and compliant elements of the full pulmonary model.


