7-2022

Optimizing Left Ventricular Assist Device Hemodynamics via Patient Specific Computational Analysis

Jasmine Josefina Martinez

Optimizing Left Ventricular Assist Device Hemodynamics via Patient Specific Computational Analysis

by

Jasmine Josefina Martinez

A thesis submitted to the College of Engineering and Science of
Florida Institute of Technology
in partial fulfillment of the requirements
for the degree of

Master of Science
in
Biomedical Engineering

Melbourne, Florida
July, 2022

We the undersigned committee hereby approve the attached thesis, “Optimization of Left Ventricular Assist Device Hemodynamics via Computational Patient Specific Analysis.” by Jasmine Josefina Martinez, be accepted as fulfilling in part the requirements for the degree of Master of Science in Biomedical Engineering

_____

Venkat Keshav Chivukula, Ph.D.
Assistant Professor
Biomedical and Chemical Engineering and Sciences
Major Advisor

_____

Mehmet Kaya, Ph.D.
Associate Professor
Biomedical and Chemical Engineering and Sciences

_____

James R. Brenner, Ph.D.
Associate Professor
Biomedical and Chemical Engineering and Sciences

_____

Andrew D. Knight, Ph.D.
Professor and Department Head
Biomedical and Chemical Engineering and Sciences

Abstract

Optimizing Left Ventricular Assist Device Hemodynamics via Patient Specific Computational Analysis

Author: Jasmine Josefina Martinez

Advisor: Venkat Keshav Chivukula, Ph.D.

The best treatment for patients with end stage heart failure is a heart transplant but given the scarcity of donor hearts, a promising alternative treatment has become left ventricular assist devices (LVAD). However, complications such as right heart failure, stroke, and adverse hemodynamic outcomes continue to occur. This thesis will cover investigations into continuous flow LVAD treatment optimization techniques to improve patient outcomes. Optimization techniques explored include an in-house developed optimization algorithm that is completed in three phases on a computational lumped parameter model that is representative of the cardiovascular system using an electrical circuit analogy. This three-phase optimization technique is tested on two patient cohorts by (1) specifying the model to the patient, (2) performing virtual blood pressure management, and (3) LVAD speed optimization. Another optimization technique investigated is the use of speed modulation waveforms. Changes to characteristics of the waveform are explored to assess the effects on the cardiovascular system via the computational model. These waveform characteristics include baseline speed, duration of speed modulation, and the drop in speed. Speed modulation waveforms allow pressure to build up in the left ventricle, allowing for the aortic valve to open. In the treatment of continuous flow LVADs the aortic valve is an area of stagnation, where platelet activation can occur, thereby leading to thrombi formation.

Results from these investigations reveal that understanding the pump-patient interaction is essential to improving patient hemodynamics. Furthermore, changes must be made to both blood pressure and LVAD speed to meet hemodynamic targets. In addition, both sets of patient data revealed that patients operating at higher LVAD speeds and with higher flows may benefit most from speed optimization. The exploration of the square speed modulation waveform reveals that lower baseline speeds, longer duration of speed modulation, and bigger drops in speed lead to increased chances for the aortic valve to open, thus improving thrombogenicity. The information obtained from this work provides clinicians with insights into improvement techniques for LVAD therapy that may lead to better patient outcomes.

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Acknowledgement

I would like to acknowledge my research professor Dr. Venkat Keshav Chivukula for always supporting me and being there for me. I cannot imagine going through my research journey with anyone else. He has supported me, listened to me, and showed much kindness to me. I could not have done all that I have without his guidance and help. I would also like to thank my mom for always listening to me and being there for me no matter what. She is my best friend, and I will always cherish and appreciate her support. I would also like to acknowledge Ruth White who is my lab sister for always being the person I could go to for help and for being the amazing person whose light can brighten up anyone's day. Lastly, I would also like to thank all my teachers from Florida Tech for providing me with the tools and knowledge I needed to succeed during each step of my undergraduate and graduate studies.

Chapter 1
Introduction

1.1 A Statement of the Problem

According to the American Heart Association in 2021 the estimated prevalence of heart failure in America is 6 million people, about 1.8% of the US population.[1,2] For those with end-stage heart failure waiting on a heart transplant, there is an increasing disparity between donor hearts available and those in need of a heart transplant or alternative treatment. [3,4,5,6] Patients can't receive a donor heart if comorbidities exist, and such comorbidities are becoming more common amongst heart failure patients.[6] The need for an alternative treatment has led to the widespread use of mechanical circulatory support devices such as left ventricular assist devices (LVADs). LVADs are progressively being used as a destination therapy increasing about 20% from 2008 to 2010, to about 50% of all device implants in 2014. [6] Despite the benefits of this alternative treatment, there are still numerous complications with LVAD treatment. LVADs can be implanted as bridge to transplant devices or as destination therapy (DT) where the LVAD will be utilized by the patient for a long duration of time when transplantation is not possible. Recent studies suggest that the life expectancy declined to about 50% after 4 years for LVAD destination therapy, [7] while 1-year survival rates for LVAD patients approaches 90%,[5,8,9] several complications such as thrombosis, stroke, nonoptimal hemodynamics, right heart failure, and hypervolemia continue to be an impediment to the success of LVAD therapy.[10,11,12,13,14]

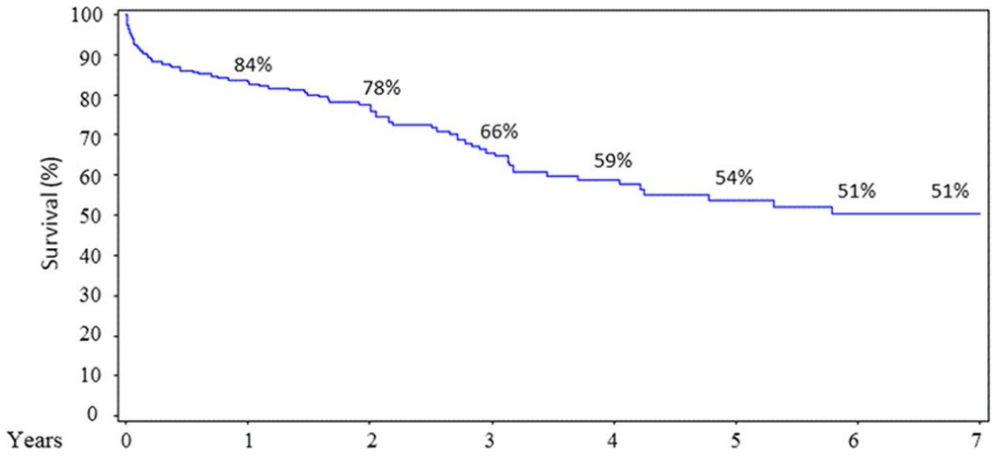

Figure 1: Overall long-term survival (Kaplan - Meier survival analysis) of patients receiving LVAD (HeartWare) treatment[7]

In this work, investigations into LVAD hemodynamics will be explored via development of custom optimization techniques and their application to patient data sets, in addition to the development and implementation of LVAD speed modulation waveforms for improving patient outcomes.

1.2 Literature Review

1.2.1 The Epidemic of Heart Failure

Heart failure is an epidemic that affects 1% to 2% of the worldwide population. [15] Heart failure (HF) in its most basic definition is when a person's heart is unable to produce a cardiac output (CO) that can supply enough blood to all parts of the body. The degree of heart failure can be broken down into stages. Multiple classification systems have been developed to characterize patients with HF and define those with advanced disease.[2] The New York heart Association (NYHA) classes are defined by symptoms felt during physical activity and when at rest.[2] The American College of Cardiology separates patients into stages where stage D differentiates patients who may have residual symptoms despite maximal medical therapies.[2] The interagency registry for mechanically assisted circulation divides heart failure patients by risk.[2] The classifications of heart failure systems as defined by the American College of Cardiology (ACC), the New York Heart Association (NYHA), and the

Interagency Registry for mechanically assisted circulation (INTERMACS) are shown in Figure 2 .

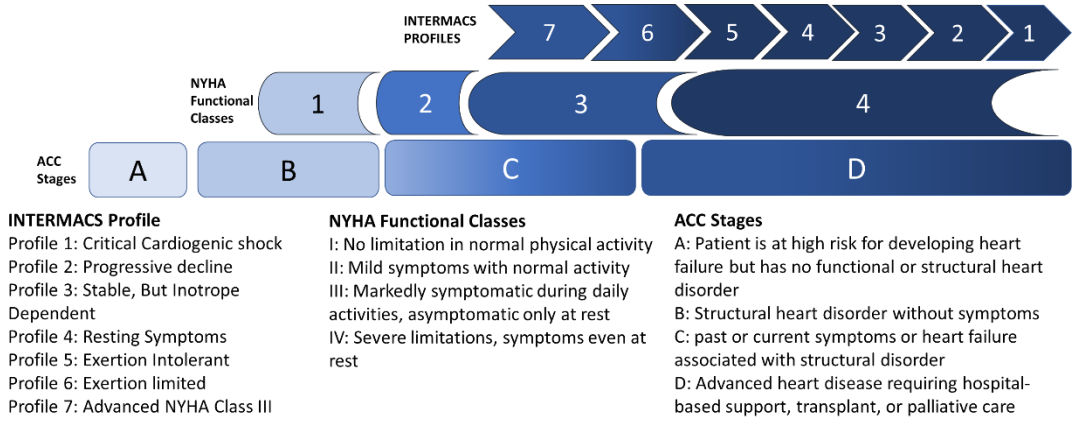

Figure 2: The classifications systems of heart failure systems as defined by the American College of Cardiology (ACC), the New York Heart Association (NYHA), and the Interagency Registry for Mechanically Assisted Circulation (INTERMACS).[2]

These classifications have been developed to tackle defining HF and prognosis as well as urgency of intervention. Professional societies have also published consensus definitions to improve the early identification and treatment of patients that rely on combinations of symptoms, objective data, and therapeutic interventions. [2] Advanced heart failure or stage D disease affects >10% of the heart failure population.[16] Heart transplantation remains the best option for stage D heart failure patients with median survival time being estimated at 11 years overall and 13 years for patients who survive one year post transplant.[17] Statistics shows that 20,000 patients could benefit from a donor heart, but in 2011 there were only about 2000 heart transplants performed in the United States while mortality of patients on the donor heart wait list was 12.4 deaths per 100 years they were on the waitlist.[17] Despite shortages, comorbidities (i.e. diabetes, immunosuppression disorders, etc.) that commonly accompany heart failure patients make the chances of receiving a donor heart less likely. Patients suffering from end stage heart failure undergo an initial evaluation when referred to a transplant center where the severity of HF, reversibility, and adequacy of current medical treatments are assessed.[16] These challenges with heart transplants show the need for an alternative treatment for advanced heart failure patients. The LVAD serves as a

specialized intervention when symptoms exist outside of maximal medical therapy, [2] and has become a highly used alternative therapy for heart failure patients.

1.2.2 Progression of LVADs

1.2.2.1 From Pulsatile to Continuous Flow Pumps

LVADs are mechanical pumps that direct blood by creating a pressure differential between the inflow and outflow cannulas. The pump pulls blood from the inlet, typically the left ventricle, and sends it to the rest of the body via the outlet, which is sutured on or around the aorta. The first generation LVADS were pulsatile pumps made to simulate the heart's pulsatile nature. These LVADS were not sustainable given the need for longer therapy durations and a treatment that could be put in place of heart transplantation. The pulsatile pumps tended to fail after 2 years of use.[18] Pulsatile LVADs became continuous flow pumps to decrease size allowing for women and children to be implanted as well as improvement in life expectancy.[18] 2nd generation centrifugal (CF)-LVADs were designed with contact bearings. 2nd generation LVADs have been able to provide patients with a bridge to transplant treatment, although the contact-bearing design has been proven to have its limitations. These limitations include wear from friction caused by blood against the bearing that holds the rotor/impeller resulting in potential device failure as well as thrombus formation due to improper bearing washout. These contact bearings also play a role in disturbing the blood flow giving more chances of thrombus development. The 3rd generation LVADs were developed to combat these issues by modifying the contact bearing design to a non-contact levitation mechanism. The non-contact bearing or centrifugal design is implemented via magnetic and/or hydrodynamic levitation of the impeller.[19] The 3rd generation LVADs have become more prominent and are widely used today.

1.2.2.2 LVADs being investigated

HVAD

The Medtronic (formerly HeartWare) ventricular assist device (HVAD) was developed by Medtronic and approved as a bridge to heart transplantation treatment for patients who were at risk of end-stage heart failure November 2012. The HVAD contains a dual levitation system that uses magnetic and hydrodynamic forces. The impeller speed produces a hydrodynamic lift while the magnetic levitation bearings rotate the impeller/rotor with no mechanical contact between the rotating and stationary parts of the pump. [20,21] Please refer to Figure 3 for an image of the HVAD device.[22] The HVAD was removed from the market on July 3rd of 2021 for having battery issues, adverse neurological events occurring, and delays in pump mechanism restart upon stasis of the impeller.[23,24]

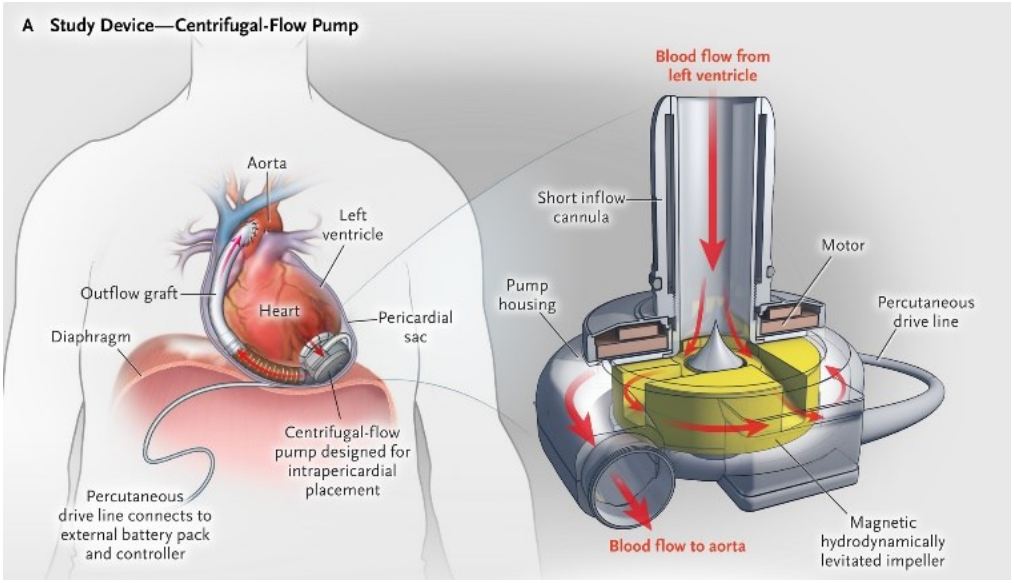

Figure 3: The Heart Ware ventricular assist device system is shown

Heartmate III

The Heartmate III is manufactured by Thoratec Corp., which was later acquired by Abbott (North Chicago, IL, USA) with the purpose of providing hemodynamic support to heart failure patients as a bridge to transplant or destination therapy.[25] It is a centrifugal CF-LVAD that utilizes a magnetic bearing to fully levitate its rotor allowing for wide blood flow gaps between the impeller and the pump housing. This set up has a built-in pulse designed to avert any stagnation zones. [26] The magnetic bearing is a bearing-less system where both the drive and the levitation coils share the same stator core. The stator core contains electromagnetic coils, and levitation coils. The motor technology consists of all these components as well as hall/distance sensors and microcontroller. [25] In a bearing-less system, the impeller's rotation is caused by a moving magnetic field generated by the drive coils. [19]

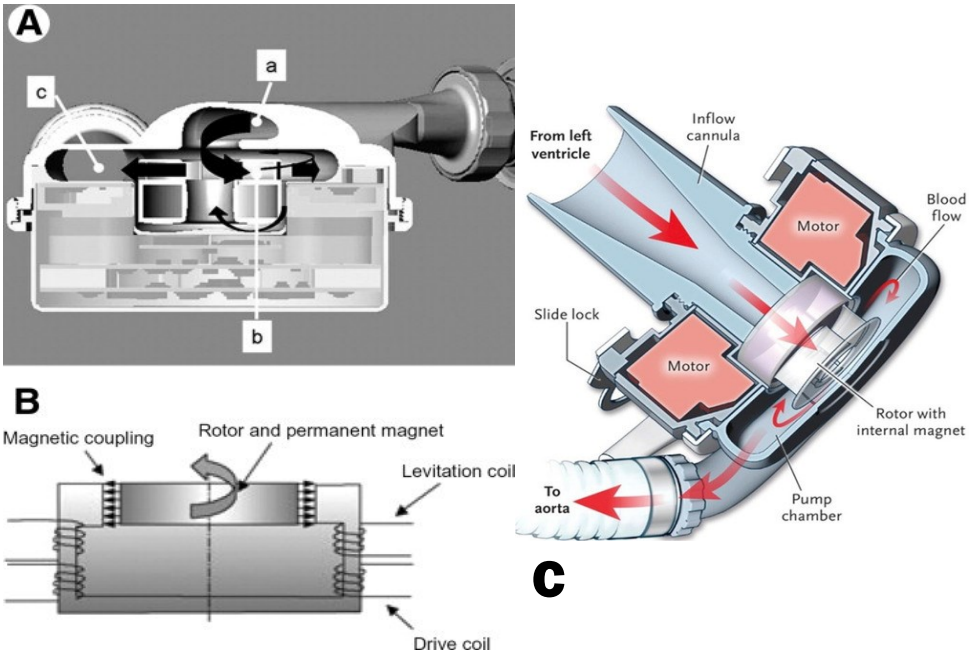

Figure 4: Example of a 3rd generation continuous-flow rotary pump with centrifugal design incorporating active magnetic levitation and coupling of the internal impeller with a bearing-less drive system. (A) Schematic representation of the HeartMate III (Thoratec Corp.). (a) The main flow path from the inflow section; (b) blood flow path through the impeller and the backflow paths above the shroud and between the rotor and motor; (c) outflow path. [27](B) Schematic representation of a self-bearing or bearing-less drive system in a 3rd generation continuous-flow rotary pump. In a self-bearing system, both the drive and levitation coils share the same stator core. [28](C) Cross-section of the HM3 with parts labeled [29]

EVAHEART

The EVAHEART 2 (EH2) was developed by Sun Medical Technology Research Corporation in Nagano, Japan, refer to Figure 5. The EH2 is a CF centrifugal pump that features hydrodynamically levitated bearing rotating without any contact to the pump housing.[26] This hydrodynamic levitating system features a "cool seal unit" (CSU) where sterile fluid is continuously sent through a driveline, around a rotating impeller shaft, and bearing interface that applies a hydraulic levitation force allowing for the rotating impeller to circulate blood from the left ventricle via the blood inlet to the aorta via the outlet cannula, refer to Figure 6. The pump has an exclusive design with large gaps (700-1,000 μm) between the impeller and the pump housing minimize wall shear stress. [30]

Figure 5: EVAHEART device developed by Sun Medical Technology Research Corporation

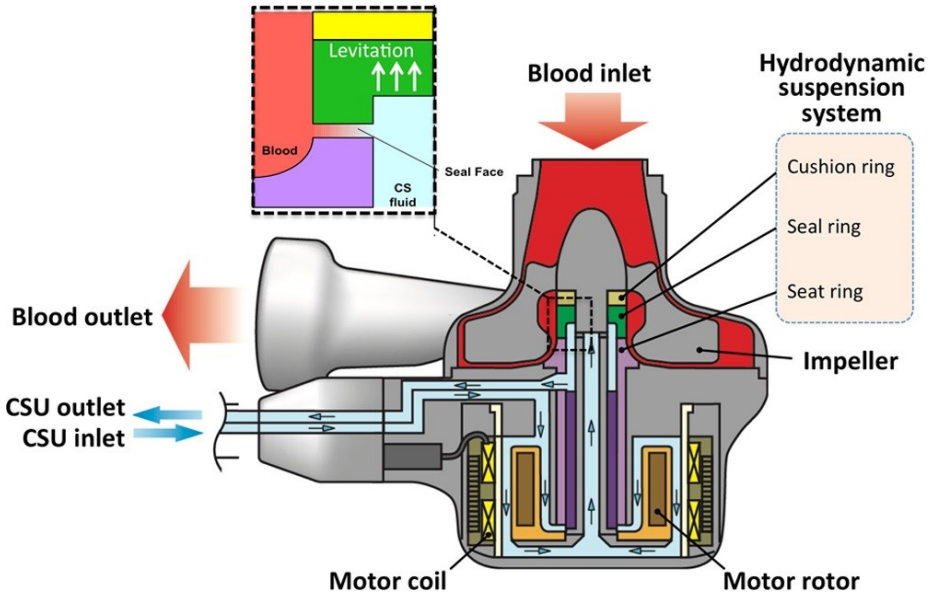

Figure 6: The cross-sectional schematic view of the EVAHEART 2 hydraulically levitated impeller [30]

The only LVAD currently available on the market is the Heartmate III (HM3) in the United States, given the HVAD has been recalled as of 2021.[24] The EVAHEART device is undergoing the process of FDA approval for usage in the United States but has been implemented in Japan since 2005.[30] Investigations carried throughout this thesis are pertaining to these devices given patient data received and collaborations with EVAHEART Inc.

1.2.2.3 Current Challenges with LVADs and Possible Solutions

The current challenges with LVADs-DT include complications that come with the implantation of the device as well as the interactions that can occur from unnatural flows being inflicted on the cardiovascular system, refer to Figure 7. LVAD-related complications can occur in up to 60% of patients by six months post-implantation, and, by two years, 80% of patients experience at least one adverse event.[31] The most common adverse event experienced by LVAD users is bleeding; patients are predisposed to bleeding given the use of anticoagulation medicines to aid in preventing thrombus formation. Non-surgical, early bleeding (within 30 days after implant) occurs in anywhere from 20 to 40% of patients. The incidence of hemorrhagic events within six months of discharge is 13%. [31] The cumulative risk of GI bleeding for patients receiving the HeartMate II and the HeartWare is 21%, 27% and 31%, at one, three, and five years, respectively. [31] GI bleeding could be the cause of abnormal flow rates being experienced by blood vessels as well as high amounts of shear stress and intraluminal pressures commonly experienced by LVAD patients. Other complications include aortic insufficiency, right heart failure, thromboembolic events, and infections. *De novo* aortic insufficiency (AI) is a frequent occurrence in patients supported with an LVAD, ranging between 11% and 42%.[32] Complications such as thromboembolic events can lead to device malfunction early on post-surgery.[33] Thromboembolic events (TEs), even despite adequate anticoagulative therapy, are a feared complication in up to 20% of patients (especially pump thrombosis and ischemic cerebrovascular events) and require in the case of a pump thrombosis immediate lifesaving strategies such as device replacement or urgent transplantation.[34] Right ventricle failure (RVF) occurs in approximately 11% of patients after the insertion of the LVAD. [35] RVF can be a result of septal shift due to changes in pump speed, as well as occurrences of volume overload and hypertension. The rates of LVAD-related infections are high, ranging from 30 to 50%.[31] Currently, research is geared towards improving 3rd generation LVADs by investigating ways to reduce pump thrombosis, thromboembolism, bleeding, stroke, infection, and aortic insufficiency.[3637,38,39,40] This thesis aims to expand the knowledge of the

filed by investigating optimization techniques and speed modulation waveforms in hopes of improving patient outcomes.

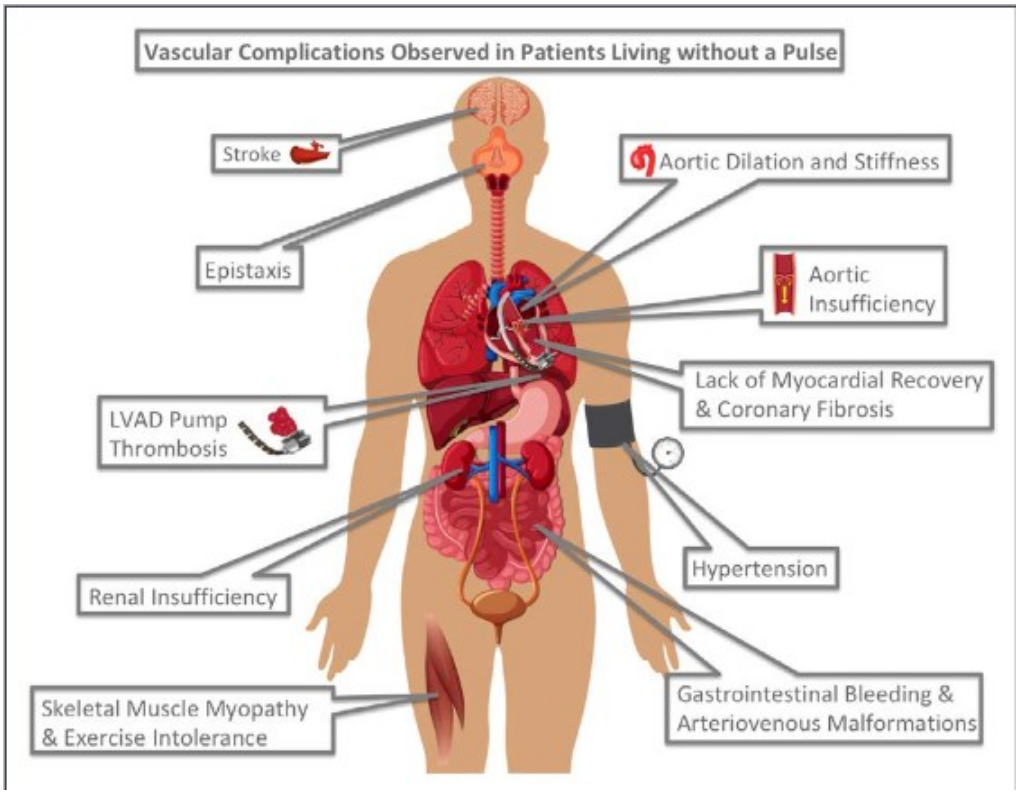

Figure 7: Vascular complications that occur in patients with continuous flow LVADs, who are observed to lack a pulse [41]

Current Optimization Techniques

Post-implantation techniques for setting patient's LVAD speeds currently are a balancing act for clinicians where a pump speed that delivers enough cardiac output and doesn't overload the right side must be determined based on the patient's hemodynamic parameters (i.e., flow through the VAD, contractility of the heart, right and left ventricle pressures, and ventricular afterload).[42] Clinicians must determine this "ideal" speed based on

their medical expertise, and this is often done without consideration of the pump's mechanical performance characteristics, i.e. pressure-flow curves of the pump.[42] The pressure-flow curves are vital piece of determining the best LVAD speed to meet the hemodynamic needs of the patient. Furthermore, clinicians do not have adequate guidelines for adjusting speed as the patient's blood volumes may fluctuate or as adverse events such as hypovolemia, RV failure, Tamponade, and systemic hypertension occur.[42]

When discharging the patient, optimal speed settings for long-term management are not clear.[42] Techniques for speed optimization can vary based on the hospital, although a recent optimization protocol, the Columbia Ramp study, was published instructing clinicians to determine the optimal speed by ramping up speeds while assessing the blood pressure, heart rate, LV size, frequency of AV regurgitation, severity of mitral valve regurgitation, and estimated RV systolic pressure of the patient.[42] The optimal speed is chosen based on intermittent AV opening, obtaining a mean arterial pressure (MAP) above 65 mm Hg and that minimizes mitral valve regurgitation.[42] According to the published study by Uriel and others, the Columbia Ramp study limitations include the fact that it is laborious and cumbersome.[43] In addition, this technique still does not provide clinicians with a quantitative approach to optimizing the LVAD speed or for defining the speed upon device implementation.

Speed Optimization

A LVAD speed optimization technique using a computational hemodynamic model will be explored in this thesis. This technique will take into consideration the complex interplay between the pump and the patient. Speed optimization will provide clinicians with a technique for quantitatively defining an LVAD speed given the patients specific cardiovascular response. Moreover, reducing the possibilities of adverse events occurring such as right heart failure, and gastrointestinal bleeding. Right heart failure (RHF) is a common occurrence in LVAD users, prevention of RHF includes maintaining a preload and afterload that is sustainable by the right side of the heart. Apart of maintaining the preload is finding the optimal speed of the LVAD by not only ensuring sufficient blood is being

supplied to the organs but also overloading of the right side doesn't occur especially given the unnatural flow that comes with continuous flow LVADS. Furthermore, this technique will allow clinicians to explore how changes to the LVAD speed and mean arterial pressure can affect the patient's hemodynamics, allowing for hemodynamic targets to be met. This technique is applied to two sets of patient data; both data sets reveal trends that can serve as predictors for patients who will benefit the most from speed optimization. Current techniques are limited by time available and fail to ensure that hemodynamic objectives are met with consideration of patients' circulatory responses.[44]

Speed Modulation

Speed modulation is a method of transitioning the LVAD between speeds in hopes of not shocking the system from a sudden drop or increase in speed. Given the complications mentioned with current LVADs, aortic valve opening is a major concern. Continuous flow LVADs have increasingly become more common in treating end stage heart failure patients, unfortunately, a part of the pumps functionality is when the LVAD speed is increased there is more suction of blood from the left ventricle, causing left ventricle unloading. This unloading creates a pressure differential where any pulsatility that can be generated by the LV becomes overshadowed by the pump. This leads to an area of stagnation in the heart, specifically at the aortic valve/aortic root where thrombi can form and possibly lead to a stroke.[45] A study reported the development of *de novo* aortic insufficiency in 25% of CF-LVADs users who received therapy for at least 1 year.[43] Aortic insufficiency is caused by blood accumulating above the valve due to improper blood washout from the aortic valve not being opened/closed intermittently. This data demonstrates the need for a technique that encourages intermittent AV opening. Speed modulation has been shown to increase the chances for pulsatility or AV opening, thus minimizing adverse events.[46,47] An investigation into sinusoidal and trapezoidal speed modulation shapes showed that the sinusoidal wave was better at creating pulsatile flow when investigating axial pumps.[48] The HM3 and the HVAD speed modulation waveforms are square waves with different characteristics, although both have been shown to reduce stagnation zones but have failed to prevent platelet activation or reduce thrombotic risk, [49] indicating more investigations into speed modulation

techniques are necessary for CF-LVADs. This thesis includes a deep dive into gaining a better understanding of the square wave speed modulation waveform by identifying trends in changes that occur in a virtual patient given various characteristics of the square waveform are explored.

In this work, my research objectives are (1) to develop a computational hemodynamic analysis methodology for LVAD therapy; (2) customize hemodynamic algorithms for patient specific analysis; (3) optimize LVAD and patient management settings, and finally (4) investigate LVAD speed modulation algorithms for hemodynamic optimization. In completing these objectives, Chapter 2 will describe the computational lumped parameter model and how it is representative of the cardiovascular system in addition to how it is utilized in MATLAB with adjustments to incorporate LVAD support. Chapter 3 will focus on the optimization process that can be applied to patient data (specifically HM3 and HVAD patients) by specification of the model. Furthermore, this chapter covers the results and conclusions drawn from applying the in-house developed optimization algorithm. Chapter 4 will discuss the other optimization technique explored: the exploration of speed modulation waveforms. This chapter will include information regarding how speed modulation works, the benefits of it, and the effect its implementation can have on the cardiovascular system in hopes of achieving better patient outcomes. The final chapter will conclude all analysis and highlight key observations gained from the completion of objectives.

Chapter 2
Methods

This chapter gives insight into a lumped parameter model that is representative of a virtual patient by modeling the cardiovascular system using an electrical analogy. The model components include the four chambers of the heart, all valves with unidirectional flow, as well as the pulmonary and systemic circulations. This model of the cardiovascular system can be utilized to assess the effect that speed optimization or speed modulation can have on a patient. This model makes it possible to explore what if scenarios in a clinical timeframe without the need to make any changes to the patient's hemodynamics.

2.1 Computational Lumped Parameter Model (LPM)

2.1.1 Modeling the Cardiovascular System

The model utilized in the optimization of the LVAD is a 0D LPM. The model is based on an analogy of the cardiovascular system to a hydraulic-electrical system. This analogy is applicable because the behaviors of an electrical system are like those in the cardiovascular system.[50] For example, pressure differentials created by the heart drive blood flow, this is like a battery that creates voltage differentials that drive current throughout a circuit. Furthermore, blood flow experiences resistive forces that include the diameter of the blood vessel walls while current experiences electrical impedances. These similarities are why the cardiovascular system can be modelled by electrical components.

The four chambers of the heart, the systemic and pulmonary circulations can be modelled by using electrical components or combinations of electrical components including inductors, resistors, and capacitors. The equations for these electrical elements are shown by equation (1) and (3). Equation (1) is Ohm's law where V is voltage and i is current and R is resistance. Equation (2) is used to determine the current through a capacitor by multiplying

the capacitance, C, and the change in voltage with respect to time. Equation (3) is the relationship for an inductor where L is the inductance.

$$\boldsymbol{V = iR} \quad \textbf{(1)}$$

$$\boldsymbol{i = C\frac{dV}{dt}} \quad \textbf{(2)}$$

$$\boldsymbol{V = L\frac{di}{dt}} \quad \textbf{(3)}$$

By creating a model that represents the cardiovascular system using these electrical equations one ends up with a system of differential and algebraic equations (DAE) that can be solved simultaneously to get time-varying pressure and flow at specific locations of interest. When considering resistance as vascular resistance, *R[mmHg-s/ml]*, from changes to the diameter of blood vessels, current as blood flow, *Q[ml/s]*, and voltage as pressure, *P[mmHg]*, these equations become equations **(4)** thru **(6)** when converted to measurements of the cardiovascular system.

$$\boldsymbol{P = QR} \quad \textbf{(4)}$$

$$\boldsymbol{Q = C\frac{dP}{dt}} \quad \textbf{(5)}$$

$$\boldsymbol{P = L\frac{dQ}{dt}} \quad \textbf{(6)}$$

An example of creating an electrical circuit that represents the cardiovascular system are the Windkessel models.[51] A two element Windkessel model uses a circuit analogy to describe the heart and systemic arterial system as a closed hydraulic circuit comprising of a water pump connected to a chamber. When water is being pumped to the chamber or Windkessel, an empty space in the chamber allows for the compression of air that forces water out of the chamber back to the pump. The compression of air is representative of the elasticity of major arteries also known as the arterial compliance. The resistance the water

encounters when leaving the chamber represents the resistance to blood flow from the heart through the blood vessels as the diameter of the vessels decreases. This is known as the peripheral resistance. A two element Windkessel model shown in Figure 8 uses a capacitor and a resistor to model this behavior assuming blood volume and blood pressure are directly correlated and that blood flow through the pipe connecting the Windkessel to the pump follows Poiseuille's law and is proportional to the fluid pressure. The capacitor models the compliance of the veins while the resistor reflects the total peripheral resistance**.** [51] Using the equations for a resistor **(4)** and a capacitor **(5)** in terms of the current going through the circuit equation **(7)** can be used to predict blood flow through an arterial bed which is represented by the two element Windkessel model. The Windkessel model can be made to be more complex by including more electrical components that model more behaviors of the cardiovascular system. The three element Windkessel model adds in another resistor to represent the resistance to flow due to the pulmonary and aortic valves. This model is shown in Figure 9. The equation for the three element Windkessel model is shown by equation (8).

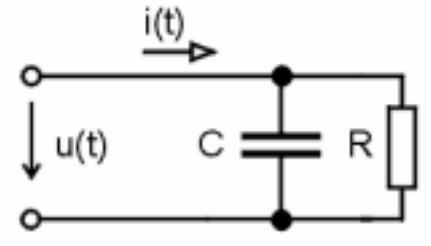

Figure 8: Two-element Windkessel Model [51]

$$\boldsymbol{i_1(t) = \frac{u(t)}{R} + C\frac{du(t)}{dt}} \qquad \textbf{(7)}$$

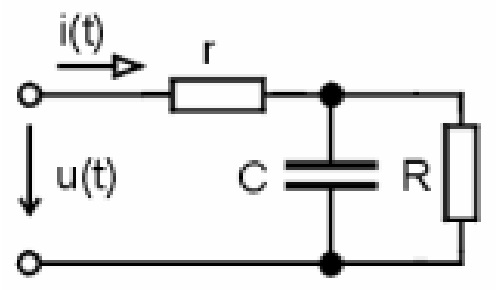

Figure 9: Three-element Windkessel Model [51]

$$\boldsymbol{i_1(t) = \frac{u_c(t)}{R} + C\frac{du_c(t)}{dt}} \quad \textbf{(8)}$$

The four element Windkessel model is the last of the basic models that used to model the cardiovascular system. A four element Windkessel model considers not only the same considerations of the other two Windkessel models, but also incorporates an inductor to represent inertia of blood flow. This model is shown in Figure 10. This model can be defined by equation (9)

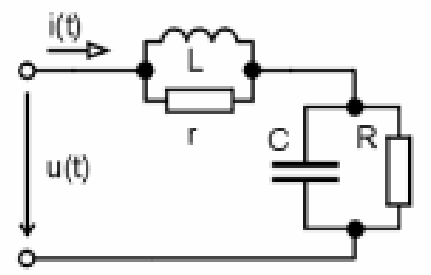

Figure 10: Four-element Windkessel Model [51]

$$\frac{du_C(t)}{dt} = -\frac{1}{RC}u_C(t) + \frac{1}{C}i_1(t)$$
$$\frac{di_L(t)}{dt} = -\frac{r}{L}i_L(t) + \frac{r}{L}i_1(t) \quad \textbf{(9)}$$

The pulmonary and systemic circulations can be modelled by formulating a network of Windkessel models. The pulmonary and systemic circuits can be broken down into four components including the arteries, arterioles, capillaries, and veins. These individual components can be described as simple Windkessel models depending on the behavior of the blood vessel. The electrical components can be combinations or singular electrical components including (i) a resistor due to the resistance of the blood vessel walls, (ii) a capacitor due to the ability of the larger vessels to hold blood, and finally (iii) an inductor that accounts for the inertia characteristic of blood. The arteries are modelled similar to the four element Windkessel models where a combination of an inductor, capacitor, and resistor are used to model the behavior of the blood flow through these vessels. The intermediate sections of the cardiovascular network includes arterioles that are modeled by a component that includes a resistor and a capacitor for their comparable properties to the larger blood vessels, but pulsatility has less of an effect on the blood flow through these vessels. Therefore, the inductor is omitted from this component. The third component is the capillaries, which are represented by strictly a resistive element due to the decrease in elasticity of the vessels as the cardiovascular system branches into the blood vessels with extremely small diameters. The final component that is represented by the lumped parameters is the veins and the vena cava, which is modeled as a capacitor and a resistor. Veins and the vena cava are larger blood vessels similar to arteries, but blood flow is not driven by the pulsatility of the heart, so this component contains a resistor and capacitor for similar reasons to the arteries but lacks the inductor component due to this lack of pulsatility serving as a driving force. Blood flow at this point is driven through these vessels from the lower pressure that is maintained upon the return of the blood to the right side of the heart. An example of deriving equations for an element shown in Figure 11, the systemic arteries highlighted by the green box, can be seen below. Equation (10) is an algebraic equation

which is used for the *Rsat* resistor while (11) and (12) are differential equations used for the *Csat* and *Lsat* components respectively.

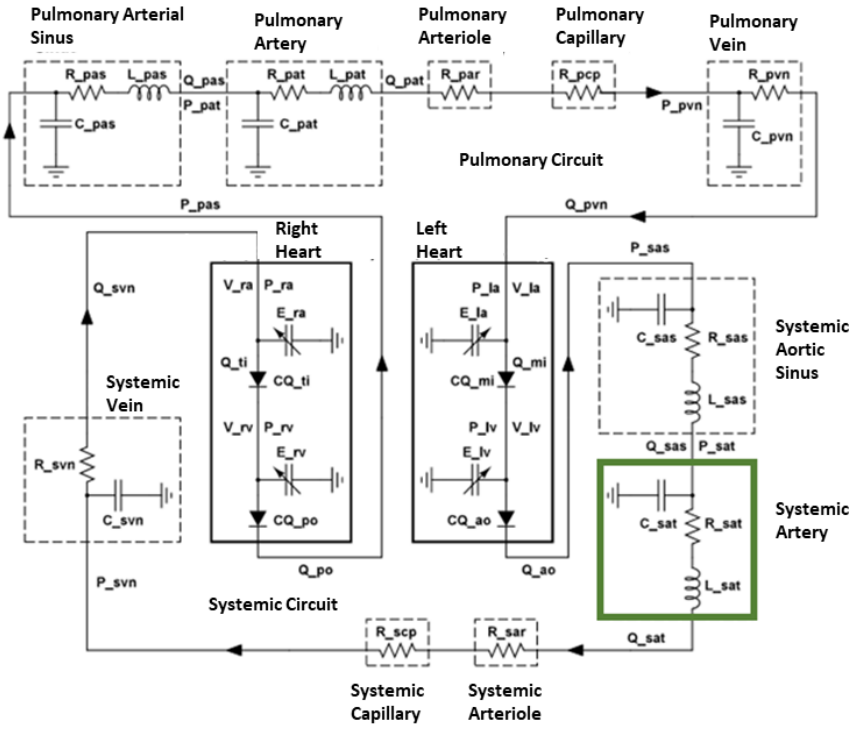

Figure 11: The lumped parameter model with its electrical components.[52]

$$\boldsymbol{P_{sat} - P_{svn} = Q_{sat} * (R_{sat+sar+scp}) => Q_{sat} = \frac{P_{sat} - P_{svn}}{R_{sat+sar+scp}}} \quad \textbf{(10)}$$

$$\boldsymbol{Q_{sas} - Q_{sat} = C_{sat} * \frac{dP_{sat}}{dt} => \frac{dP_{sat}}{dt} = \frac{Q_{sas} - Q_{sat}}{C_{sat}}} \quad \textbf{(11)}$$

$$\boldsymbol{P_{sat} - P_{svn} = L_{sat} * \frac{dQ_{sat}}{dt} => \frac{dQ_{sat}}{dt} = \frac{P_{sat} - P_{svn}}{L_{sat}}} \quad \textbf{(12)}$$

The heart serves as a source of pressure and flow. The four chambers of the heart are represented by two time-varying elastance functions that are respective to the right and left side with an equation for the ventricles and atriums. These functions relate pressure and volume to model functionality of the chambers within the LPM. The functions can be seen by equation (13). [52] A graph of the time varying elastance functions is shown in Figure 12.

The graph shows the behavior of the left ventricle where filling occurs (diastole) until the maximum elastance is reached. Upon reaching maximum capacity, the blood flow must be directed elsewhere, the left ventricle contracts (systole) and the blood empties, circulating throughout the rest of the body. The buildup of pressure caused by the filling of the left ventricle leads to the activation of the aortic valve. In general, the valves are modeled as diodes where flow only occurs in one direction given the pressure in the left ventricle has exceeded the pressure in the aorta (for the aortic valve). The model also includes flow from the aortic valve and the pulmonary valve to the aortic and pulmonary arterial sinuses by a capacitor, resistor, and inductor combination due to the ability to hold blood, provide resistance, and inertial propulsion of blood from the effect of pulsatility.

(13)

$$\begin{aligned}
\frac{dV_{la}}{dt} &= Q_{pvn} - Q_{mi}, \\
P_{la} &= P_{la,un} + E_{la}(V_{la} - V_{la,un}), \\
Q_{mi} &= \begin{cases} CQ_{mi}AR_{mi}\sqrt{P_{la} - P_{lv}}, & \text{if } P_{la} \geq P_{lv}, \\ -CQ_{mi}AR_{mi}\sqrt{P_{lv} - P_{la}}, & \text{if } P_{la} < P_{lv}, \end{cases}
\end{aligned}$$

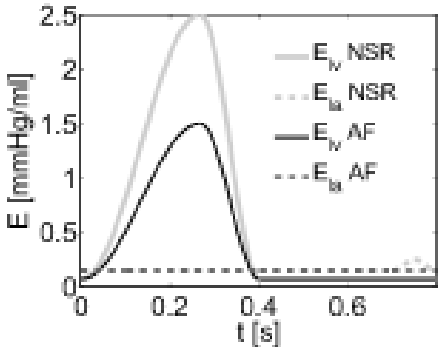

Figure 12: The left heart elastances (light color) with a cardiac cycle of 0.8 s. Left atrium (la), left ventricle (lv) and normal sinus rhythm (NSR) [52]

2.1.2 The Foundation for the Model

The LPM is implemented using an in-house developed code in MATLAB that is formulated by 27 equations that all describe the components that are being modelled. The built in MATLAB DAE4 solver is used to solve the 27 equations, which allows for the user

to assess pressure and flows at any specific location or point in time in the model.[53],[54] The DAE4 solver utilizes a Jacobian matrix to correlate variables to their derivatives, serving as a connectivity matrix between the system variables. A system constants file defines the lumped parameters (resistance, capacitance, and inductance) for each electrical component. The initial conditions are set to provide initial conditions (guesses) for initiating solving the system of equations. The differential algebraic equations are solved simultaneously utilizing these mentioned components. The lumped parameter model in its entirety is comprised of the DAE4 solver as well as its components (system constants and initial conditions files). The lumped parameter model stores the solution at the prespecified time steps in a matrix, which is then accessed for postprocessing. The initial conditions that are used to give the DAE4 solver a starting point are shown in

Table 1. The parameters for the heart, systemic, and pulmonary circulations are shown in Table 2.

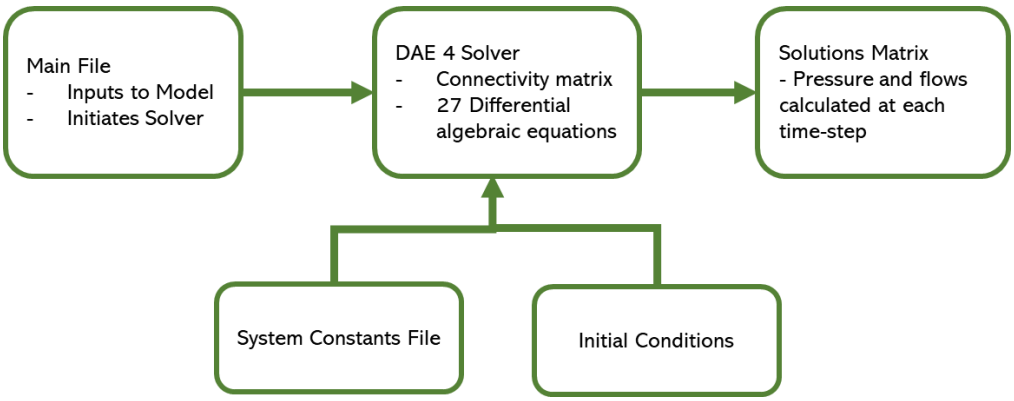

Figure 13: The flow pathway for LPM algorithm

Table 1: Initial Conditions pressures, volumes, and flows for model components [52]

Variable	**Value (t = 0)**
$V_{la,0}$	60 ml
$V_{lv,0}$	130 ml
$V_{ra,0}$	39 ml
$V_{rv,0}$	110 ml
$P_{sas,0}$	100 mm Hg

$Q_{sas,\ 0}$	0 ml/s
$P_{sat,0}$	100 mm Hg
$Q_{sat,0}$	0 ml/s
$P_{svn,0}$	10 mm Hg
$P_{pas,0}$	20 mm Hg
$Q_{pas,0}$	0 ml/s
$P_{pat,0}$	20 mm Hg
$Q_{pat,0}$	0 ml/s
$P_{pvn,0}$	10 mm Hg

Table 2: Values used for model components including systemic, pulmonary, heart, and valve parameters [52]

	Parameter	**Value**
Heart	CQ_{ao}	350 ml/(s mm Hg^0.5)
	CQ_{mi}	400 ml/(s mm Hg^0.5)
	$E_{lv,max}$	2.5 mm Hg/ml
	$E_{lv,min}$	0.07 mm Hg/ml
	$P_{lv,un}$	1 mm Hg
	$V_{lv,un}$	5 ml
	$E_{la,max}$	0.25 mm Hg/ml
	$E_{la,min}$	0.15 mm Hg/ml
	$P_{la,un}$	1 mm Hg
	$V_{la,un}$	4 ml
	CQ_{po}	350 ml/ (s mm Hg^0.5)
	CQ_{ti}	400 ml/ (s mm Hg^0.5)
	$E_{rv,max}$	1.15 mm Hg
	$E_{rv,min}$	0.07 mm Hg/ml
	$P_{rv,un}$	1 mm Hg
	$V_{rv,un}$	10 ml
	$E_{ra,max}$	0.25 mm Hg/ml
	$E_{ra,min}$	0.15 mm Hg/ml
	$P_{ra,un}$	1 mm Hg
	$V_{ra,un}$	4 ml
Systemic	C_{sas}	0.08 ml/mm Hg
	R_{sas}	0.003 mm Hg s/ml
	L_{sas}	0.000062 mm Hg s^2/ml
	$P_{sas,un}$	1 mmHg

	$V_{sas,un}$	25 ml
	C_{sat}	1.6 ml/mm Hg
	R_{sat}	0.05 mm Hg s/ml
	L_{sat}	0.0017 mm Hg s/ml
	$P_{sat,un}$	1 mm Hg
	$V_{sat,un}$	775 ml
	R_{sar}	0.5 mm Hg s/ml
	R_{scp}	0.52 mmHg s/ml
	R_{svn}	0.075 mm Hg s/ml
	C_{svn}	20.5 ml/mm Hg
	$P_{svn,un}$	1 mm Hg
	$V_{svn,un}$	3000 ml
Pulmonary	C_{pas}	0.18 ml/mm Hg
	R_{pas}	0.002 mm Hg s/ml
	L_{pas}	0.000052 mm Hg s^2/ml
	$P_{pas,un}$	1 mm Hg
	$V_{pas,un}$	25 ml
	Cpat	3.8 ml/mm Hg
	Rpat	0.01 mm Hg s/ml
	L_{pat}	0.0017 mm Hg s/ml
	$P_{pat,un}$	1 mm Hg
	$V_{pat,un}$	175 ml
	R_{par}	0.05 mm Hg s/ml
	R_{pcp}	0.07 mm Hg s/ml
	R_{pvn}	0.006 mm Hg s/ml
	C_{pvn}	20.5 ml/mm Hg
	$P_{pvn,un}$	1 mm Hg
	$V_{pvn,un}$	300 ml
Valve Dynamics	T_{ac}	0.875 RR s
	T_{me}	0.3 (RR)^1/2 s
	T_{ce}	3.2 Tme s

2.1.3 Incorporating the LVAD into the Cardiovascular System LPM

There are several types of LVADs including the HeartMate3 (Abbott), HVAD (Medtronic, now discontinued), and EVAHEART (Evaheart Inc). The first generation of LVADs were pulsatile pumps but were not durable given the mechanical loading of having a pulsatile pump while also having to maintain flow through the patient especially in long term treatments as patients needing destination therapy over a bridge to transplant treatment grows.[55] The second generation of LVADs were continuous flow pumps. These pumps feature an impeller that is driven by a power source, that sucks in the blood from its inflow cannula, through the LVAD to the outflow cannula. For this research, third-generation centrifugal LVADs are analyzed. were installed in patients with the inflow cannula beginning in the left ventricle followed by the impeller/pump mechanism leading to the ascending aorta where the outflow cannula is inserted. Refer to Figure 14 and Figure 15 for how the LVAD is implanted into the heart and the pathway blood flow takes throughout the LVAD. [56],[57]

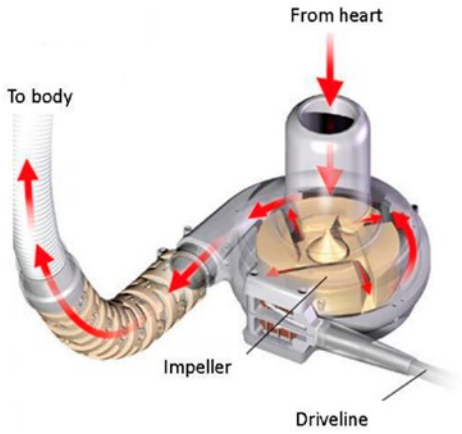

Figure 14: The impeller inside a centrifugal pump (LVAD) is shown, which directs blood from the left ventricle to the aorta

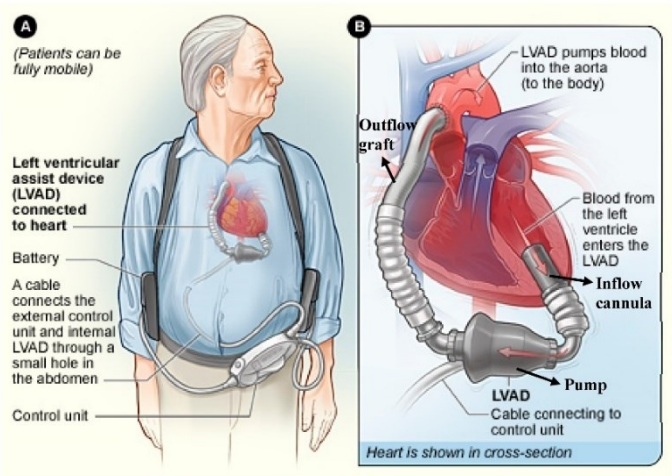

Figure 15: The implantation of an LVAD and its relevant components contained inside and outside of the patient

The LVAD's speed can be adjusted by external controllers that cause the impeller to rotate at specific revolutions per minute. The pump is continuously pulling blood from the left ventricle to the aorta, which is how the pump delivers blood throughout the body given the heart's inability to do so on its own. LVADs operate the same way, but their construction differs based on the manufacturer. These different constructions of the LVAD result in different operating conditions for each LVAD. The manufacturer runs experiments that include running the pump as different speeds producing certain flows an find the pressure head (preload - afterloads) that occur over the pump operation, thus obtaining the pump pressure-flow (H-Q) curves. The H-Q curves describe the flow that occurs through the LVAD at any operating speed specified by the user given the pressures experienced at the inlet and outlet of the LVAD. Typically, manufacturers obtain the pump performance curves (i.e. H-Q curves) by conducting benchtop mock loop tests under static conditions. Pressure sensors and flow sensors are placed to determine the pressure flow relationships given different operating speeds. LVAD nominal speed is based on LVAD design and impeller. These pressure-flow relationships based on bench top from the pump's H-Q curves can be used to incorporate the pump's behavior into the LPM model for the cardiovascular system, as described below.

The H-Q curves are obtained from the manufacturer of the device. For a selected speed, the flows *[L/min]* and respective pressure heads *[mmHg]* for manufacturer-specified H-Q curves are provided as inputs to a dedicated MATLAB function. Given the self-similar behavior of centrifugal pump H-Q curves, a custom algorithm extracts the relevant H-Q curve parameters for a desired LVAD speed (even if it is not provided by the manufacturer) using standard pump affinity laws. [58] The affinity laws of a pump indicate the influence the change in speed of the LVAD influences the volume capacity and head (pressure), equations (14) and (15) show the pump affinity laws for a specific centrifugal pump to obtain volume capacity and head of the pump.

$$\textbf{(Volume Capacity)}\ \frac{q_1}{q_2} = \frac{n_1}{n_2} * \frac{d_1}{d_2} \qquad \textbf{(14)}$$

$$\textbf{(Head)}\ \frac{dp_1}{dp_2} = \left(\frac{n_1}{n_2}\right)^2 * \left(\frac{d_1}{d_2}\right)^2 \qquad \textbf{(15)}$$

q = volume flow capacity

n = wheel velocity or revolution per minute

d = wheel diameter

dp = head or pressure

The pump affinity laws utilize the ratio between the known speed and the desired speed to obtain the performance curve at the desired speed. The user specifies an order for the polynomial to obtain the best fit of the curve using the *polyfit* MATLAB function.[59] These coefficients are provided in the system parameters file of the code where the speed calculation can be carried through to the equations used for solving for flows and pressures where the LVAD is implemented in the model, the left ventricle, and the aorta. Using this method, the H-Q curves allow the model to calculate any operating speeds not explored experimentally. The model uses the pressure flow curves in conjunction with the other electrical components to allow for the pressure and flow to be calculated throughout the system preceding and following each component of the model. In this research, the LVAD is placed in parallel with the aortic valve to allow for blood flow through the aortic valve

when possible. When pressure is high enough in the left ventricle as calculated by the model to overcome or outweigh the pressure in the aorta the aortic valve is opened, and flow can pass through it (flow is no longer set to zero). Please refer to Figure 17, for a comprehensive look at the complete model of the cardiovascular system with LVAD support.

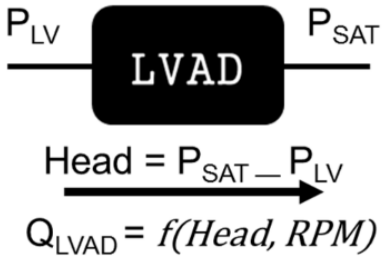

Figure 16: LVAD pump parameters in LPM governed by preload (LV pressure) and afterload (aortic pressure) P_{LV}: left ventricular pressure, P_{SAT}: pressure in the aortic arch

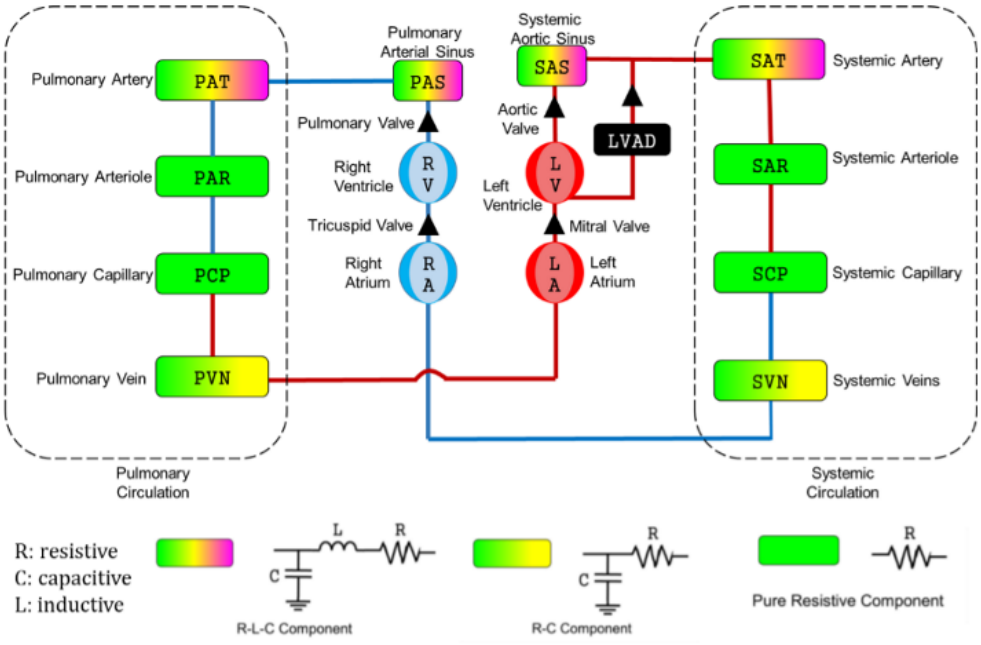

Figure 17: This figure shows the lumped parameter model in its entirety including the systemic and pulmonary circulations, LVAD support, as well as the pulmonary and systemic arterial/aortic sinuses, the four chambers of the heart, and the four valves.

Chapter 3
Optimization

In this chapter, an in-house developed optimization algorithm is explored and applied to clinically relevant patient data to better understand the pump-patient interplay. The first set of data comes from the University of Washington Medical Center in Seattle, WA, USA where patients are supported by the HVAD, and the other data set comes from the San Camillo Hospital in Rome, Italy, where patients are maintained by the HM3. The goal of performing optimization is to improve patient outcomes. Furthermore, we expect to gain a perspective on trends that can give clinicians an indication of which patients would benefit the most from optimization.

3.1 Preparing the Model for Optimization

Optimization is performed in three phases which includes specifying the model to the patient, performing virtual map management, and conducting speed optimization. The phases are outlined by Figure 18. The first phase involves utilizing patient specific parameters obtained from clinicians. These parameters serve as inputs to the model allowing

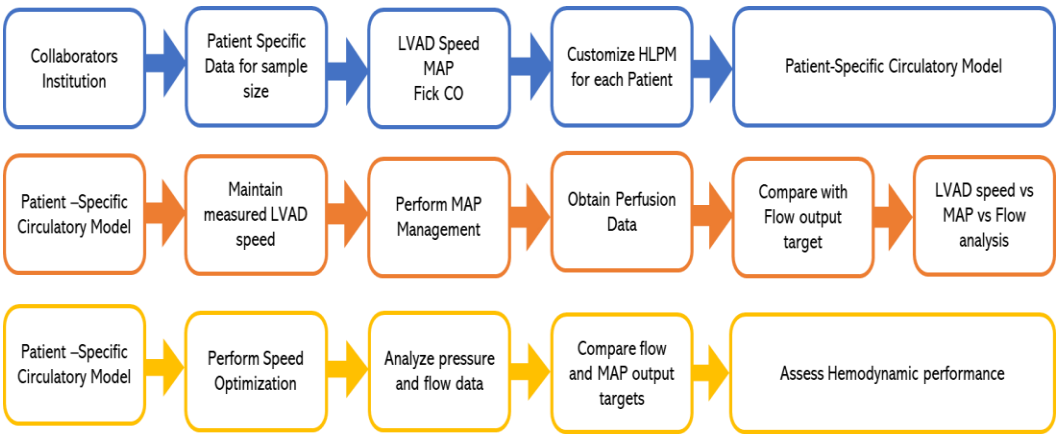

Figure 18: The three phases for optimizing pump-patient interplay using patient specific data

for the model to match the most important hemodynamic parameters, specifically pressure and flows obtained to those described by clinicians.

This patient specific model is then utilized in the subsequent phases to predict what vascular resistance and LVAD speed allows for the patient to meet clinician-specified hemodynamic targets. The second phase explores the effects that blood pressure management alone may have on the patient in terms of meeting MAP and flow targets. The third and final phase allows for manipulation of LVAD speed and vascular resistance to assess not only the effect of manipulating these parameters may have on the patient's hemodynamic performance, but also to find the best operating conditions that would best suit the patient.

3.2 Ability to Specify the Model to the Patient

The ability to specify the model to the patient is vital for investigating the pump-patient interplay as well as being able to draw conclusions from observed results regarding the possible ways in which a patient's cardiovascular system responds to the changes we may make. Previous models have failed to incorporate specification of the model using patient specific values leading to erroneous interpretations and invalid conclusions.

When specifying the model to the patient, the contractility of the left ventricle (Elv_max) provides the model with a quantifiable measurement of the degree of heart failure the patient has. The vascular resistance (VR) parameter provides insight into the dilation / contraction of the blood vessels. To determine the values of the vascular resistance and contractility, the steps are to evaluate a range of these values and compare the outputs of the model to those obtained by clinicians. The vascular resistance and contractility that match up to +/- 5% of what was recorded by the clinicians is used to specify the model to the patient.

To do this the user provides the model with an Excel sheet containing patient data recorded by the clinicians. The model defines the recorded parameters as the targets for the cardiac output (CO) and mean arterial pressure (MAP) as well as defines the LVAD speed

for each patient. The code then uses the H-Q curves to produce coefficients for each patient's specific LVAD speed; this is provided to the solver via the system constants file. The solver proceeds to simultaneous solve the equations over the given span of time. The lumped parameter model computes the solution matrix for each value of the vascular resistance and contractility over a prespecified range of plausible values. The CO and MAP obtained from the model for each iteration of the vascular resistance and the Elv_max values are compared to the targets during post processing of the solution matrix. The VR and Elv_max values that are found to meet the target flow rates and MAPs are used for the patients throughout the remaining phases of optimization of LVAD treatment. The specification algorithm takes 15 seconds per patient. Please refer to Figure 19 for an overview of the pathway the algorithm takes for specifying the model to the patient.

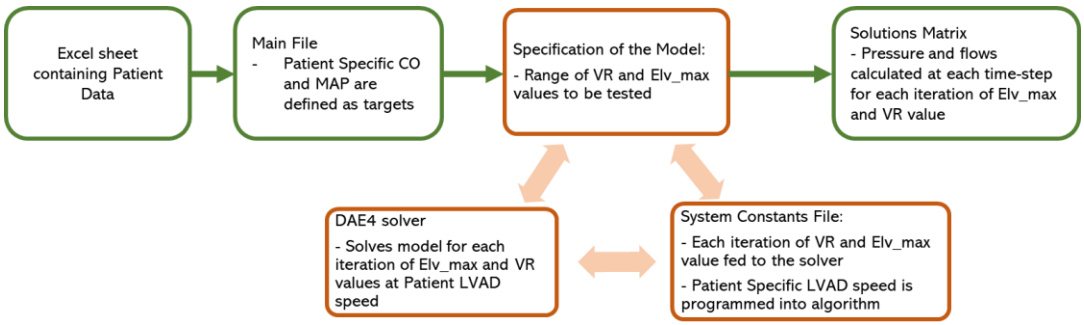

Figure 19: The flow path the algorithm takes when customizing the hemodynamic lumped parameter model for each patient

3.3 Performing Optimization

Clinicians only have two options for hemodynamically optimizing a LVAD-implanted patient, these options are to perform MAP management or adjusting the speed of the LVAD. When performing MAP management, the clinician can prescribe vasodilators or vasoconstrictors to the patient to either bring up or lower the patient's blood pressure. The effect of a vasoconstrictor would be an increase in pressure (increasing resistance), thereby decreasing blood flow. The opposite effect happens when vasodilators are given to the patient. The blood vessels dilate causing a drop in blood pressure and less resistance to blood

flow. Adjustments made to the LVAD speed can either increase or decrease the pulling of the blood from the left ventricle causing the CO to rise or fall. When adjustments are made to the vascular resistance the MAP of the patient is affected. When making changes to either of these options, the effects of these changes are intertwined; therefore, understanding the relationship between blood flow, pressure, and LVAD speed is vital. Optimization begins with phase I, specifying the model to the patient, while phases II and III explore the pump-patient interaction with the patient specific model. Phase II explores virtual MAP management at a constant speed followed by Phase III performing speed optimization in conjunction with MAP manipulation.

When performing Phase II, the patient specific model is used from phase 1 (the Elv_max value is maintained), the LVAD speed is left unchanged, and the vascular resistance is manipulated to meet the MAP target. The same procedure followed in phase I is used for phase II, with only the VR value being changed. The solution matrix is post processed to ensure the MAP obtained is within +/- 5% of the target MAP. Furthermore, the CO is analyzed to see if patients overshoot or undershoot the flow target. Please refer to Figure 20, for an overview of the algorithm pathway completed during phase II.

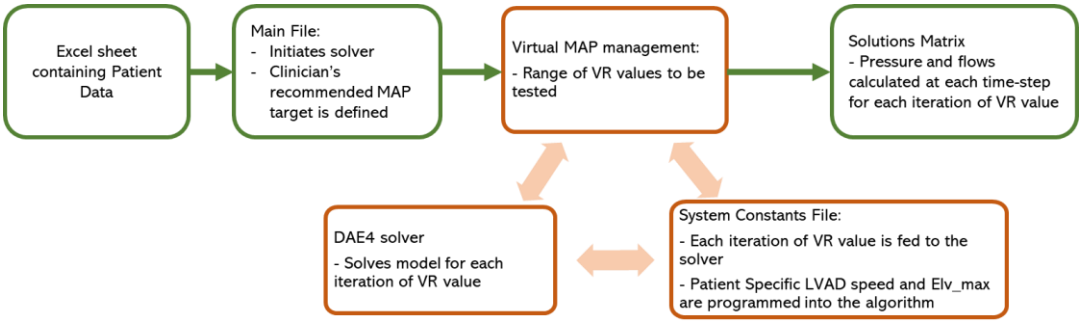

Figure 20: The pathway the algorithm takes for performing phase II virtual MAP management for each patient

The final phase of speed optimization is finding the most optimal speed to assess the effects that both MAP management and speed optimization have on the MAP and CO. Optimization is performed using a built-in MATLAB function called *lsqnonlin*, which uses a non-linear least squares approach applied to a cost function to determine the optimal speed

and vascular resistance that results in a hemodynamically optimized virtual patient.[60] The cost function is formulated to minimize the difference between the values obtained from the model and the target values for MAP and flow. The non-linear least squares approach includes minimizing the output of the cost function, providing a quantifiable way for the lsqnonlin function to provide direction and size of adjustment needed, Refer to equations (16-18) for a description of the least squares method.

$$\min(\sum||F(x_i) - y_i||^2) \tag{16}$$

$$\min_x \|f(x)\|_2^2 = \min_x \left(f_1(x)^2 + f_2(x)^2 + \ldots + f_n(x)^2\right) \tag{17}$$

$$f(x) = \begin{bmatrix} f_1(x) \\ f_2(x) \\ \vdots \\ f_n(x) \end{bmatrix}. \tag{18}$$

The optimization function *lsqnonlin* determines how to change the LVAD speed and vascular resistance based on each iteration of the optimization. The process begins by initializing the model with the patient data obtained in phase II including the VR value that met the MAP target, the LVAD speed and Elv_max that specified the model to the patient. The solver solves the lumped parameter model with these values. The optimization function then begins assessing the difference in obtained values to target values using the cost function. Following this the optimization function adjusts the LVAD speed and vascular resistance in an iterative manner just as the clinician would in a clinical setting. This process repeats until both targets are met and upon completion the information is stored into a solution matrix that can be analyzed for further post processing. The in-house developed optimization algorithm comprised of the three phases previously mentioned takes under 10 mins per patient. An overview of the final phase can be seen in Figure 21.

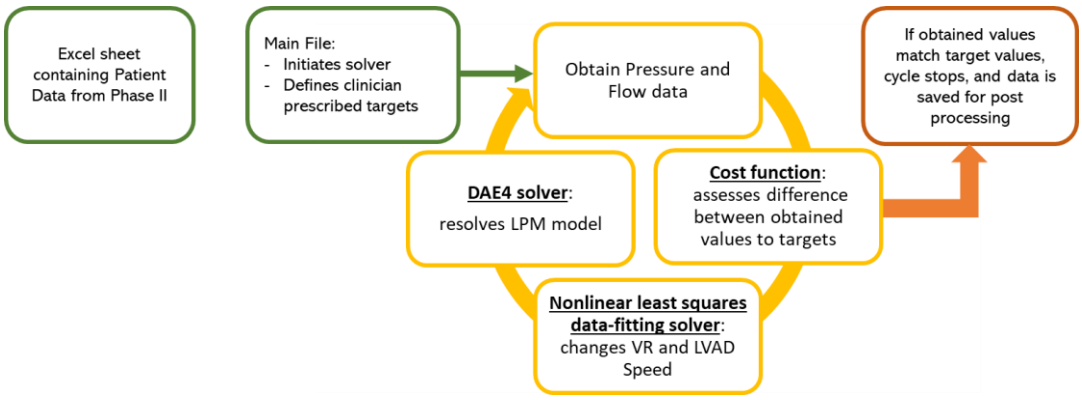

Figure 21: Algorithm pathway for the final phase of optimization

3.4 Optimization Using Patient Data

3.4.1 Investigating University of Washington Medical Center Patient Cohort

Hemodynamic patient data include those who underwent LVAD (Medtronic HVAD) implantation at the University of Washington Medical Center (UWMC) between January 2015 and April 2018 was analyzed retrospectively after de-identification, with IRB approval. Pressure flow curves for the HVAD are shown in Figure 22.

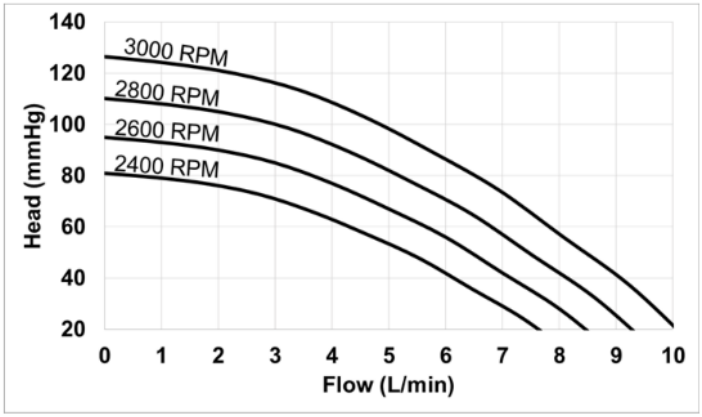

Figure 22: Schematic of LVAD pressure-flow characteristics (Courtesy of Medtronic).

61 patients for whom right heart catheterization was performed for invasive hemodynamics measurements (Fick CO, thermodilution CO, pulmonary system pressures and MAP) were included for comparison in our study. LVAD operational speeds that were recorded on the same day (within a few hours) of the cardiac catheterization procedure were used for this study. Clinicians at UWMC recommended patients to have a MAP of 70 mmHg and CO of 5 L/min. All patients were clinically stable at the time of data collection, including VAD speed, mean arterial pressure, and antihypertensive regimen. Patients were then classified into four major categories: (i) cat 1: those with MAP > 70 mmHg and CO > 5 L/min, (ii) cat 2: those with MAP > 70 mmHg and CO < 5 L/min, (iii) cat 3: those with MAP < 70 mmHg and CO < 5 L/min and (iv) cat 4: those with MAP < 70 mmHg and CO > 5 L/min, to quantify the interplay between performing MAP management while maintaining LVAD speed, and its influence on CO.

For all 61 patients, phases I thru III were completed. Phase 1 included creating a customized patient-specific model for each patient that mimicked hemodynamics (specifically measured MAP, CO and LVAD speed), using multiple iteration-based customization techniques. Using the customized patient-specific model for each patient, Phase 2 was performed, where MAP was managed by changing the systemic vascular resistance until MAP reached a target of 70 ± 2 mmHg. The change in CO due to MAP management, while maintaining LVAD speed, was compared to a target flow of 5 L/min, determining the overshoot / undershoot of CO. After MAP management, the patient models were classified into those with CO > 5 L/min (overshoot category) and those with CO < 5 L/min (undershoot category). Phase 3: speed optimization was performed on all patients following MAP management where hemodynamic optimization was assessed. A schematic of this analysis is shown in Figure 23. All analysis was performed in MATLAB® (MathWorks Inc., Natick, MA, USA).

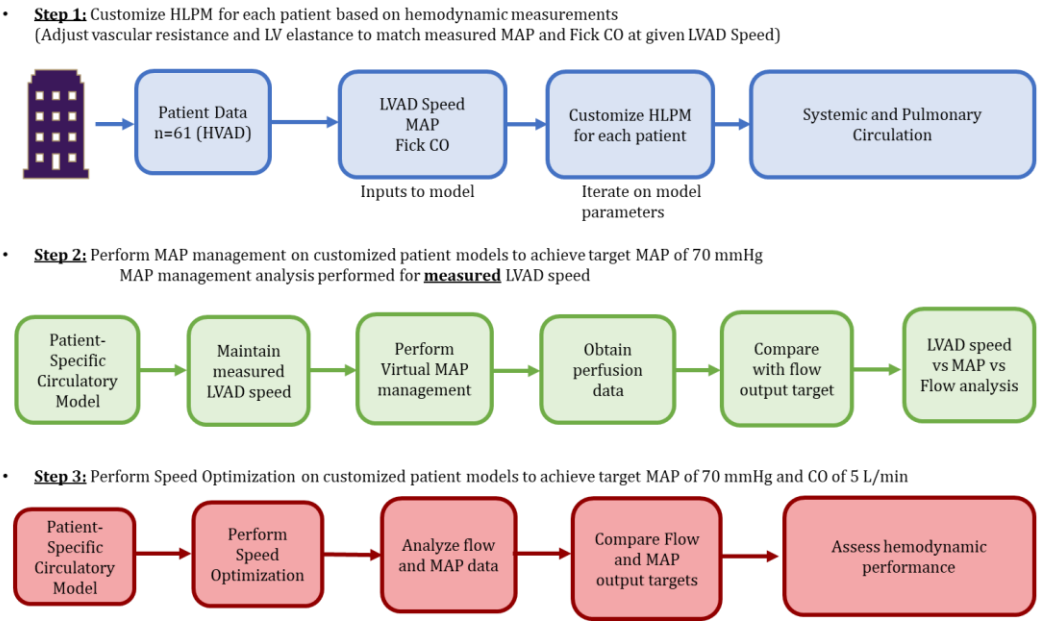

Figure 23: Patient-specific analysis workflow

3.4.1.1 Results

Of the 61 patients whose data was analyzed, 31 patients (51%) initially had a MAP > 70 mmHg and CO > 5 L/min (max MAP of 110 mmHg, max CO of 8.19 L/min). 20 patients (33%) initially had a MAP > 70 mmHg and CO < 5 L/min, (minimum CO of 3.04 L/min). Thus, nearly 84% of the patients had a MAP > 70 L/min. Table 3 indicates the distribution of patients in all four categories defined earlier.

Table 3: Distribution of patients based on MAP and CO as measured. MAP: Mean Arterial Pressure, CO: Cardiac Output

	MAP > 70 mmHg	**MAP < 70 mmHg**
CO > 5 L/min	31 (51%) Cat 1	9 (15%) Cat 4
CO < 5 L/min	20 (33%) Cat 2	1 (1%) Cat 3

LVAD speeds ranged from 2320 RPM to 3080 RPM. Figure 24 shows the scatter plot of MAP, CO and LVAD speeds. Barring four patients, the remaining 57 patient parameters did not closely match both MAP and flow targets.

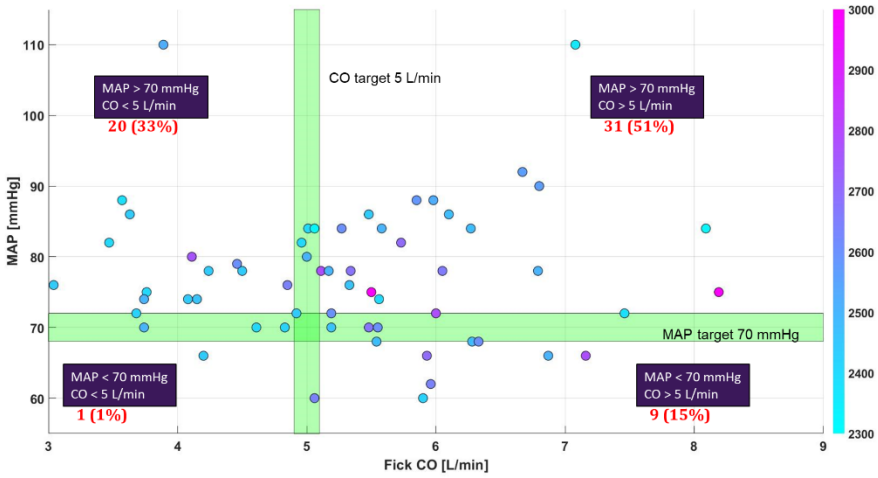

Figure 24: Distribution of hemodynamic parameters MAP, Fick CO and LVAD speed measured in 61 LVAD patients at the UWMC

After patient model customization and virtual MAP management, while keeping LVAD speed constant, the hemodynamic conditions for every patient with an initial MAP > 70 mmHg shifted towards the right on the MAP-Flow scatter (see Figure 25). Of the 61 patients, 51 patients (84%) overshot the CO target, resulting in a CO > 5 L/min. 10 patients (16%) undershot the CO target and had a final CO < 5 L/min, as indicated in Table 4.

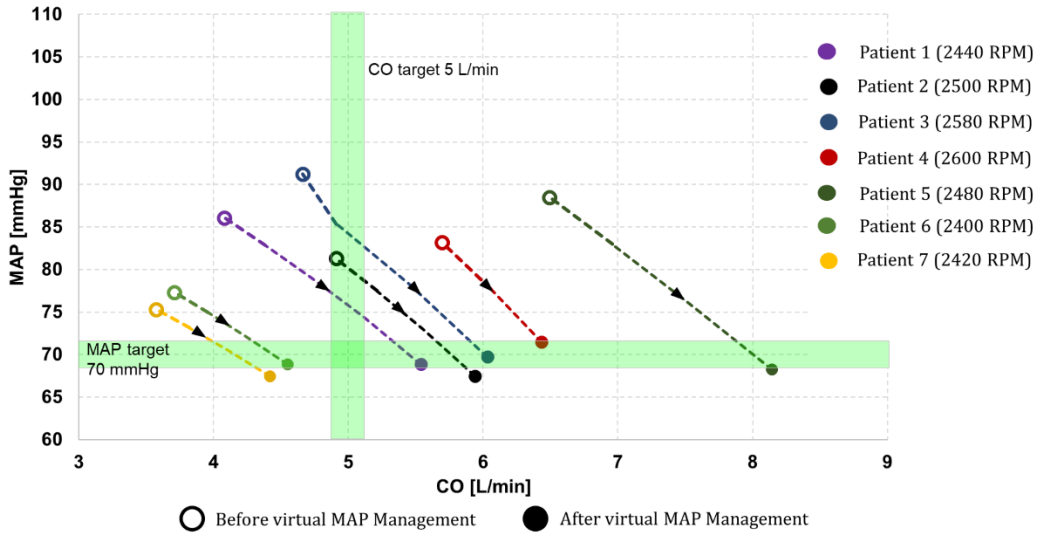

Figure 25: Shifting LVAD operating point after MAP management for representative patients, indicating overshoot for patients 1-5 and undershoot for patients 6 and 7, depending on their LVAD speed and pre-MAP management parameters. Note: Hollow circles indicate pre-MAP management condition. Filled circles indicate hemodynamic operating point after virtual MAP management

Table 4: Percentage of patients undershooting or overshooting CO target after virtual MAP management was performed. MAP: Mean Arterial Pressure, CO: Cardiac Output

Category	# of Patients (%)
MAP ~ 70 mmHg and CO > 5 L/min **(Overshoot)**	51 (84%)
MAP ~ 70 mmHg AND CO < 5 L/min **(Undershoot)**	10 (16%)
Total	61 (100%)

Among the 51 overshoot patients, median CO was 6.79 L/min, a 35.8% overshoot. Among the undershoot patients, median CO was 4.61 L/min. Arrows in Figure 25 show the direction of change in hemodynamics for five representative overshoot patients (patient #s 1-5), with the resulting CO considerably higher than the 5 L/min target, and for two representative undershoot patients (patient #s 6 and 7). LVAD speeds for each patient are indicated in Figure 25. Figure 26 shows the resulting hemodynamics for all 61 patients after virtual MAP management.

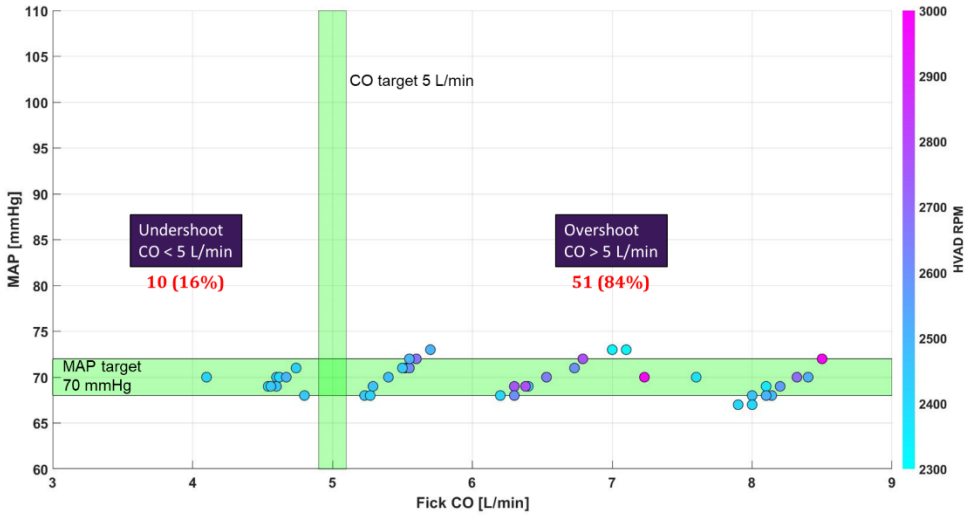

Figure 26: Distribution of CO for all 61 patients after patient customization and virtual MAP management. 51 patients overshot CO target.

Upon performing speed optimization, manipulating the LVAD speed and VR, 76% of patients needed their speeds to be reduced to meet MAP and flow targets. A median speed change of -76 RPM and a standard deviation of 150 RPM were predicted by the model to hemodynamically optimize the virtual patient models. Table 5: The spreadsheet of patient data before and after speed optimization shows the speeds before and after speed optimization as well as the amount of change needed to optimize each patient. Figure 27 illustrates the predicted change in speed needed to optimize all 61 patients.

Table 5: The spreadsheet of patient data before and after speed optimization

Patient Index	Original Speed	Final Speed	Change in Speed
1	2420	2544	124
2	2640	2544	-96
3	2440	2362	-78
4	2680	2544	-136
5	2680	2517	-163
6	2440	2506	66
7	2480	2409	-71
8	2600	2363	-237
9	2500	2365	-135
10	2760	2544	-216
11	2460	2532	72
12	2440	2393	-47
13	2440	2425	-15
14	2560	2365	-195
15	2520	2394	-126
16	2480	2393	-87
17	2660	2365	-295
18	2480	2393	-87
19	2580	2394	-186
20	2700	2394	-306
21	2780	2376	-404
22	2700	2376	-324
23	2560	2394	-166
24	2480	2394	-86
25	2520	2436	-84
26	2420	2394	-26
27	2420	2449	29
28	2600	2544	-56
29	2400	2487	87
30	2400	2393	-7
31	2640	2544	-96
32	2780	2544	-236
33	2780	2544	-236
34	3080	2360	-720
35	2320	2364	44

36	2460	2426	-34
37	2400	2393	-7
38	2500	2394	-106
39	3000	2543	-457
40	2320	2365	45
41	2440	2366	-74
42	2600	2544	-56
43	2600	2411	-189
44	2600	2544	-56
45	2400	2512	112
46	2380	2393	13
47	2360	2436	76
48	2380	2387	7
49	2460	2393	-67
50	2440	2544	104
51	2500	2544	44
52	2440	2366	-74
53	2500	2544	44
54	2500	2393	-107
55	2400	2393	-7
56	2500	2394	-106
57	2400	2364	-36
58	2400	2393	-7
59	2440	2523	83
60	2500	2365	-135
61	2600	2394	-206

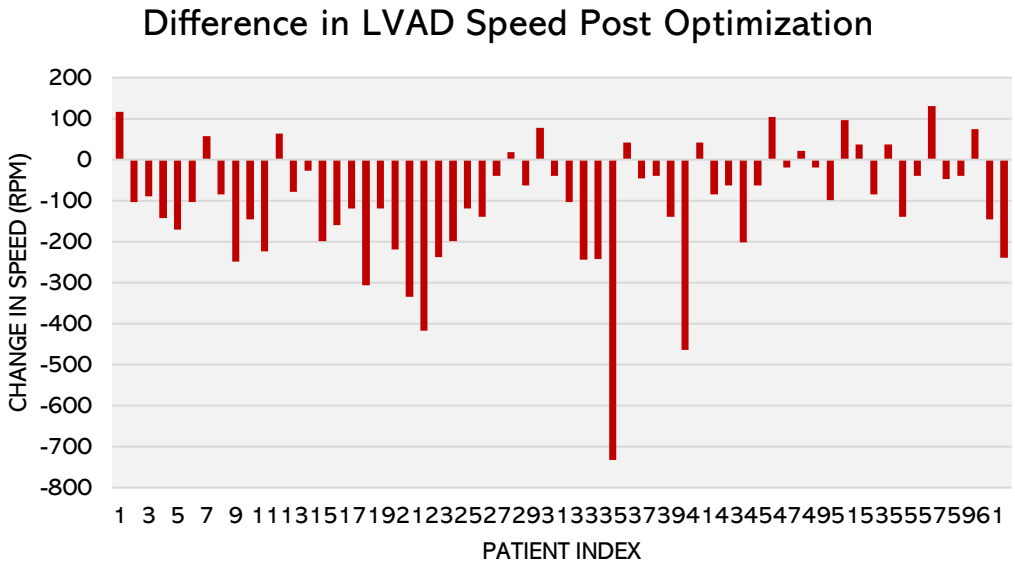

Figure 27: The difference in LVAD speed post optimization

Figure 28 shows all 61 patients at their initial starting point prior to optimization, where the size of the data points indicates the magnitude of speed change needed for each patient, whereas the boundary of the data points indicates whether the patients needed their speeds to be reduced (black) or increased (red).

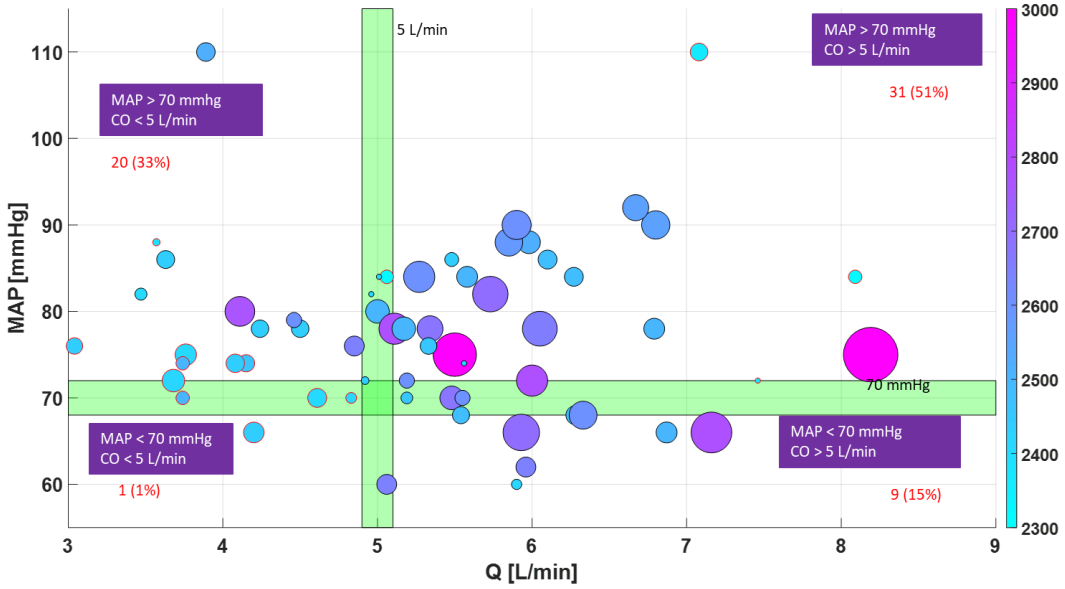

Figure 28: 61 patients at their initial starting point prior to optimization, where the size of the data points indicates the magnitude of speed change needed of each patient, whereas the boundary of the data points indicate whether the patients needed their speed to be reduced (black) or increased (red).

3.4.1.2 Discussion

Currently, there is no standardized procedure for optimizing LVAD speed settings to achieve hemodynamics objectives in LVAD patients. Optimizing LVAD speed is essential for achieving target MAP and flow; this optimization should be performed in a quantitative manner that considers the patient's circulatory response.[44] In this study, we implement a computational model of the cardiovascular system including the systemic and pulmonary circuits and each chamber of the heart. LVAD support is a novel aspect of the study, and it incorporates for the first time the LVAD pressure-flow relationships for multiple speeds. The LVAD/circulatory system response to performing MAP management is studied computationally for the first time, in a large cohort. Virtual patient MAP management was achieved by lowering the peripheral (systemic) vascular resistance, simulating

pharmacological blood pressure management. Furthermore, speed optimization is implemented by completing virtual MAP management in conjunction with LVAD speed optimization.

In this study, the patient cohort was divided into four classifications based on their measured MAP and Fick CO: (1) cat 1: those with MAP > 70 mmHg and Fick CO > 5 L/min, (2) cat 2: those with MAP > 70 mmHg and Fick CO < 5 L/min, (3) cat 3: those with map < 70 mmHg and Fick CO < 5 L/min and (4) cat 4: those with MAP > 70 mmHg and Fick CO > 5 L/min, as shown in Figure 4. No patient's hemodynamics matched both MAP and flow targets (4 patients had MAP and Fick CO close to both targets). 31 patients (51%) had a MAP > 70 mmHg and CO > 5 L/min, indicating a large proportion of patients potentially requiring hemodynamic optimization. Median values for MAP, CO and RPM were 77 mmHg, 5.3 L/min and 2500 RPM, respectively. There was poor correlation between LVAD speed, MAP and CO; this demonstrates the need to jointly consider the interplay between them, in addition to each patient's vascular characteristics, as key factors in determining optimal VAD settings.

The computational model was customized for each patient to replicate their LVAD speed, MAP and Fick CO, as a starting point for the analysis. Thus, 61 patient-specific models were created. Using each patient's model, MAP management was simulated by independently lowering or increasing the systemic vascular resistance to achieve the target MAP of 70 mmHg, keeping LVAD speed unchanged. The resulting CO was compared to a 5 L/min target. As shown in Figure 26, for all patients with initial high MAP, MAP management effectively moved the hemodynamics downward and to the right, depending on the level of lowered MAP, resulting in higher LVAD flows.

After MAP management, 51 patients (84%) overshot CO, with a median overshoot of approximately 35%, i.e., final predicted CO of 6.79 L/min. This phenomenon occurs due to the response of the LVAD to lower afterload, from lowered systemic vascular resistance. Second-generation LVADs, such as the Heartmate II (Abbott, St. Paul, MN, USA) were primarily axial flow pumps with a low dependency on afterload (and preload). The steep

pressure-flow curve of axial flow pumps enables supplying blood at high pressures, even at low-flow conditions, at the expense of increased risk of suction events. In contrast, the flatter pressure-flow relationship in current, third-generation centrifugal flow pumps such as the Heartmate III (Abbott, St. Paul, MN, USA) and HVAD (Medtronic, Minneapolis, MN, USA), cause large changes in flow rate due to relatively small changes in pre- and/or afterload.[61] Patient's blood pressure management is critical and needs to be taken into consideration when setting LVAD speed. For all patients in the overshoot category, this complex interdependence results in potentially excess flow that can have negative consequences on right heart health.[55],[14],[13],[11]

To understand this interdependency, a single representative patient was analyzed separately in detail. For this representative patient model, prior to implantation of the LVAD, the LV elastance was modified to represent heart failure (HF), resulting in a severely diminished CO to approximately 2 L/min. LVAD support (HVAD) at various speeds was then included in the model, and MAP management performed to match the target of 70 mmHg, as shown in Figure 29. Using the representative patient model, as LVAD speed increases, both MAP and CO increase beyond target values (arrow pointing upward and to the right). Blood pressure management to lower MAP resulted in significantly increased CO (arrow pointing downward and towards the right), as seen previously from the patient cohort analysis. At 2600 rpm, LVAD flow is 5.1 L/min at a MAP of 82 mmHg; it goes up to 5.5 L/min when MAP is lowered to 76 mmHg, an overshoot of 10.13% over target CO. When MAP management lowers the value to the target of 70 mm Hg, CO approaches 6 L/min, an overshoot of 18.2%. At higher speeds (2800 RPM and 3000 RPM), MAP of 70 mmHg results in flows of 6.5 L/min and 7.3 L/min respectively (30% and 47% over the physiological target for CO). This behavior is summarized in Figure 29, where aggressive MAP management could potentially reach MAP target, but would significantly overshoot target CO if the LVAD speed is not modified. LVAD speed reduction, in conjunction with MAP management would meet both MAP and CO targets, especially for patients who have a MAP > 70 mmHg and CO > 5 L/min prior to MAP management.

According to the computational analysis conducted in this study, for the 51 patients in this study who had elevated CO target after MAP management, LVAD speed should be reduced to avoid RV pressure / volume overload and risk of right heart failure. As shown in Figure 29, the optimal LVAD speed for each patient is dependent on their hemodynamics parameters: MAP, CO and vascular resistance. Of the representative patients shown in Figure 29, patient 1 overshot the CO target slightly, but patient 5 overshot the CO target significantly, even though their speeds are very similar (2440 and 2480 RPM, respectively). This indicates that some patients may need a speed reduction, in conjunction with more aggressive blood pressure control, while others' physiology may be more tolerant to maintaining a constant LVAD speed that does not result in excessive flow.

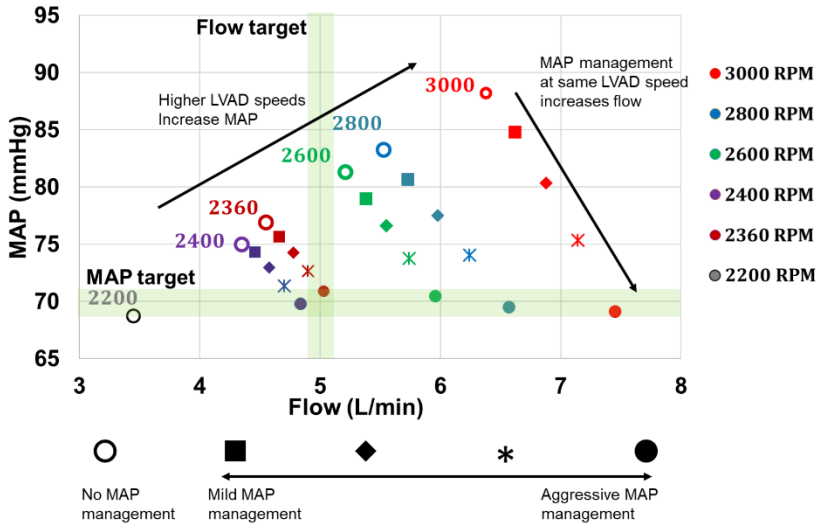

Figure 29:. Virtual controlled study for a single representative patient indicating interplay between LVAD speed, MAP and CO. MAP increases as LVAD speed increases. MAP management at same LVAD speed increases LVAD flow, thereby shifting operating point towards excessive volume, potentially leading to volume overload for higher LVAD speeds and more aggressive MAP management. CO, cardiac output; LVAD, left ventricular assist devices; MAP, mean arterial pressure.

Following initial analysis (post speed optimization) results showed 76% of patients did indeed need a speed reduction whereas 24% needed a speed increase. In addition, computational analysis showed a median speed change of -76 RPM for this patient data set indicating that MAP management alone can lead to overloading of the right side when no adjustment to LVAD speed is made, therefore further proving the need for speed optimization. Figure 22 shows patients with a higher MAP (afterload) tend to need bigger adjustments to the LVAD speed to become hemodynamically optimized. Clinicians may use this information as a predictor of patients who may benefit from speed optimization. This emphasizes the need to not only consider patient specificity, but also the interdependence between changes in afterload and LVAD pressure flow curves to fully optimize the patient.

Hemodynamic optimization involves managing the interplay between patient cardiovascular system response, LVAD speed, MAP and flow. A recent study indicates that only 50% of LVAD patients may have optimal LVAD speed settings that match hemodynamic goals[62]. LVAD speed reduction in conjunction with MAP management could work for many patients. LVAD speed in patients vary widely in the literature [10],[63] – the results of the ENDURANCE trial states that the average device speed at discharge for the LVAD (Medtronic HVAD) was 2700 ± 200 rpm.[64] Our analysis, coupled with previously published studies on hemodynamics optimization, indicates that LVAD speed setting should be dependent on hemodynamic parameters, and needs to be carefully evaluated after taking into account the complex interplay between MAP, CO, vascular resistance, and LVAD pressure-flow curves.

It is to be noted that pump speed is only part of the LVAD-patient management: ultimately, the flow through the LVAD is a result of the preload and afterload in conjunction with the LVAD speed (i.e. the pressure-flow curves). For a given speed, if the MAP is too high, the increased afterload will reduce the effective ‘pump head’, causing reduced perfusion for the patient, and less flow through the pump. Conversely, if the pump speed is too high (for a relatively low MAP), the effective low afterload will cause excess flow, which will result in right heart pressure / volume overload, precipitating right heart failure. Thus, a trade-off exists between these complications, further emphasizing the need to optimize

hemodynamics of LVAD patients. Managing LVAD patients requires appreciation of the LVAD operating mechanics and its coupling to the entire patient's circulatory system. Non-optimal LVAD speeds are detrimental to the patient's cardiovascular system, delaying or even preventing possible patient recovery. Even slight variations in patients' blood pressure can cause large shifts in LVAD operating conditions (and consequently in the cardiovascular system) with potentially critical impact on patient outcomes. The current work provides a foundation to explore and optimize the pump-patient interaction. The algorithms used in this work can be modified to optimize speed while achieving specific MAP and CO targets by iterating over several combinations of hemodynamic parameters. Such algorithms take a short time to compute (often less than ten minutes); this may make them applicable in a clinically relevant timeframe.

Excess VAD speed causes pressure/volume overload in the right ventricle [11], pulmonary hypertension, and when uncorrected, ultimately right heart failure.[65–6970]

3.4.2 Analyzing HM3 Patients from San Camillo Hospital in Rome, Italy

In collaboration with the San Camillo Hospital in Rome, Italy, hemodynamic patient data was provided for patients who were undergoing LVAD treatment with the HeartMate3 (Abbott), with patient identification information removed. Figure 30 shows the pressure flow curves for the HM3 device. For 38 patients Fick CO, catheterization laboratory measured MAP, and LVAD speed were provided. Patients were investigated using the in house developed three phase algorithm with clinicians specifying hemodynamic targets for MAP and flow to be 77 mmHg and 5 L/min respectively. A schematic of this analysis is shown in Figure 31. All analysis was performed in MATLAB® (MathWorks Inc., Natick, MA, USA).

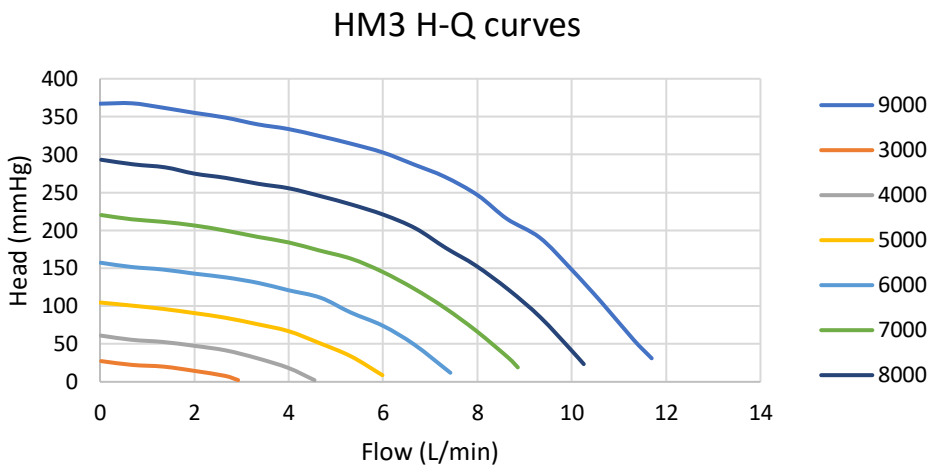

Figure 30: The pressure flow curves for the HM3. Speeds shown in the legend are in RPM

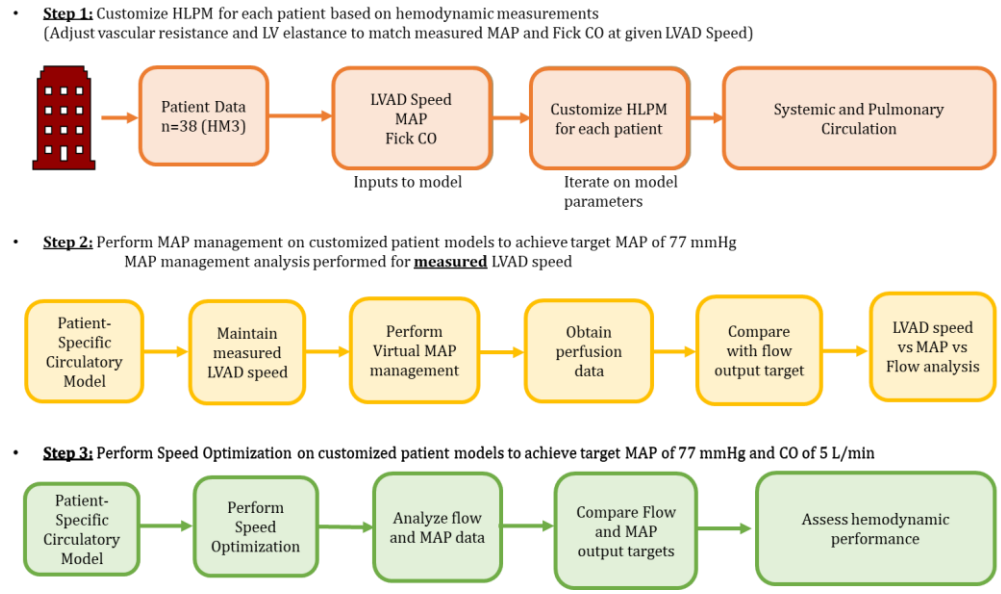

Figure 31: Patient specific analysis workflow for San Camillo Hospital data set

3.4.2.1 Results

Upon completing the first phase, 38 patient specific models were obtained, Figure 32 shows the distribution of patients prior to phases II and III. 37% of patients were above the flow target while 84% were above the MAP target.

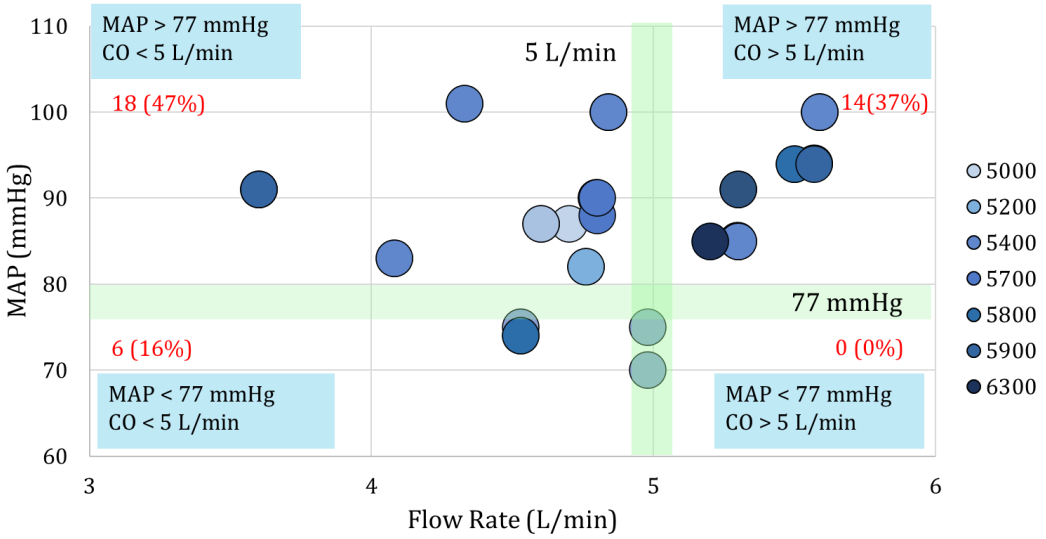

Figure 32: Distribution of patients prior to optimization

Upon completing phase II, 5 patients were eliminated due to an inability to meet MAP targets within threshold of +/-5% of target value. Figure 33 shows the distribution of patients following performing BP management without adjusting LVAD speed, which resulted in 10 patients operating at speeds above 5500 (30%) overshooting the flow target and 20 patients at speeds below 5500 (60%) undershooting the CO target of 5 L/min.

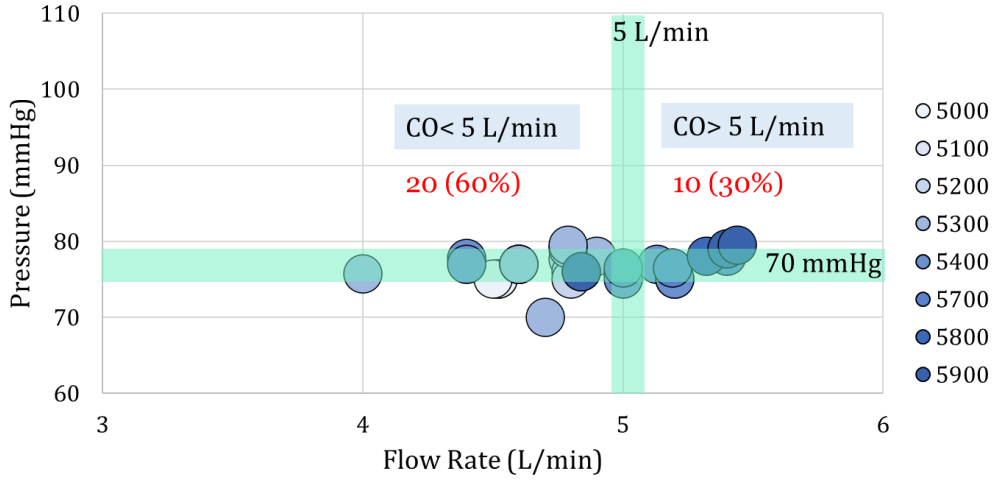

Figure 33: Patients following Phase II virtual MAP management with LVAD speed being left unchanged

Subsequently speed optimization was performed in conjunction with MAP management, 50% of patients needed a speed reduction, and the remaining patients needed a speed increase, as shown in Figure 34. Table 6 shows the results of the final phase of speed optimization for the Italian data patient cohort. The maximum speed reduction needed was 700 RPM for this patient data set. Figure 35 shows the comparison of the change in LVAD speed post optimization verses original LVAD speed pre-optimization where a trend in the change in LVAD speed can be seen by a clear division at 5500 RPM. Patients operating at a

speed greater than 5500 RPM needed a speed reduction, while patients at a speed lower than 5500 RPM needed a speed reduction.

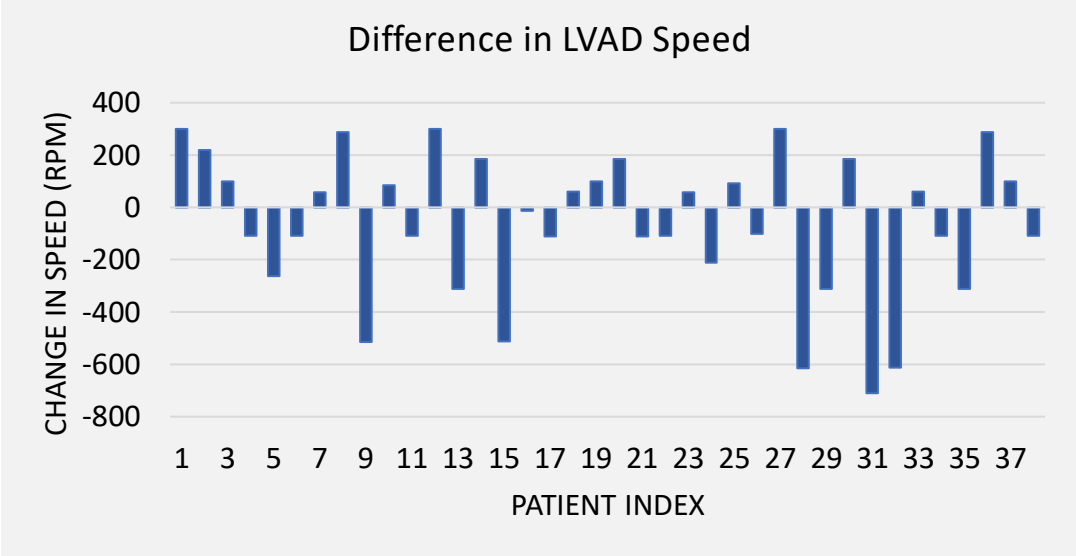

Figure 34: Difference in LVAD speed for each patient to become hemodynamically optimized

Table 6: Spreadsheet of patient data for the HM3 cohort where speed before and after speed optimization is shown for each patient

Patient Index	Original Speed	Final Speed	Change in Speed
1	5000	5300	300
2	5300	5518	218
3	5200	5300	99
4	5400	5293	-107
5	5700	5436	-263
6	5400	5291	-108
7	5400	5457	56
8	5300	5589	288
9	5800	5286	-514
10	5200	5286	85
11	5400	5291	-108
12	5000	5300	299
13	5900	5589	-311
14	5100	5286	185
15	6100	5589	-511

16	5300	5286	-14
17	5700	5589	-111
18	5300	5360	60
19	5200	5300	99
20	5100	5286	185
21	5700	5589	-111
22	5400	5291	-108
23	5400	5457	56
24	5800	5589	-211
25	5200	5291	91
26	5400	5300	-100
27	5000	5300	299
28	5900	5286	-614
29	5900	5589	-311
30	5100	5286	185
31	6300	5589	-711
32	6200	5589	-611
33	5300	5360	60
34	5400	5293	-107
35	5900	5589	-311
36	5300	5589	288
37	5200	5300	99
38	5400	5291	-108

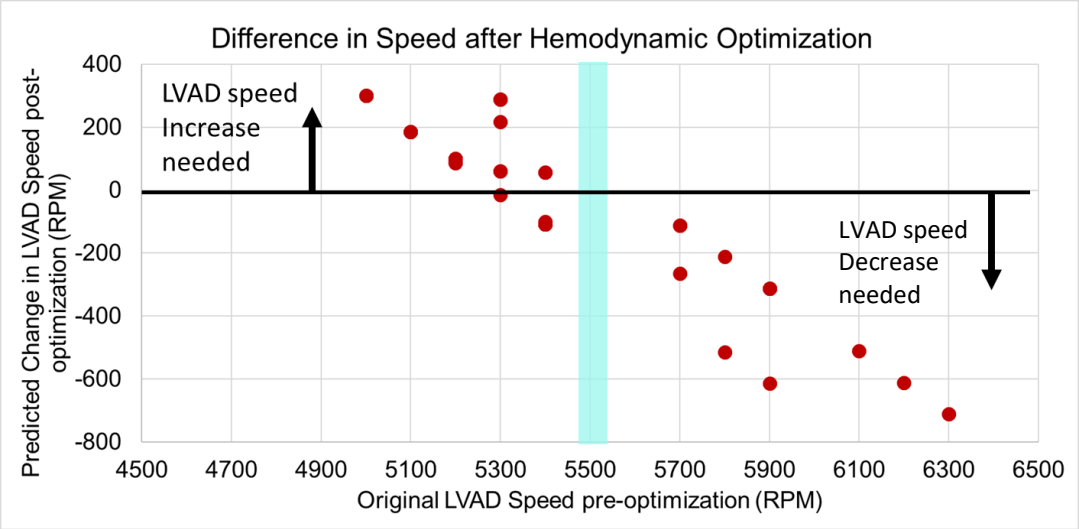

Figure 35: Distribution required change in speed to achieve hemodynamic optimization based on original non-optimized speed, demonstrating that LVAD speeds higher than 5500 rpm most likely necessitated a speed reduction, while most LVAD speeds lower than 5500 rpm required an increase in LVAD speed to optimize the patient.

3.4.2.2 Discussion

For this study, we again implemented the same procedure on this smaller dataset but with the treatment of the Heartmate 3, we were able to see similar trends to the other dataset, including patient's beginning at various points that do not match clinician's recommendations for MAP (77 mmHg) and flow (5 L/min). Furthermore, after specifying the model to the patients and performing virtual MAP management to achieve the MAP target, the resulting CO was compared to the 5 L/min target. The patients were seen to overshoot the flow target when they were originally operating at a speed greater than 5500 RPM, while patients undershot the flow target when operating at an RPM below 5500 RPM. This data shows a similar trend to the previous dataset, confirming that MAP management alone cannot hemodynamically optimize the patient. The pump-patient interaction must be understood to achieve hemodynamic targets. The final phase of speed optimization where VR and LVAD speed are both manipulated simultaneously to minimize the difference between obtained and targeted values was applied to this patient data set and unlike before resulted in a 50/50 split of patients who needed their speeds reduced compared to those that

needed their speeds increased. The results indicate that patient's specificity in treatment is necessary due to the differences between patients' hemodynamics as well as how the LVAD interacts with the system. Figure 34 and Figure 35 indicate in this dataset a clear division between the need for a speed reduction and a speed increase with LVAD speeds above and below 5500 RPM, respectively. Furthermore, these results give an indication that patients operating at a higher speed as well as a higher MAP and CO may benefit most from speed optimization.

The results from these datasets give a clear insight into understanding the pump patient interaction and how clinicians can use this information to hemodynamically optimize patients. These results indicate that optimization comes when we (i) perform MAP management and LVAD speed adjustments together, (ii) consider patient specificity in treatment, and (iii) can identify predictors that may indicate which patients may benefit the most from optimization. Some trends we have been able to identify from these datasets alone include patients with higher MAPs and CO tend to benefit from speed optimization the most. Furthermore, patients operating at higher LVAD speeds tend to need a reduction in speed while the opposite is true for patients operating at lower speeds. With complications such as right-sided overload, trends like these may lead to improved patient outcomes.

Chapter 4
Speed Modulation

This chapter will cover the investigation of the application of the square wave speed modulation waveform to identify trends that exist on the effect speed modulation may have on the cardiovascular system, specifically focusing on the opening of the aortic valve.

4.1 What is Speed Modulation?

Some negative outcomes of LVAD treatment include the existence of stagnation zones such as at the aortic valve/aortic root as well as aortic insufficiency. When the LVAD speed is set to a higher RPM, more suction occurs in the left ventricle. This makes it difficult for the already stunted left ventricle to build up enough pressure to overcome pressure in the aorta, bringing down pulse pressure. This feature of LVAD operation leads to blood stagnating in the zones previously mentioned. When blood collects above the aortic valve, the weight of stagnated blood can cause the aortic valve to give out, this is when aortic insufficiency can occur. These occurrences indicate a need for a method that encourages aortic valve opening as seen in

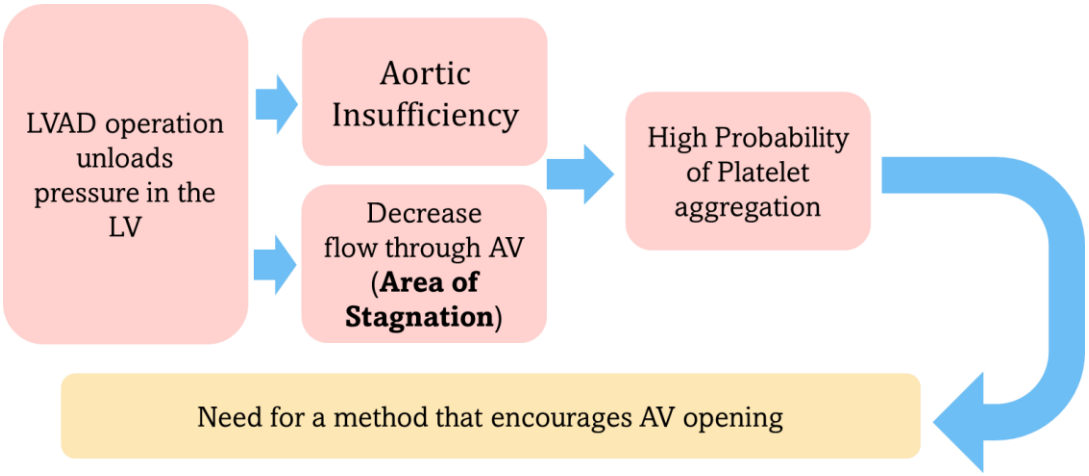

Figure 36. Speed modulation may be the solution to complications such as these by allowing for a drop in speed and thus time for a pressure differential to build up across the

aorta and left ventricle, thus permitting the aortic valve to open. When there is blood flow through the aortic valve (AV), stagnated blood can be washed out reducing chances of platelet formation as well as aortic insufficiency. Please refer to Figure 37 for a schematic of the theory behind utilizing speed modulation.

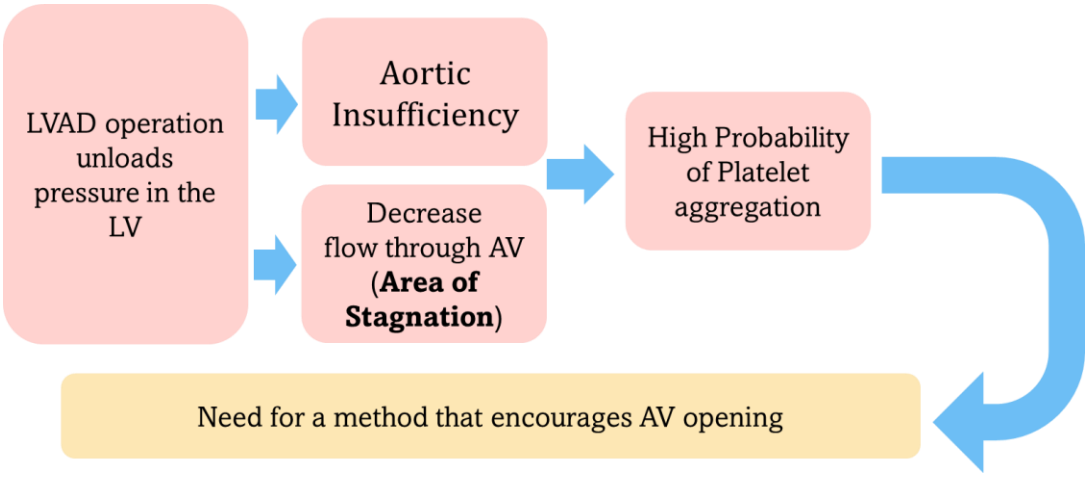

Figure 36: Schematic shows the thought process for the need to incorporate speed modulation into LVAD therapy methods

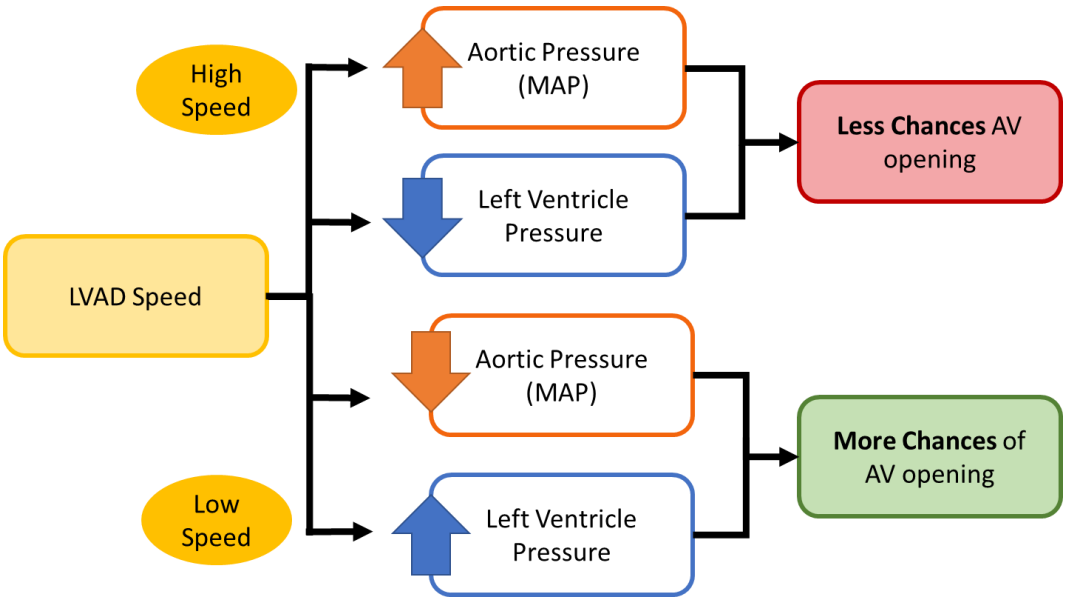

Figure 37: The relationship between LVAD speed, aortic pressure, LV pressure and how it can improve or lessen chances for AV opening. This theoretical concept is the basis for utilizing speed modulation to overcome areas of stagnation specifically at the aortic root and AV

Speed modulation is a method of changing the LVAD speed via a waveform. This waveform can be manipulated by its shape as well as the individual characteristics that make up the shape to encourage an increase in pulse pressure. In this thesis, we will explore the results of implementing a square wave speed modulation waveform. A square wave can be manipulated by a few characteristics, including where along the y-axis the square wave begins as well as the height and length of the square wave. In terms of pump settings, this means adjustments to baseline speed, the amount of speed change, as well as the duration of the speed change, respectively. For a pictorial representation, please refer to Figure 38.

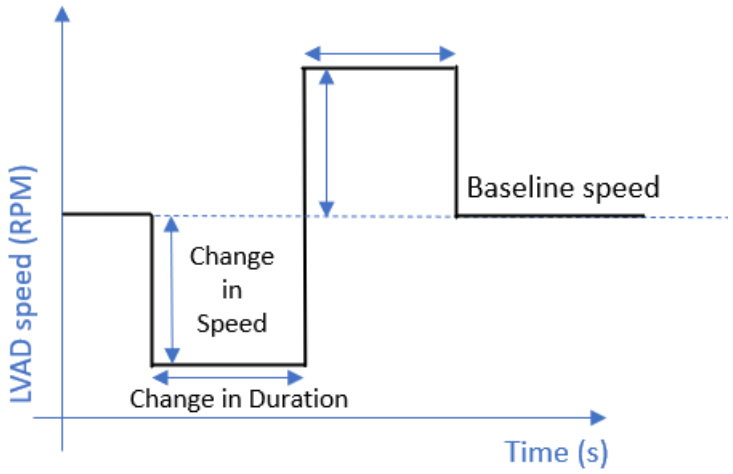

Figure 38: The square wave speed modulation waveform

The change in speed is determined by a parameter called the Rratio which is utilized by EVAHEART INC. for determining the amount of speed change implemented during speed modulation. Furthermore, the Rratio is a percentage (ranging from 75% to 95% in increments of 5%) that the baseline speed will drop to. For example, a case where the baseline speed is 1700 RPM and the Rratio is 75%, the speed will drop down to 1275 RPM. Hemodynamic parameters, as well as characteristics of the pump speed modulation (PSM) waveform, can be manipulated to see the effects PSM has on the cardiovascular system of the virtual patient. When exploring the effects of speed modulation, different MAPs (VR values) and Elv_max values are analyzed in conjunction with changes to baseline speed, Rratio and the duration of speed modulation. These changes were assessed by creating an Excel sheet that contained all the different parameter settings. Refer to Figure 39 for an example of the Excel sheet layout.

A)

No.	Baseline Speed (rpm)
1	1600
2	1625
3	1650
4	1675
5	1700
6	1725
7	1750
8	1775
9	1800
10	1825
11	1850
12	1875
13	1900
14	1925
15	1950
16	1975
17	2000
18	2025
19	2050

B)

Baseline Speed	Reduced Speed	R ratio (%)	Speed change duration
1600	1200	75	3
			5
			7
	1280	80	3
			5
			7
	1360	85	3
			5
			7
	1440	90	3
			5
			7
	1520	95	3
			5
			7

Figure 39: A snapshot showing an example of the Excel sheets containing information for the parameters to be evaluated in each simulation. A) the different baseline speeds to be explored; B) The parameters to be explored for each baseline speed (Rratio and duration of PSM)

The lumped parameter model is modified to assess the effects PSM may have on a virtual patient. A main file uses an Excel sheet to determine the characteristics of the waveform (i.e., Baseline Speed, Rratio, and duration) as well as parameters of the cardiovascular system (i.e., Elv_max and VR) being implemented. The main file then initiates the solver, where initial conditions are provided, giving the DAE solver a starting point followed by the system constants file. The system constants file feeds characteristics of the square wave provided by the Excel sheet to a custom-made MATLAB function that implements the square wave. The MATLAB function uses information provided by the system constants file to create the square wave by reducing the baseline speed to the Rratio percentage for the duration of PSM. The system constants file feeds the LVAD speed and hemodynamic parameter information to the solver. Once the simulation is completed, the

output of the solver is stored in a solution matrix that can be further explored in post processing. Please refer to Figure 40 for a flow chart of the process previously explained.

Upon completion of the simulation the average flow through the aortic valve (Mean_Qav), the LVAD (Mean_Qvad), and MAP are calculated, during PSM and post-

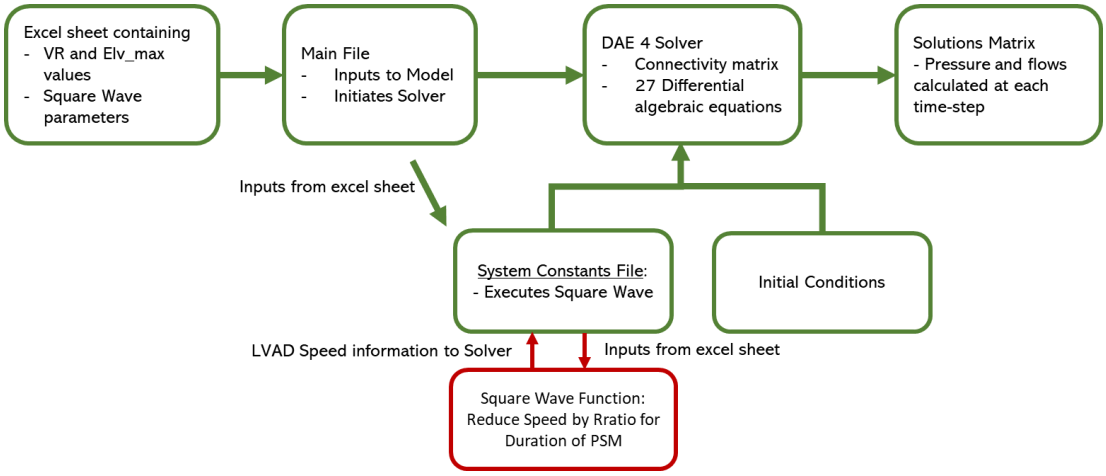

Figure 40: The lumped parameter model algorithm pathway when implementing pump speed modulation

PSM. The number of times the aortic valve opens during PSM is also recorded. For post processing, plots are created using the solution matrix. A file pathway for saving all post processing data was developed with a naming structure based on the characteristics of the waveform being explored. For hemodynamic parameters explored, new folders were added for changes to the Elv_max, and the saving process was repeated for any changes to the MAP or VR. Please refer to Figure 41 for a pictorial representation of the file system explained above.

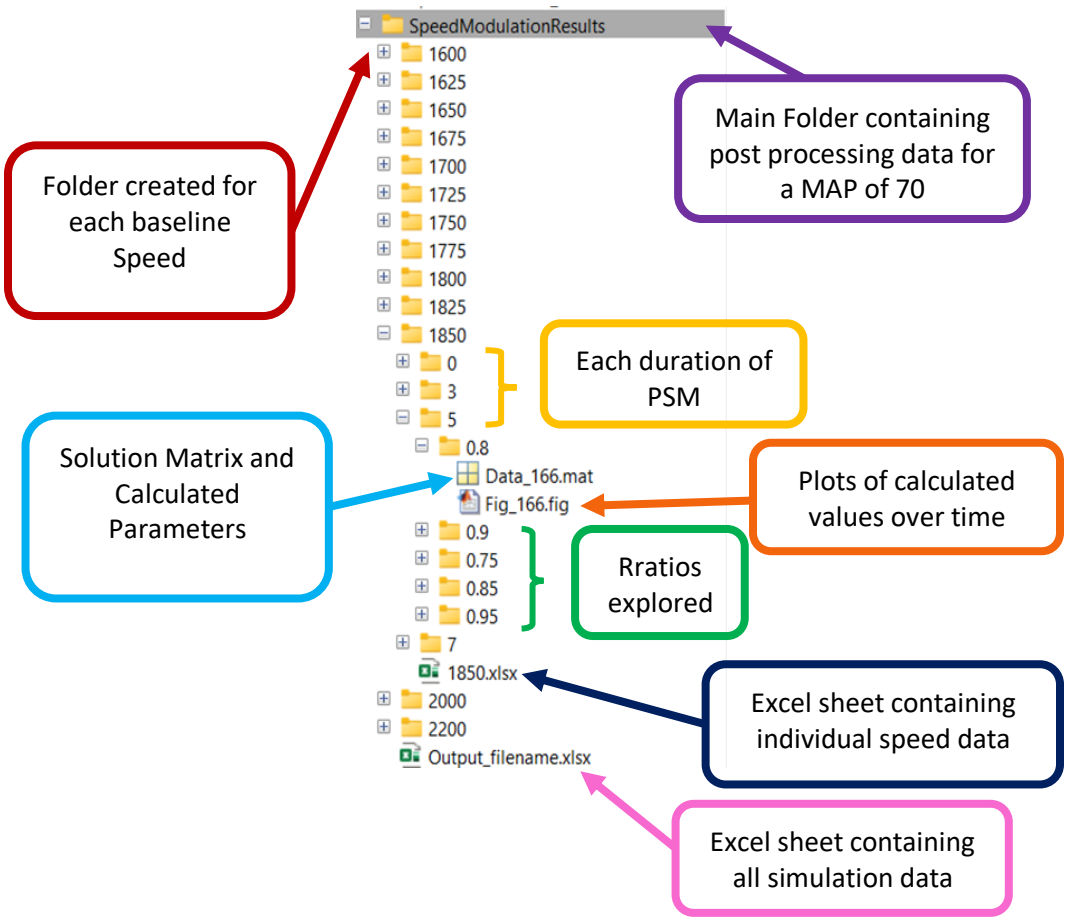

Figure 41: The file saving pathway when running the speed modulation waveform cases

This complex method of saving allows for analysis of plots to ensure results make physiological sense as well as assessing the trends that can be seen from making modifications to the square wave. Excel sheets containing all calculated parameters are created for each baseline speed, allowing trends to be established regarding changes in the duration of PSM, and Rratio for each baseline speed. Furthermore, an Excel sheet containing all simulation data allows for trends across all baseline speeds to be explored.

4.2 The Effect of Speed Modulation

Speed modulation waveforms are implemented to increase pulse pressure thereby minimizing stagnation zones via aortic valve opening. Through post processing trends can be analyzed based on changes made to MAP and VR of the virtual patient as well as manipulating features of the square wave. To assess these trends the Evaheart 2 LVAD H-Q curves were utilized in the LPM, as can be seen in Figure 42. The Evaheart 2 LVAD was utilized for pump speed modulation due to the flatness of these curves in comparison to the HM3 and HVAD. The flatter pressure flow curves allow for more flow to be driven through the LVAD without the cost of creating a bigger pressure head. The pressure head is important when assessing if the AV will open or not. A bigger pressure head means a bigger difference in pressure between pressure in the aorta, and pressure in the left ventricle. When pressure is higher in the left ventricle than in the aorta this needs to be overcome by allowing pressure to build up in the left ventricle from native pulsatility. This pulsatility has a better chance of creating the necessary difference in pressure ($P_{aorta} < P_{lv}$) when the pressure difference is smaller; this makes the Evaheart pump mechanics ideal for implementing speed modulation with the goal of increasing the chances of AV opening.

The simulation was run for a total of 25 secs, the first 10 secs allowing for the model to adjust to the input parameters, followed by the implementation of the PSM for a given duration of time. The speed of the LVAD is set back to baseline speed for the remainder of the simulation following PSM. The results for the lowest, median, and highest baseline speeds at a MAP of 70 mmHg and an Elv_max of 1.0 will be explored throughout the remainder of this chapter.

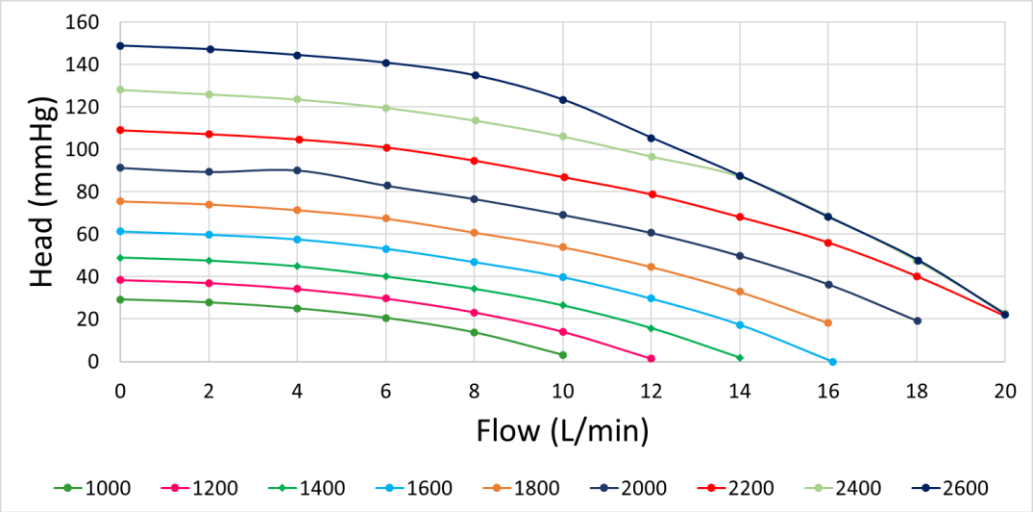

Figure 42: The pressure flow curves for the EVAHEART 2 device

For a baseline speed of 1600 RPM, a PSM duration of 5 seconds, and the lowest Rratio, the plot of pressure in the aorta and left ventricle over time is shown in Figure 43. Figure 43 shows an increase in pressure in the left ventricle during pump speed modulation (shown in the green box). This buildup of pressure is enough to overcome the pressure in the aorta resulting in the aortic valve opening six times. The flow through the aortic valve displayed in Figure 44 has six peaks, where the amount of flow through the aortic points are large enough to be visible when compared to flow through the VAD. Furthermore Figure 44 shows a negative flow occurring every cardiac cycle, this is representative of back flow that can occur during PSM in patients receiving LVAD therapy. Occurrences of backflow are not measured or considered significant. This parameter if measured would allow for better fine tuning of the model to create patient specific models or for analysis of trends assessed in this thesis. Backflow can be seen in all plots that show blood flow through the AV and LVAD for some or all cardiac cycles at each baseline speed discussed in this thesis. The Mean_Qav, Mean_Qlvad, and MAP during and post-PSM are shown in Table 7 for the baseline of 1600 RPM.

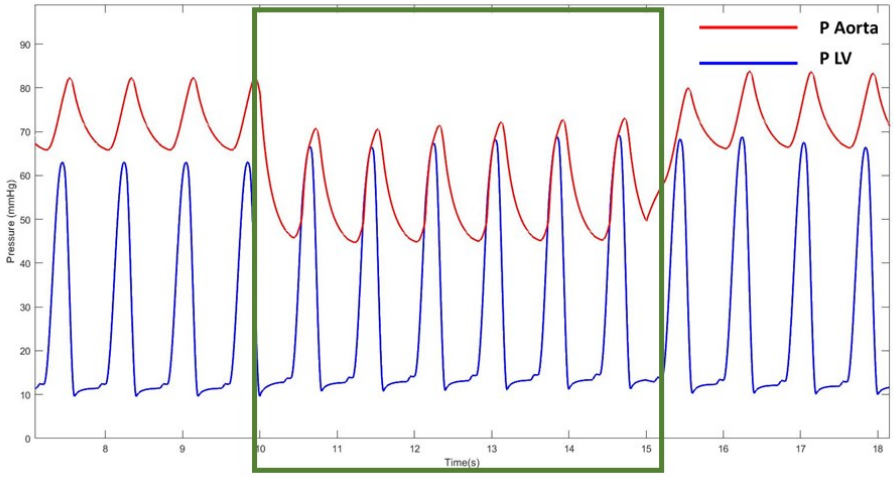

Figure 43: Plot of pressure in the aorta (shown in red) over time, as well as pressure in the left ventricle (shown in blue) over time for a baseline speed of 1600 RPM, duration of PSM of 5 seconds, and an Rratio of 75%. The green box indicates when PSM is occurring.

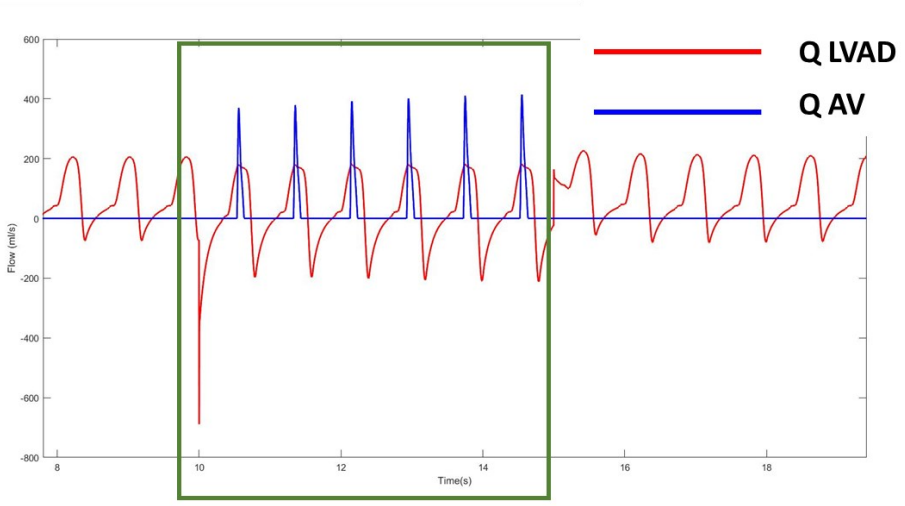

Figure 44: Flow through the aortic valve (shown in blue) and flow through the LVAD (shown in red) over time. The green box indicates PSM occurring. This plot is for a baseline of 1600 RPM, Rratio of 75%, and a duration of 5 seconds.

Table 7: Overview of calculated parameters for baseline speed of 1600, Rratio of 75% and duration of 5 secs PSM

Mean_Qlvad (PSM)	Mean_Qlvad (Post- PSM)	Mean_Qav (PSM)	Mean_Qav (Post-PSM)	MAP (PSM)	MAP (Post-PSM)
0.81447 L/min	4.1134 L/min	1.4552 L/min	0 L/min	55.6 mmHg	71.7 mmHg

For a baseline speed of 1800 RPM, Rratio of 75%, and duration of 5 seconds results show again a buildup of pressure in the left ventricle during speed modulation, but the pressure only overcomes pressure in the aorta towards the end of the PSM allowing the aortic valve to open four times as can be seen in Figure 45. Figure 46 shows flow through the aortic valve and through the LVAD, indicating flow through aortic valve at the same points where the pressure in the left ventricle overcomes pressure in the aorta in Figure 45. Table 8 shows an overview of the calculated flows and MAPs for these waveform characteristics during and post-PSM. For a higher baseline speed of 2000 RPM, the native pulsatility is minimally seen, while pressure in the left ventricle is around 10 mm Hg and able to build up during

PSM to a maximum of 40 mm Hg. The buildup of pressure during PSM is insufficient and the AV does not open with these PSM settings. This can all be seen in Figure 47. Flow through the LVAD and aortic valve can be seen by Figure 48, the pressure in the left ventricle never overcomes pressure in the aorta therefore there is never any flow through the aortic valve throughout the simulation. Table 9 shows the MAP, flow through the VAD, and aortic valve during and post-PSM.

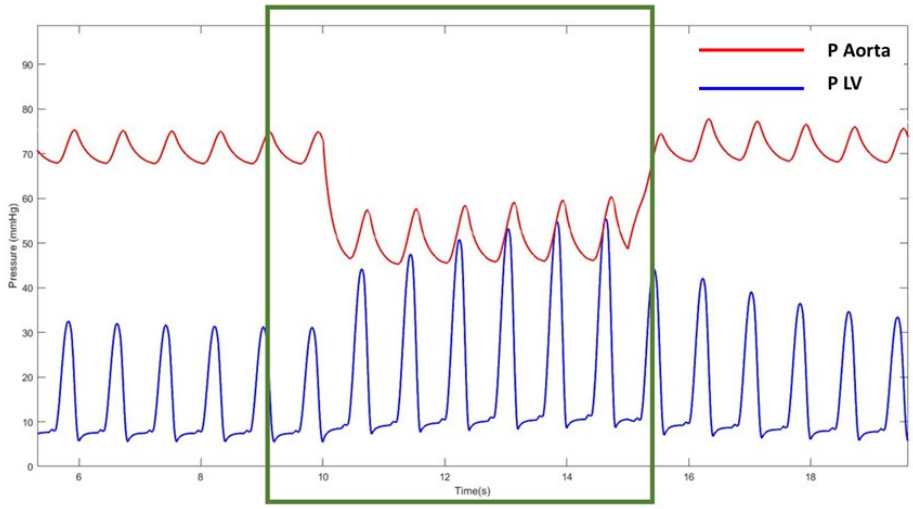

Figure 45: Plot of pressure in the aorta (shown in red) over time, as well as pressure in the left ventricle (shown in blue) over time for a baseline speed of 1800 RPM, duration of PSM of 5 seconds and an Rratio of 75%. The green box indicates when PSM is occurring.

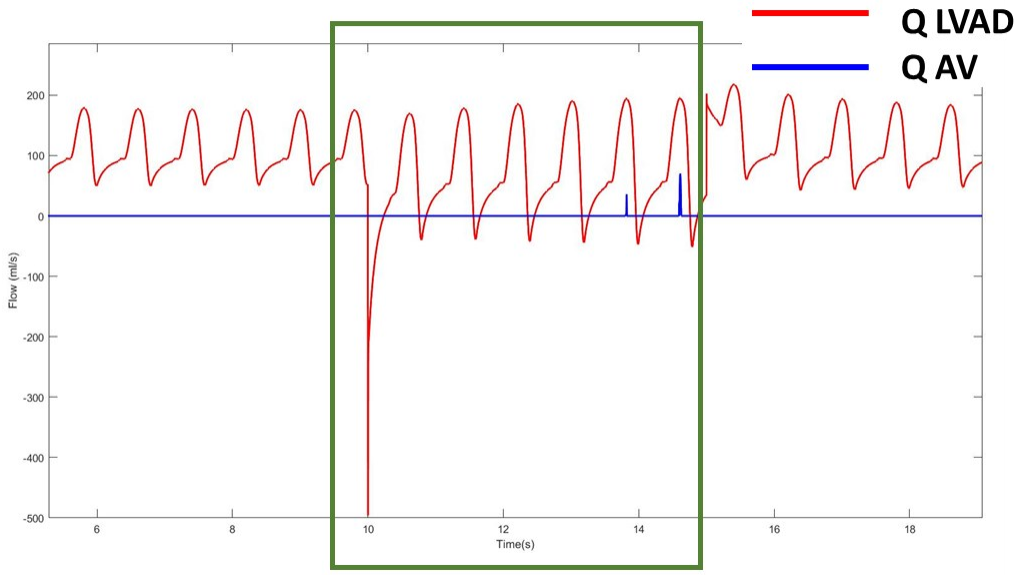

Figure 46: Flow through the aortic valve (shown in blue) and flow through the LVAD (shown in red) over time. The green box indicates PSM occurring. This plot is for a baseline of 1800 RPM, Rratio of 75% and a duration of 5 seconds.

Table 8: Overview of calculated parameters for baseline speed of 1800 RPM, Rratio of 75% and duration of 5 secs PSM

Mean_Qlvad (PSM)	Mean_Qlvad (Post- PSM)	Mean_Qav (PSM)	Mean_Qav (Post-PSM)	MAP (PSM)	MAP (Post-PSM)
3.8321 L/min	6.6946 L/min	0.0189 L/min	0 L/min	51.06 mmHg	70.4 mmHg

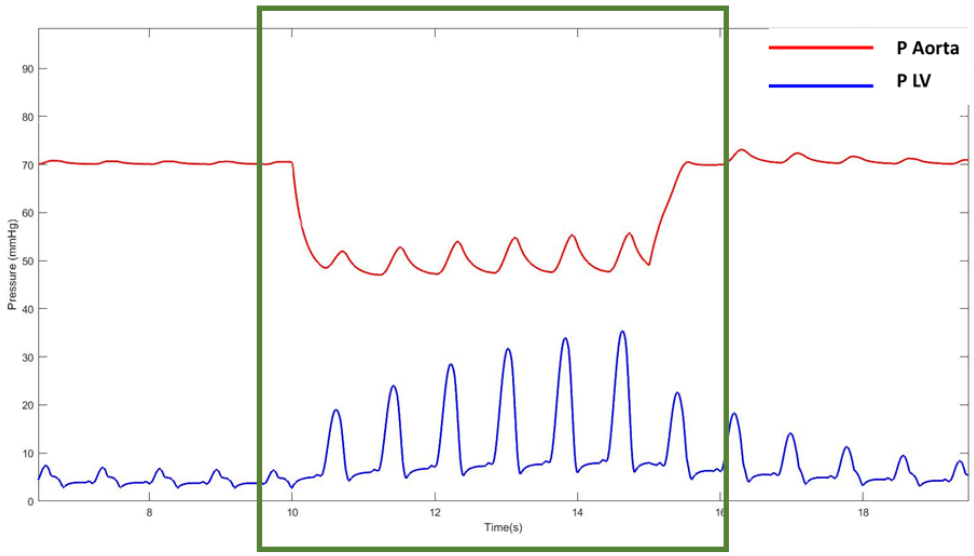

Figure 47: Plot of pressure in the aorta (shown in red) over time, as well as pressure in the left ventricle (shown in blue) over time for a baseline speed of 2000 RPM, duration of PSM of 5 seconds, and an Rratio of 75%. The green box indicates when PSM is occurring.

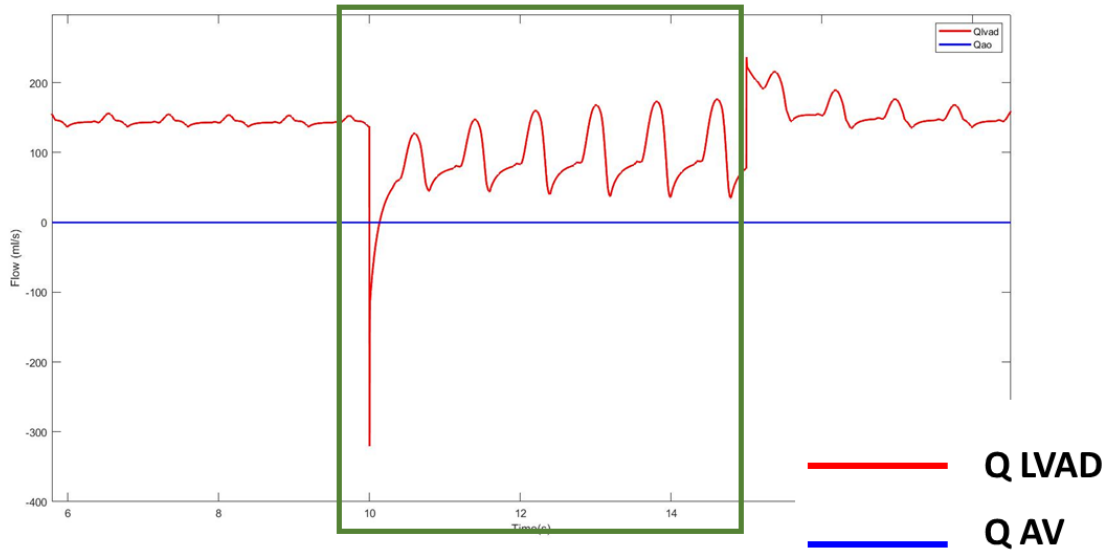

Figure 48: Flow through the aortic valve (shown in blue) and flow through the LVAD (shown in red) over time. The green box indicates PSM occurring. This plot is for a baseline of 2000 RPM, Rratio of 75% and a duration of 5 seconds.

Table 9: Overview of calculated parameters for baseline speed of 2000 RPM, Rratio of 75% and duration of 5 secs PSM

Mean_Qlvad (PSM)	Mean_Qlvad (Post- PSM)	Mean_Qav (PSM)	Mean_Qav (Post-PSM)	MAP (PSM)	MAP (Post-PSM)
5.286 L/min	9.0018 L/min	0 L/min	0 L/min	50.4 mmHg	70.04 mmHg

For the baseline speed of 1600 RPM, at the same Elv_max and MAP of 70 mmHg, increasing the duration of PSM increased the amount of flow through the AV and through the VAD. Figure 49 also shows that when the Rratio is increased the amount of flow through the AV decreases while the flow through the VAD remains relatively consistent. For the baseline of 1600 RPM in Figure 50, the results show that the AV opens more times with an increase in PSM duration while an increase in Rratio results in less occurrences of AV opening. This trend is consistent as the baseline speed increases to 1800 and 2000 RPM. In

Figure 51 we see that for the 1800 RPM baseline, there is aortic valve opening only at the lowest Rratio, with the number of times the AV opens increasing with longer durations of PSM. This was seen with the baseline speed 1600 RPM, but the number of incidents of AV opening has gone down. At the highest baseline, we don't see any occurrences of AV opening. Overall, the results show a decline in the number of times the AV opens as well as the amount of flow through the AV with increasing baseline speeds. Please refer to Figures 49-52 to see this trend.

From these results, we can see trends where larger durations of PSM allow for the pulse pressure to build up, and therefore, more chances for the aortic valve to open are created, allowing for more flow to occur through the aortic valve. Furthermore, bigger drops in speed (smaller Rratios) result in more occurrences of AV opening and more flow through the AV, which can be due to a counteraction to unloading of the left ventricle, caused by LVAD operation. In addition, results showed higher baseline speeds, resulting in a decrease in native pulsatility as well as a decrease in pulse pressure, therefore decreasing the chances as well as the number of times the AV opened. These trends indicate for the virtual patient lower baseline speeds, longer durations of PSM, and a higher percentage drop of baseline speed results in an increased frequency of AV opening, less stagnation in the aortic root, and consequently the possibility for a reduction in thrombogenicity outcomes in patients.

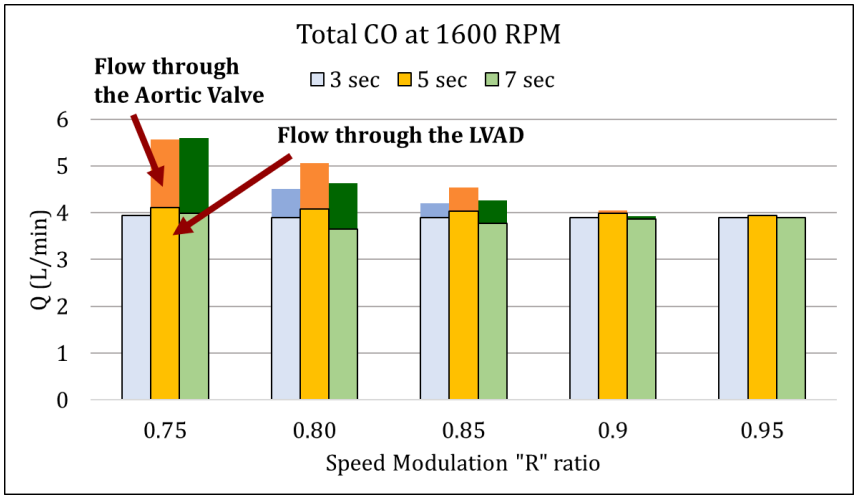

Figure 49: The cardiac output through the aortic valve and the LVAD for the PSM durations 3, 5, 7 at Rratios of 75% to 95% for a baseline speed of 1600 RPM

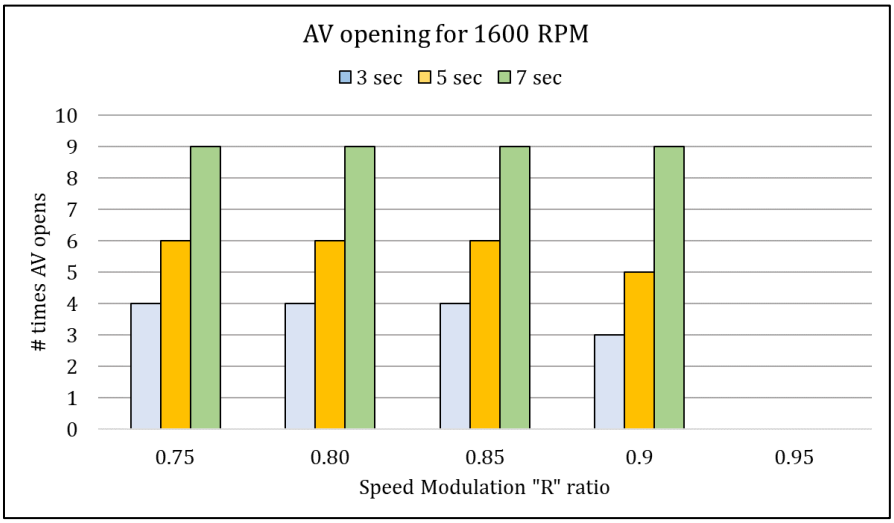

Figure 50: The number of times the AV opens for the PSM durations 3, 5, 7 at Rratios of 75% to 95% for a baseline speed of 1600 RPM

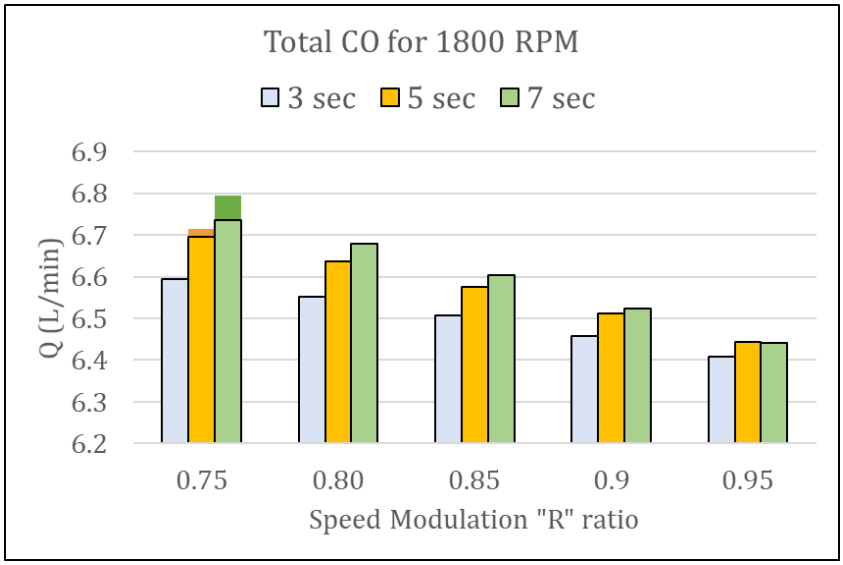

Figure 51: The cardiac output through the aortic valve and the LVAD for the PSM durations 3, 5, 7 at Rratios of 75% to 95% for a baseline speed of 1800 RPM

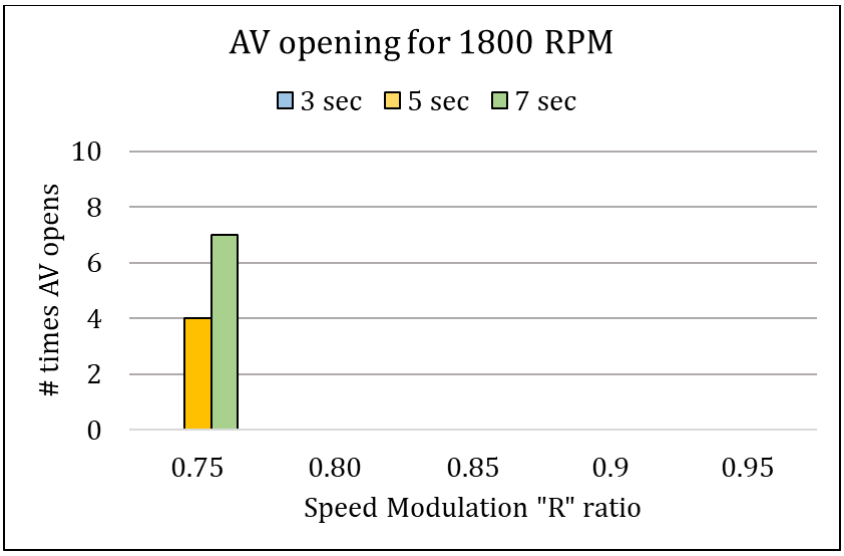

Figure 52:The number of times the AV opens for the PSM durations 3, 5, 7 at Rratios of 75% to 95% for a baseline speed of 1800 RPM

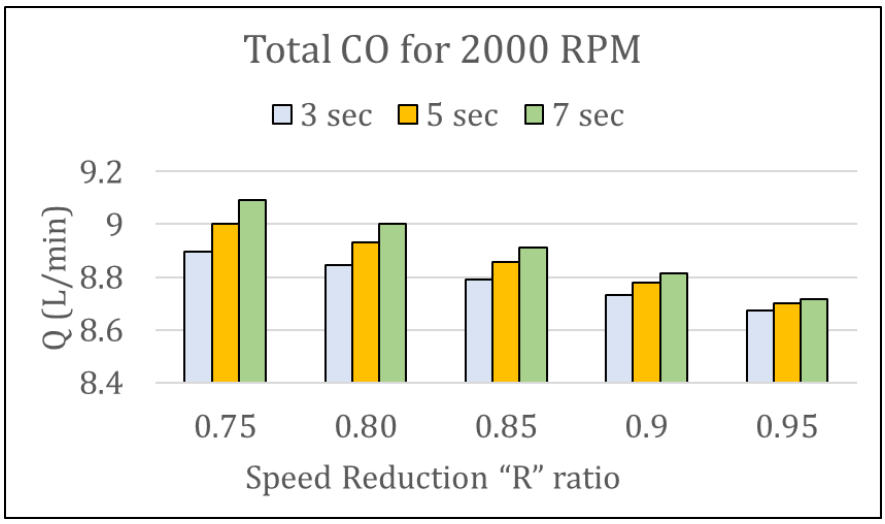

Figure 53: The cardiac output through the aortic valve and the LVAD for the PSM durations 3, 5, 7 at Rratios of 75% to 95% for a baseline speed of 2000 RPM

Chapter 5
Conclusions

In this chapter we will discuss the conclusions obtained from optimizing the two patient data sets to develop a speed optimization technique that is a quantitative method of finding optimal pump settings in response to patients' the circulatory system and hemodynamic needs. This chapter also covers trends seen from investigating the square speed modulation waveform. The limitations and future work of these analysis will be discussed in this chapter as well.

5.1 Conclusions from Both Studies

This thesis aims to highlight and understand the impact of the complex interdependencies between LVAD speed and the native cardiovascular system, specifically the effect that the following hemodynamic parameters, MAP, speed, and flow have on the overall hemodynamics of the patient. In addition, explore the utilization of speed modulation to encourage AV opening, in turn reducing thrombogenicity and improving patient outcomes. Overall, providing proof that the application of optimization in conjunction with speed modulation will improve patient outcomes when patient specificity and the pump-patient interplay are taken into consideration.

Using a novel computational hemodynamic lumped parameter model that incorporates LVAD pressure-flow characteristics, we optimized hemodynamics for 61 HVAD patient-specific models and 38 HM3-supported patient-specific models. Customizing our computational LPM for each patient, we performed virtual MAP management on the models until the MAP target specified by the clinicians was reached and evaluated the impact of this pharmacological intervention on the LVAD outflow. Prior to MAP management, for the UWMC dataset, 84% of patients had a MAP above 70 mmHg. After MAP management, 84% of the patients overshot the CO target of 5 L/min (median CO of 6.79 L/min, or 36% median overshoot). The San Camillo Hospital dataset showed 84%

of patients had a MAP over 77 mmHg. Post virtual MAP management 11 patients were operating at speeds below 5500 RPM (29%) undershooting the flow target and 14 patients at speeds above 5500 RPM (37%) overshooting the CO target of 5 L/min. Our model demonstrated MAP management results in LVAD flows upwards of 6.5 L/min in the UWMC dataset, causing right ventricular dysfunction if the pump speed is not reduced appropriately. The San Camillo Hospital data set resulted in flows upwards of 5.93 L/min. In both studies MAP management alone was not sufficient for meeting both MAP and CO targets. Both studies showed that when MAP management and LVAD speed optimization are done concomitantly, 50% or more of patients need to have their speeds reduced to reach MAP and flow targets. Furthermore, these studies show trends of optimization being most beneficial for patients operating at higher LVAD speeds, therefore operating with high flow rates. These indicators have the potential to reduce complications and improve patient outcomes. In addition, speed modulation data shows stagnation zones specifically at the aortic valve/ aortic root have the potential for improved blood wash out with the implementation of a square wave with specific characteristics. The optimization section of this thesis highlights the proven benefits for patients when LVAD speeds are reduced (This is true for the patient cohorts explored in this thesis.). Speed modulation waveforms originating at lower baseline speeds with bigger drops in speed (25 % drop), and longer speed modulation durations (upwards 7 secs) prove to increase chances of AV opening. Information gathered from optimization and speed modulation together can create the possibility of improving the therapeutics of LVAD destination therapy as well as aiding clinicians in optimizing patient hemodynamics as patients' needs are ever changing.

5.2.1 Limitations

Limitations of Optimization

There are inherent limitations to this study. The lumped parameter model is a 0-D model; therefore it does not fully capture all hemodynamic effects on vascular pressure drops and thrombogenicity. The pressures and volumes as functions of time in the system may be subject to uncertainty, owing to the need to satisfy continuity instantaneously in the 0-D

network. This may be corrected to an extent by modifying the values of the capacitances such that they capture the circulatory system's ability to store fluid over periods of time, but the trends described here are robust. The LVAD H-Q curves come from mock loop studies operating under constant conditions and steady flow and may not represent dynamic performance *in vivo*. They are, however, state of the art in characterizing LVAD support. Finally, incorporating additional patient cardiovascular system parameters (such as native LV contractility, which was not available in this study) in addition to those described here would improve the customization of the computational models and provide more insight into changes in response to LVAD speed; such data is not typically collected in standard of care and further investigation is warranted into using existing patient data to tune the parameters of the LPM. Furthermore, the extent of vascular resistance changes evaluated in the current work may not be fully applicable to all patients and needs to be evaluated based on individual patient physiology.

Limitations of Speed Modulation

The results obtained are limited to a virtual patient model, and results at these operating speeds may change with patient specification. In addition, the current work only evaluated a square waveform for speed modulation; additional waveforms such as gradual increase/decrease, sinusoidal, etc. would need to be investigated in the future.

5.2 Future Work

Future iterations of the model may include the integration of more diseased patient specific measurements in lieu of lumped parameters included in the model. In addition, the integration of the cardiovascular system's long-term dynamic response to changes in blood pressure, also known as the baroreceptor response, into the model. Furthermore, the incorporation of functions that are clinically derived, describing changes to patient hemodynamic parameters based on activity level of the patient, would further fine tune the prediction capabilities of the model. Conclusions drawn from the speed modulation simulations are currently being investigated using patient-specific data; analysis of these

results will expand or confirm the trends drawn from the virtual patient representative model. The speed modulation data can be expanded by investigating other speed modulation waveforms that may produce less of a shock to the system, providing a smoother transition between speeds. Utilizing the optimization and speed modulation algorithms together can prove to make the model dynamic to patients' needs as they evolve and would be beneficial for future studies. The goal of exploring more patient data using these algorithms would be to develop a cellular application that provides clinicians with a diagnostic database containing pre-run patient scenarios to give optimization settings based on patient specific needs.

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Appendix

A.1 Pump Affinity Laws

(Volume Capacity) $\frac{q_1}{q_2} = \frac{n_1}{n_2} * \frac{d_1}{d_2}$

(Head) $\frac{dp_1}{dp_2} = (\frac{n_1}{n_2})^2 * (\frac{d_1}{d_2})^2$

q = volume flow capacity

n = wheel velocity or revolution per minute

d = wheel diameter

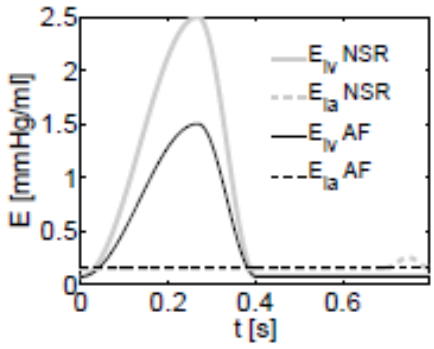
dp = head or pressure

A.2 LPM Equations for Different Components

Left Atrium

$$\frac{dV_{la}}{dt} = Q_{pvn} - Q_{mt},$$
$$P_{la} = P_{la,un} + E_{la}(V_{la} - V_{la,un}),$$
$$Q_{mt} = \begin{cases} CQ_{mt}AR_{mt}\sqrt{P_{la} - P_{lv}}, & \text{if } P_{la} \geq P_{lv}, \\ -CQ_{mt}AR_{mt}\sqrt{P_{lv} - P_{la}}, & \text{if } P_{la} < P_{lv}, \end{cases}$$

un: unstressed pressure and volume levels of each cardiovascular section



Left heart elastances: (light) NSR

Heart-beat in both cases is RR = 0.8 s

la = left atrium

lv = left ventricle

The time-varying elastance is

$$E_{la}(t) = E_{la,min} + \frac{E_{la,max} - E_{la,min}}{2} e_a(t),$$

and the atrium activation function is

$$e_a(t) = \begin{cases} 0, & \text{if } 0 \le t \le T_{ac}, \\ 1 - \cos\left(\frac{t - T_{ac}}{RR - T_{ac}} 2\pi\right), & \text{if } T_{ac} < RR, \end{cases}$$

$Ela_{,min}$ = minimum elastance value

$Ela_{,max}$ = maximum elastance value

T_{ac} = beginning of atrial contraction

Left Ventricle

$$\frac{dV_{lv}}{dt} = Q_{mt} - Q_{ao},$$
$$P_{lv} = P_{lv,un} + E_{lv}(V_{lv} - V_{lv,un}),$$
$$Q_{ao} = \begin{cases} CQ_{ao}AR_{ao}\sqrt{P_{lv} - P_{sas}}, & \text{if } P_{lv} \geq P_{sas}, \\ -CQ_{ao}AR_{ao}\sqrt{P_{sas} - P_{lv}}, & \text{if } P_{sas} < P_{lv}, \end{cases}$$

The time-varying elastance is

$$E_{lv}(t) = E_{lv,min} + \frac{E_{lv,max} - E_{lv,min}}{2} e_v(t),$$

and the ventricle activation function is

$$e_v(t) = \begin{cases} 1 - \cos\left(\frac{t}{T_{me}}\pi\right), & \text{if } 0 \leq t < T_{me}, \\ 1 + \cos\left(\frac{t - T_{me}}{T_{ce} - T_{me}}\pi\right), & \text{if } T_{me} \leq t < T_{ce} \\ 0, & \text{if } T_{ce} \leq t < RR, \end{cases}$$

$Elv_{,min}$ = minimum elastance value

$Elv_{,max}$ = maximum elastance value

T_{me} & T_{ce} = instances where elastance reaches its maximum and constant values respectively

Right Atrium

$$\frac{dV_{ra}}{dt} = Q_{svn} - Q_{ti},$$
$$P_{ra} = P_{ra,un} + E_{ra}(V_{ra} - V_{ra,un}),$$
$$Q_{ti} = \begin{cases} CQ_{ti}AR_{ti}\sqrt{P_{ta} - P_{tv}}, & \text{if } P_{ta} \geq P_{tv}, \\ -CQ_{ti}AR_{ti}\sqrt{P_{rv} - P_{ra}}, & \text{if } P_{ra} < P_{rv}, \end{cases}$$

The time-varying elastance is

$$E_{ra}(t) = E_{ra,min} + \frac{E_{ra,max} - E_{ra,min}}{2} e_a(t),$$

$$e_a(t) = \begin{cases} 0, & \text{if } 0 \leq t \leq T_{ac}, \\ 1 - \cos\left(\frac{t - T_{ac}}{RR - T_{ac}} 2\pi\right), & \text{if } T_{ac} < RR, \end{cases}$$

$Era,_{min}$ = minimum elastance value

$Era,_{max}$ = maximum elastance value

Right Ventricle

$$\frac{dV_{rv}}{dt} = Q_{tt} - Q_{po},$$
$$P_{rv} = P_{rv,un} + E_{rv}(V_{rv} - V_{rv,un}),$$
$$Q_{po} = \begin{cases} CQ_{po}AR_{po}\sqrt{P_{rv} - P_{pas}}, & \text{if } P_{rv} \geq P_{pas}, \\ -CQ_{po}AR_{po}\sqrt{P_{pas} - P_{rv}}, & \text{if } P_{pas} < P_{rv}, \end{cases}$$

The time-varying elastance is

$$E_{rv}(t) = E_{rv,min} + \frac{E_{rv,max} - E_{rv,min}}{2} e_v(t),$$

$Erv_{,min}$ = minimum elastance value

$Erv_{,max}$ = maximum elastance value

Systemic Circuit

$$\begin{cases} \frac{dP_{sas}}{dt} = \frac{Q_{ao}-Q_{sas}}{C_{sas}}, \\ \frac{dQ_{sas}}{dt} = \frac{P_{sas}-P_{sat}-R_{sas}Q_{sas}}{L_{sas}}, \\ P_{sas} - P_{sas,un} = \frac{1}{C_{sas}}(V_{sas} - V_{sas,un}), \end{cases}$$

$$\begin{cases} \frac{dP_{sat}}{dt} = \frac{Q_{sas}-Q_{sat}}{C_{sat}}, \\ \frac{dQ_{sat}}{dt} = \frac{P_{sat}-P_{svn}-(R_{sat}+R_{sar}+R_{scp})Q_{sat}}{L_{sat}}, \\ P_{sat} - P_{sat,un} = \frac{1}{C_{sat}}(V_{sat} - V_{sat,un}), \end{cases}$$

$$\begin{cases} \frac{dP_{svn}}{dt} = \frac{Q_{sat}-Q_{svn}}{C_{svn}}, \\ Q_{svn} = \frac{P_{svn}-P_{ra}}{R_{svn}}, \\ P_{svn} - P_{svn,un} = \frac{1}{C_{svn}}(V_{svn} - V_{svn,un}), \end{cases}$$

Pulmonary Circuit

$$\begin{cases} \frac{dP_{pas}}{dt} = \frac{Q_{po} - Q_{pas}}{C_{pas}}, \\ \frac{dQ_{pas}}{dt} = \frac{P_{pas} - P_{pat} - R_{pas}Q_{pas}}{L_{pas}}, \\ P_{pas} - P_{pas,un} = \frac{1}{C_{pas}}(V_{pas} - V_{pas,un}) \end{cases}$$

$$\begin{cases} \frac{dP_{pat}}{dt} = \frac{Q_{pas} - Q_{pat}}{C_{pat}}, \\ \frac{dQ_{pat}}{dt} = \frac{P_{pat} - P_{pvn} - (R_{pat} + R_{par} + R_{pcp})Q_{pat}}{L_{pat}}, \\ P_{pat} - P_{pat,un} = \frac{1}{C_{pat}}(V_{pat} - V_{pat,un}), \end{cases}$$

$$\begin{cases} \frac{dP_{pvn}}{dt} = \frac{Q_{pat} - Q_{pvn}}{C_{pvn}}, \\ Q_{pvn} = \frac{P_{pvn} - P_{la}}{R_{pvn}}, \\ P_{pvn} - P_{pvn,un} = \frac{1}{C_{pvn}}(V_{pvn} - V_{pvn,un}). \end{cases}$$

A.3 Code for Optimization

```
function jac = calcJac_wVAD(t,y)
% This function calculates the non-constant Jacobian at every time step

% Obtain system constants
B = system_constants_Shi_et_al_wVAD(t,y);

jac = zeros(27,27);

jac(1,24) = -1;
jac(1,3) = 1;

jac(2,1) = -B(2);
jac(2,2) = 1;

if(y(2) > y(5))
jac(3,2) = -B(4)/(2*sqrt(y(2) - y(5)));
jac(3,5) = B(4)/(2*sqrt(y(2) - y(5)));
jac(3,3) = 1;
else
    jac(3,3) = 1;
end

jac(4,3) = -1;
jac(4,6) = 1;
jac(4,27) = 1;

jac(5,4) = -B(6);
jac(5,5) = 1;

%%%%% ONLY IF INCLUDING AORTIC VALVE
if(y(5) > y(13))
    jac(6,5) = -B(8)/(2*sqrt(y(5) - y(13)));
    jac(6,13) = B(8)/(2*sqrt(y(5) - y(13)));
    %jac(6,25) = 1;
    jac(6,6) = 1;
else
    jac(6,6) = 1;
end


jac(7,9) = 1;
jac(7,18) = -1;

jac(8,7) = -B(10);
jac(8,8) = 1;
```

```
if(y(8) > y(11))
    jac(9,8) = -B(12)/(2*sqrt(y(8) - y(11)));
    jac(9,11) = B(12)/(2*sqrt(y(8) - y(11)));
    jac(9,9) = 1;
else
    jac(9,9) = 1;
end

jac(10,9) = -1;
jac(10,12) = 1;

jac(11,10) = -B(14);
jac(11,11) = 1;

if(y(11) > y(19))
    jac(12,11) = -B(16)/(2*sqrt(y(11) - y(19)));
    jac(12,19) = B(16)/(2*sqrt(y(11) - y(19)));
    jac(12,12) = 1;
else
    jac(12,12) = 1;
end

jac(13,6) = -1/B(17);
jac(13,14) = 1/B(17);

jac(14,13) = -1/B(19);
jac(14,15) = 1/B(19);
jac(14,14) = B(18)/B(19);


 jac(15,14) = -1/B(20);
 jac(15,16) = 1/B(20);
 jac(15,26) = -1/B(20);


jac(16,15) = -1/B(22);
jac(16,16) = B(21)/B(22);
jac(16,17) = 1/B(22);

jac(17,16) = -1/B(23);
jac(17,18) = 1/B(23);

jac(18,18) = 1/B(24);
jac(18,17) = -1/B(24);
jac(18,18) = 1;

jac(19,12) = -1/B(25);
jac(19,20) = 1/B(25);
```

```
jac(20,19) = -1/B(27);
jac(20,20) = B(26)/B(27);
jac(20,21) = 1/B(27);

jac(21,20) = -1/B(28);
jac(21,22) = 1/B(28);

jac(22,21) = -1/B(30);
jac(22,22) = B(29)/B(30);
jac(22,23) = 1/B(30);

jac(23,22) = -1/B(31);
jac(23,24) = 1/B(31);

jac(24,2) = 1/B(32);
jac(24,23) = -1/B(32);
jac(24,24) = 1;


%%%%%%%%%%%%%%%%%%%% LVAD %%%%%%%%%%%%%%%%%%%
jac(25,26) = 1/B(33);
jac(25,27) = -1/B(33);

jac(26,15) = 1/B(35);
jac(26,25) = -1/B(35);
jac(26,26) = B(34)/B(35);
%%%%%%%%%%%%%%%%%%%% LVAD %%%%%%%%%%%%%%%%%%%

%%%%%%%%%%%%%%%%%%%% LVAD %%%%%%%%%%%%%%%%%%%
% %   %%%%%%%%% LVAD - VARIABLE SPEED CONTROL %%%%%
%
%   %%%Initiate variable speed cycle
%  init_varspeed = 8.00;
%
%  % HVAD
%  t_pre = 2.00;
%  t_post = 1.00;
%   if (t > init_varspeed - t_pre && t <= init_varspeed)
%      % Reduce speed from 2600 to 2400 RPM
%      dp_thresh = 80;
%
%  elseif ( t > init_varspeed && t <= init_varspeed + t_post)
%      % Increase speed to 2800 RPM
%      dp_thresh = 110;
%  else
%      % Run at normal speed of 2600 RPM
%      dp_thresh = 95;
```

```
%   end


  dp_thresh = 140;

  if((y(25) - y(5)) < dp_thresh && (y(25) - y(5)) > 0)

     % Quintic curve
     jac(27,5) = B(36)*5*((y(25) - y(5)))^4 + B(37)*4*((y(25) - y(5)))^3
+ B(38)*3*((y(25) - y(5)))^2 ...
         + B(39)*2*((y(25) - y(5))) + B(40);
     jac(27,25) = - B(36)*5*((y(25) - y(5)))^4 - B(37)*4*((y(25) -
y(5)))^3 - B(38)*3*((y(25) - y(5)))^2 ...
         - B(39)*2*((y(25) - y(5))) - B(40);

     jac(27,27) = 1;

 else
     jac(27,27) = 1;
 end

%%%%%%%%%%%%%%%%%%% LVAD %%%%%%%%%%%%%%%%%%

%%%

%jac = jac*-1;



end
```

```
function y = calldae(tempval,tspan,y0new,init)

tempval

y = dae4('shi_dae_wVAD',tspan,y0new,init);


end
```

```
CardiacInitialConditions_Shi_et_alwVAD.txt
60
0
0
130
0
0
39
0
0
110
0
0
80
5
80
0
10
0
20
0
20
0
10
0
60
0
0
```

```
function f = cardiac_lpn_system_Shi_et_al_ALG_ONLY_wVAD(y)

t=0;

% Obtain system constants
B = system_constants_Shi_et_al_wVAD(t,y);

% Specify system of equations

% Left Atrium
f(1) = y(1) - 60;
f(2) = y(2) - B(1) - B(2)*(y(1) - B(3));
if(y(2) > y(5))
    f(3) = y(3) - B(4)*sqrt(abs(y(2) - y(5)));
else
    f(3) = y(3) - 0;
end

f(4) = y(4) - 130;
f(5) = y(5) - B(5) - B(6)*(y(4) - B(7));
if(y(5) > y(13))
    f(6) = y(6) - B(8)*sqrt(abs(y(5) - y(13)));
else
    f(6) = y(6) - 0;
end

f(7) = y(7) - 39;
f(8) = y(8) - B(9) - B(10)*(y(7) - B(11));
if(y(8) > y(11))
    f(9) = y(9) - B(12)*sqrt(abs(y(8) - y(11)));
else
    f(9) = y(9) - 0;
end

f(10) = y(10) - 110;
f(11) = y(11) - B(13) - B(14)*(y(10) - B(15));
if(y(11) > y(19))
    f(12) = y(12) - B(16)*sqrt(abs(y(11) - y(19)));
else
    f(12) = y(12) - 0;
end

f(13) = y(13) - 80;
f(14) = y(14) - 0;

f(15) = y(15) - 80;
f(16) = y(16) - 0;
```

```
f(17) = y(17) - 10;
f(18) = y(18) - (y(17) - y(8))/B(24);

f(19) = y(19) - 20;
f(20) = y(20) - 0;

f(21) = y(21) - 20;
f(22) = y(22) - 0;

f(23) = y(23) - 10;
f(24) = y(24) - (y(23) - y(2))/B(32);

f(25) = y(25) - 60;
f(26) = y(26) - 0;

%%%%%%%%%%%%%%%%%%% LVAD %%%%%%%%%%%%%%%%%%%
 if((y(25) - y(5)) < 140 && (y(25) - y(5)) > 0)

    % Quintic qurve
    f(27) = y(27) - B(36)*((y(25) - y(5)))^5 - B(37)*((y(25) - y(5)))^4 -
B(38)*((y(25) - y(5)))^3 ...
        - B(39)*((y(25) - y(5)))^2 - B(40)*((y(25) - y(5))) - B(41);

 else
     f(27) = y(27) - 0;
 end
%%%%%%%%%%%%%%%%%%% LVAD %%%%%%%%%%%%%%%%%%%

end
```

```
function f = cardiac_lpn_system_Shi_et_al_Implicit_wVAD(t,y,yp)


% Obtain system constants
B = system_constants_Shi_et_al_wVAD(t,y);

% Specify system of equations

% Left Atrium
f(1,1) = yp(1) - y(24)+ y(3);
f(2,1) = y(2) - B(1) - B(2)*(y(1) - B(3));
if(y(2) > y(5))
    f(3,1) = y(3) - B(4)*sqrt(abs(y(2) - y(5)));
else
    f(3,1) = y(3) - 0;
end

f(4,1) = yp(4) - y(3) + y(6) + y(27);
f(5,1) = y(5) - B(5) - B(6)*(y(4) - B(7));

if(y(5) > y(13))
    f(6,1) = y(6) - B(8)*sqrt(abs(y(5) - y(13)));
else
    f(6,1) = y(6) - 0;
end



f(7,1) = yp(7) - y(18) + y(9);
f(8,1) = y(8) - B(9) - B(10)*(y(7) - B(11));
if(y(8) > y(11))
    f(9,1) = y(9) - B(12)*sqrt(abs(y(8) - y(11)));
else
    f(9,1) = y(9) - 0;
end

f(10,1) = yp(10) - y(9) + y(12);
f(11,1) = y(11) - B(13) - B(14)*(y(10) - B(15));
if(y(11) > y(19))
    f(12,1) = y(12) - B(16)*sqrt(abs(y(11) - y(19)));
else
    f(12,1) = y(12) - 0;
end

f(13,1) = yp(13) - (y(6) - y(14))/B(17);
f(14,1) = yp(14) - (y(13) - y(15) - B(18)*y(14))/B(19);

f(15,1) = yp(15) - (y(14) + y(26) - y(16))/B(20);
```

```
f(16,1) = yp(16) - (y(15) - y(17) - B(21)*y(16))/B(22);

f(17,1) = yp(17) - (y(16) - y(18))/B(23);
f(18,1) = y(18) - (y(17) - y(8))/B(24);

f(19,1) = yp(19) - (y(12) - y(20))/B(25);
f(20,1) = yp(20) - (y(19) - y(21) - B(26)*y(20))/B(27);

f(21,1) = yp(21) - (y(20) - y(22))/B(28);
f(22,1) = yp(22) - (y(21) - y(23) - B(29)*y(22))/B(30);

f(23,1) = yp(23) - (y(22) - y(24))/B(31);
f(24,1) = y(24) - (y(23) - y(2))/B(32);

f(25,1) = yp(25) - (y(27) - y(26))/B(33);
f(26,1) = yp(26) - (y(25) - y(15) - B(34)*y(26))/B(35);
%%%%%%%%%%%%%%%%%%% LVAD %%%%%%%%%%%%%%%%%%

% %  %%%%%%%%%% LVAD - VARIABLE SPEED CONTROL %%%%%
% %  % Initiate variable speed cycle
%   init_varspeed = 8.00;
%
% %  %%% HVAD
%  t_pre = 2.00;
%  t_post = 1.00;
%   if (t > init_varspeed - t_pre && t <= init_varspeed)
%      % Reduce speed from 2600 to 2400 RPM
%      dp_thresh = 80;
%
%  elseif ( t > init_varspeed && t <= init_varspeed + t_post)
%      % Increase speed to 2800 RPM
%      dp_thresh = 110;
%  else
%      % Run at normal speed of 2600 RPM
%      dp_thresh = 95;
%  end

dp_thresh = 140;

 if((y(25) - y(5)) < dp_thresh && (y(25) - y(5)) > 0)

     % Quintic curve
     f(27,1) = y(27) - B(36)*((y(25) - y(5)))^5 - B(37)*((y(25) -
y(5)))^4 - B(38)*((y(25) - y(5)))^3 ...
         - B(39)*((y(25) - y(5)))^2 - B(40)*((y(25) - y(5))) - B(41);

 else
```

```
    f(27,1) = y(27) - 0;
 end

%%%%%%%%%%%%%%%%%%% LVAD %%%%%%%%%%%%%%%%%%

end
```

```
function ys=dae4(f,tspan,y0,nint,g)
% function ys=dae4(f,tspan,y0,nint,g)
% solves a set of differential algebraic equations (DAEs)
%        f(t,y,y')=0  where y'=dy/dt
% with a 4th order method starting from y0 at time t0 and
% finishing at time tfin where tspan=[t0 t1 ... tfin].
% y0 is a column vector, tspan is a row vector.
%
% The solution is returned at all the times in tspan.
% The time steps are approx diff(ts)/nint within the domain.
% Error management is entirely up to the user via tspan & nint.
% If optional nint is omitted, then it is assumed to be 1.
% If matlab warms of matrices with high condition number,
% then increase nint.
%
% The jacobians of f, namely k=df/dy and m=df/dy', must be
% provided by f, at each time compute: [f,k,m]=func(t,y,y').
% Both m and k may be returned as sparse matrices.
% If warnings of poor convergence occur, then the coded
% jacobians probably have errors.
%
% The optional argument g is the name of a user supplied
% function g(t,y,y') that is invoked immediately the
% solution is computed at the times in tspan.
%
% The initial state y0 should be consistent with the
% algebraic part of the DAE, but if not consistent then
% transient oscillations will appear as it works towards
% consistency.
%
% The method will also work well for stiff sets of ODEs.
% It is unsuitable for problems with an oscillatory spectrum
% as non-dissipative oscillations will grow for h*omega<4 ;
% instead use dae4o.m
%
% See pendrun.m, penddae.m & pendg.m for a pendulum example.
% See also dae2.m and dae4o.m for other versions.
%
% (c) Tony Roberts, 18 Aug 1998, aroberts@usq.edu.au

if nargin<4, nint=1; end
gcall=(nargin==5);
nout=length(tspan);
ndim=length(y0);
ys=zeros(ndim,nout);
newtol=1e-6;
newtmax=10;
newtit=zeros(1,newtmax);
```

```
% weights for BDF est of deriv
wd=[0 1 1/2 1/3 1/4];
wds=sum(wd);

% to allow for varying spaced output, fit a spline
% and solve in s=[1,nts] rather than in t
% dt is dt/ds at each time s
nts=1+nint*(nout-1);
if nts<5, disp('ERROR: dae4 needs at least 4 steps'), return, end
ts=spline(1:nint:nts,tspan,(1:nts));
dt=spline(1:nint:nts,tspan,(1:nts)+1e-7);
dt=(dt-ts)/1e-7;

% initialise by solving first four steps together assuming
% a quartic between them (zero fifth difference).
yy=zeros(ndim,4); % initial guess
y=[y0 yy];
for newt=1:newtmax
      % extrapolate
      y2=rot90(cumsum(rot90(y )),-1);
      y3=rot90(cumsum(rot90(y2)),-1);
      y4=rot90(cumsum(rot90(y3)),-1);
      y5=rot90(cumsum(rot90(y4)),-1);
      % evaluate residuals
      [f2,k2,m2]=feval(f,ts(2),y2(:,1),y2*wd'/dt(2));
      [f3,k3,m3]=feval(f,ts(3),y3(:,1),y3*wd'/dt(3));
      [f4,k4,m4]=feval(f,ts(4),y4(:,1),y4*wd'/dt(4));
      [f5,k5,m5]=feval(f,ts(5),y5(:,1),y5*wd'/dt(5));
      % solve simultaneous equations
      yy(:)=-[  k2+m2/dt(2)    k2+3/2*m2/dt(2)    k2+11/6*m2/dt(2)
k2+25/12*m2/dt(2)
              2*k3+m3/dt(3)  3*k3+5/2*m3/dt(3)  4*k3+13/3*m3/dt(3)
5*k3+77/12*m3/dt(3)
              3*k4+m4/dt(4)  6*k4+7/2*m4/dt(4) 10*k4+47/6*m4/dt(4)
15*k4+171/12*m4/dt(4)
              4*k5+m5/dt(5) 10*k5+9/2*m5/dt(5) 20*k5+37/3*m5/dt(5)
35*k5+319/12*m5/dt(5)
                    ]\[f2;f3;f4;f5];
      y(:,2:5)=y(:,2:5)+yy;
      if max(abs(yy(:)))<newtol*max(abs(y(:))), break, end
end
% output as requested
ys(:,1)=y(:,1);
if gcall, feval(g,ts(1),y(:,1),y*wd'/dt(1)); end
for n=2:5
      y=rot90(cumsum(rot90(y)),-1);
    if rem(n-1,nint)==0, ys(:,1+(n-1)/nint)=y(:,1);
    if gcall, feval(g,ts(n),y(:,1),y*wd'/dt(n)); end, end
```

```
end

% take fourth order steps over domain
for n=6:nts
       h=dt(n);
       y=rot90(cumsum(rot90(y)),-1); % extrapolate a guess
       for newt=1:newtmax
       [f1,k1,m1]=feval(f,ts(n),y(:,1),y*wd'/h);
       w=-(wds*m1/h+k1)\f1;
       y=y+w*ones(size(wd));
       if max(abs(w))<newtol*max(abs(y(:))), break, end
       end
       newtit(newt)=newtit(newt)+1;
    if rem(n-1,nint)==0, ys(:,1+(n-1)/nint)=y(:,1);
    if gcall, feval(g,ts(n),y(:,1),y*wd'/dt(n)); end, end
end

% check on how many Newtonian iterations were required
newtm=sum((1:newtmax).*newtit)/sum(newtit);
if newtm>newtmax/2,
   disp('WARNING: poor or no convergence in dae4')
   newtit=newtit
end
```

```
function cost = dae_optimize_v1(MAP_target, Q_target,
tspan,y0new,init,num_iter,half_iter,tempval,t_final)

global tempfac1 tempfac2
tempfac1 = tempval(1);
tempfac2 = tempval(2);

y = calldae(tempval,tspan,y0new,init);

MAP = mean(y(15,half_iter:num_iter))

st = 1;
fin = num_iter;
%t_final = 8;

Mean_Qvad = trapz(tspan(st:fin),y(26,st:fin))*(60/t_final)*1e-3

Mean_Qav = trapz(tspan(st:fin),y(6,st:fin))*(60/t_final)*1e-3


cost(1) = MAP - MAP_target;
cost(2) = Mean_Qvad - Q_target;


end
```

```
MassPatient_input_v2
clear all
    clc
    %call patientData Excel file
    patientData = readtable('HM3_PatientData.xlsx');

%% Pre-optimized Function Work

    %seperate tables into arrays
    PI = (table2array(patientData(:,1)))';
    Q_target = (table2array(patientData(:,2)))';
    Speed = ( table2array( patientData(:,3) ) )';
    MAP_target = (table2array(patientData(:,4)))';

    %initialize global variables
    global tempfac1 tempfac2 SpeedOG poly
    tempfac1 = 0.58;
    tempfac2 = 0.5;
    poly = 1;

    %What patient to run?
    PatIndex = input('Which patient(s) would you like to run?\n (single
patient: 3)\n(patients 3 thru 5: 3 5)\n', 's');

    x = str2num(PatIndex);
    if length(x) == 1
        x(2)= x(1);
    end

%% Run Patient(s) and Put information into Structure; Save Structure
    ctr = 0;
    tic
    for i = x(1):x(2)
        tic
       %Speed for patient(i) -> find polynomials for patient i
       SpeedOG = Speed(i);
       OGspeed = SpeedOG;
        poly = PC_HM3(OGspeed,3);


      [data,patient_matrix] =
optimizedMain_Loop(MAP_target(i),Q_target(i));%Change optimizedMain to
optimizeMain_Loop to run a matrix of tempfac values
 %       patient_matrix = [test.tempfac1; test.tempfac2; test.MAP;
test.Mean_Qvad; test.Mean_Qav];
        %save data for patient i in structure
        patient(i).PatientIndex = PI(i);
        patient(i).MAP_Target = MAP_target(i);
```

```
        patient(i).Q_Target = Q_target(i);
        patient(i).LVAD_Speed = Speed(i);
        patient(i).PatientData = data;
        patient(i).flag = 1;

        patmat(i).Patient_Matrix = patient_matrix;
        %flag patient if FinalMAP =/ MAP_target or FinalQvad =/ Q_target
        if data.FinalMAP == MAP_target(i) && data.FinalQvad ==
Q_target(i)
            patient(i).flag = 0;
            ctr = ctr + 1;
        end


        %Save Patient File
        filename = strcat('PatientData/HM3/Patient_',num2str(i),'.mat');
        save(filename,'patient');

        filename =
strcat('PatientData/HM3/Patient_Matrix/PatMat_',num2str(i),'.mat');
        save(filename,'patmat');

        toc
    end
    toc
%% How many flags
    fprintf(strcat(num2str(ctr),' patients were flagged'));
```

```
function best_factor = opt_factor(fdata)
% this functions stores and uses the scaling factor which is used to
% modulate the systemic vascular resistance

%best_factor = 0.58;

fdata = temp_factor(fdata);

best_factor = a.temp_init;



end
```

```
function [data,patient_matrix] = optimizedMain_Loop(MAP_input,Q_input)
%
**********************************************************************
% Testing 2006 shi et al model (no valve angle, no reverse flow)
% Included HVAD at 2600RPM
% using DAE function written by Tony Roberts (found online)
% CVKeshav
% May 2017
%**********************************************************************
**

% clc
% clear all
% close all

global tempfac1 tempfac2
tempfac1 = 0.58;
tempfac2 = 0.5;


% Read initial conditions for original set of equations
fileID = fopen('Cardiac_Initial_Conditions_Shi_et_al_wVAD.txt');
init_c = textscan(fileID,'%f');
fclose(fileID);

ic_guess = init_c{1,1};

y0est= ic_guess;

% Use fsolve to obtain better guess for ICs

%X = fsolve(@symbolic_DAE_v3_ALG_only,ic_guess);
X = fsolve(@cardiac_lpn_system_Shi_et_al_ALG_ONLY_wVAD,ic_guess);


yp0 = zeros(length(ic_guess),1);

[y0new,yp0new] =
decic(@cardiac_lpn_system_Shi_et_al_Implicit_wVAD,0,X,ic_guess,yp0,yp0);


% determine tspan
t_final = 5; %t_final = 8; 12
num_iter = 2000; %num_iter = 8000; 6000
half_iter = num_iter/2;

tspan = linspace(0,t_final,num_iter);
init = 10;
```

```
%tic

% call DAE solver for 1st solve
%y = dae4o('shi_dae_wVAD',tspan,y0new,init);

y = dae4('shi_dae_wVAD',tspan,y0new,init);

MAP = mean(y(15,half_iter:num_iter))

% plot_params(tspan,y);

st = 1;
fin = num_iter;

Mean_Qvad = trapz(tspan(st:fin),y(26,st:fin))*(60/t_final)*1e-3

Mean_Qav = trapz(tspan(st:fin),y(6,st:fin))*(60/t_final)*1e-3


%% Test optimization
%
% x0 = [0.5; 0.5];
%
% myobj = @(x)testsq(x);
% lb = [-1; -1];
% ub = [2; 2];
%
% [bestx] = lsqnonlin(myobj,x0,lb,ub);
%
% vfinal = fminsearch(myobj,x0)
%
% %[x,fval] = fminunc(myobj,x0);
%
% bestx



%% Set up optimization **(TURNED OFF FOR LOOP CODE TO SPEED UP AND RUN
LOOP)**
% Perform Optimization
% close all
%
%  %temp_init = [0.58, 0.5];
% MAP_target = MAP_input;
% Q_target = Q_input;
% % global tempfac
% % tempfac = temp_init;
```

```
% fdata.temp_init = temp_init;
%
% cost = @(tempval) dae_optimize_v1(MAP_target,
Q_target,tspan,y0new,init,num_iter,half_iter,tempval,t_final);
% lb = [0.05, 0.05];
% ub = [1.3, 2.4];
%
% [best_res1] = lsqnonlin(cost,temp_init,lb,ub);
%
% %best_res = fminunc(cost,temp_init);
%
% %best_res = fminsearch(cost,temp_init);
%
% best_res1


%% Test optimal value
%Commented out for convenience, this is a redundant part of the code%
ctr = 0; % counter
for i = 0.01:0.1:1.5  % 0.1:0.1:1.5
    tempfac1 = i; %(0.1-0.9) Vascular Resistance
    for n = 0.05:0.2:2.4 %2.4 %0.05:0.2:2.4
        tempfac2 = n;%(0.05-0.24) Elv_max

        ctr = ctr +1

        y = dae4('shi_dae_wVAD',tspan,y0new,init);

        MAP = mean(y(15,half_iter:num_iter));

        % plot_params(tspan,y);

        st = 1;
        fin = num_iter;

        Mean_Qvad = trapz(tspan(st:fin),y(26,st:fin))*(60/t_final)*1e-3;

        Mean_Qav = trapz(tspan(st:fin),y(6,st:fin))*(60/t_final)*1e-3;


        test.tempfac1(ctr) = tempfac1;
        test.tempfac2(ctr) = tempfac2;
        test.MAP(ctr) = MAP;
        test.Mean_Qvad(ctr) = Mean_Qvad;
        test.Mean_Qav(ctr) = Mean_Qav;

%         loop(ctr).test = test;
    end
```

```
end
patient_matrix = [test.tempfac1; test.tempfac2; test.MAP; test.Mean_Qvad;
test.Mean_Qav];

clear data
data.tspan = tspan;
data.y = y;
data.optval = [tempfac1,tempfac2];
data.FinalMAP = MAP;
data.FinalQvad = Mean_Qvad;


end
```

```
function cost = dae_optimize_SO(MAP_target, Q_target,
tspan,y0new,init,num_iter,half_iter,tempval,t_final)
format long G
global tempfac1 tempfac2
tempfac1 = tempval(1);
tempfac2 = tempval(2);

y = calldae(tempval,tspan,y0new,init);

MAP = mean(y(15,half_iter:num_iter))

st = 1;
fin = num_iter;

Mean_Qvad = trapz(tspan(st:fin),y(26,st:fin))*(60/t_final)*1e-3

Mean_Qav = trapz(tspan(st:fin),y(6,st:fin))*(60/t_final)*1e-3

fileID = fopen('Patient1.txt','a')
fprintf(fileID,'%1d %2d %3d %4d %5d\n', MAP, Mean_Qvad,
Mean_Qav,tempfac1,tempfac2);
fclose(fileID);

cost(1) = MAP - MAP_target;
cost(2) = Mean_Qvad - Q_target;

end
```

```
function [poly] = PC_HM3(OGspeed,order)
%HM3 h-q curves
oldspeed = 5400;
newspeed = OGspeed;

Q = [0.005082353 0.702635294 1.434494118 2.154917647 2.863905882
3.584329412 4.316188235 5.013741176 5.7456 6.466023529];
P = [122.1175691 117.5603832 112.3565031 105.8645413 98.72891778
89.01485655 78.0111974 59.92119389 39.2512364 10.2045849];

ratio = newspeed/oldspeed;

ratiosquared = ratio^2;

NewQ = Q*ratio;
NewP = P*ratiosquared;
poly = polyfit(NewP,NewQ,order);
end
```

```
function [poly] = PerformanceCurves(speed,order)
%HVAD h-q curves
oldspeed = 2600;
newspeed = speed;

Q = [0 1 2 3 4 5 6 7 8 9];
P = [95 93 90 85 77 67 56 42 28 10];

ratio = newspeed/oldspeed;

ratiosquared = ratio^2;

NewQ = Q*ratio;
NewP = P*ratiosquared;
poly = polyfit(NewP,NewQ,order);
end
```

```
function [] = plot_params(tspan,y)

figure
subplot(211)
plot(tspan,y(5,:))
hold on
plot(tspan,y(15,:),'r')
plot(tspan,y(2,:),'k')
legend('Plv','Psat','Pla')
xlabel('Time(s)')
ylabel('Pressure (mmHg)')

subplot(212)
plot(tspan,y(4,:))
hold on
plot(tspan,y(1,:),'r')
legend('Vlv','Vla')
xlabel('Time(s)')
ylabel('Volume (ml)')

%----------------------------------
figure
subplot(221)
plot(y(4,:),y(5,:))
xlabel('Volume (ml)')
ylabel('Pressure (mmHg)')
title('LV P-V loop')

subplot(222)
plot(y(1,:),y(2,:))
xlabel('Volume (ml)')
ylabel('Pressure (mmHg)')
title('LA P-V loop')

subplot(223)
plot(y(10,:),y(11,:))
xlabel('Volume (ml)')
ylabel('Pressure (mmHg)')
title('RV P-V loop')

subplot(224)
plot(y(7,:),y(8,:))
xlabel('Volume (ml)')
ylabel('Pressure (mmHg)')
title('RA P-V loop')

%----------------------------------
figure
subplot(211)
plot(tspan,y(8,:))
```

```
hold on
plot(tspan,y(11,:))
plot(tspan,y(19,:))
legend('Pra','Prv','Ppas')
xlabel('Time(s)')
ylabel('Pressure (mmHg)')

subplot(212)
plot(tspan,y(10,:))
hold on
plot(tspan,y(7,:),'r')
legend('Vrv','Vra')
xlabel('Time(s)')
ylabel('Volume (ml)')

%-------------------------------------
figure
subplot(211)
plot(tspan,y(3,:))
hold on
plot(tspan,y(6,:))
plot(tspan,y(26,:))
legend('Qmi','Qao','Qvad')
xlabel('Time(s)')
ylabel('Flow (ml/s)')

subplot(212)
plot(tspan,y(9,:))
hold on
plot(tspan,y(12,:))
legend('Qti','Qpa')
xlabel('Time(s)')
ylabel('Flow (ml/s)')


end
```

```
function [f,k,m] = shi_dae_wVAD(t,y,yp)


% This function assembles the system of DAE equations, along with the
% jacobians k=df/dy and m = df/dy'

% Get system of DAEs
f = cardiac_lpn_system_Shi_et_al_Implicit_wVAD(t,y,yp);

% Obtain jacobian k = df/dy
k = calcJac_wVAD(t,y);

% obtain jacobian m = df/dy'
% This jacobian is based on y' variables
J = zeros(27,27);
J(1,1) = 1;
J(4,4) = 1;
J(7,7) = 1;
J(10,10) = 1;
J(13,13) = 1;
J(14,14) = 1;
J(15,15) = 1;
J(16,16) = 1;
J(17,17) = 1;
J(19,19) = 1;
J(20,20) = 1;
J(21,21) = 1;
J(22,22) = 1;
J(23,23) = 1;
J(25,25) = 1;
J(26,26) = 1;

m=J;


end
```

```
function B = system_constants_Shi_et_al_wVAD(t,y)

% Empirical numbers obtained from literature for healthy individuals
% Determine cardiac cycle time

RR = 0.8;                       % Length of cardiac cycle = 0.8 s
tcar = mod(t,RR);

% Specify time thresholds for activation functions
Tac = 0.875*RR;
Tme = 0.3*sqrt(RR);
Tce = 1.5*Tme;

% Determmine activation function for atrium
if(tcar >= 0 && tcar <= Tac)
    ea = 0;
else
    ea = 1 - cos((tcar-Tac)*2*pi/(RR-Tac));
end

% Determine activation function for ventricle
if(tcar >=0 && tcar < Tme)
    ev = 1 - cos(tcar*pi/Tme);
elseif(tcar >= Tme && tcar < Tce)
    ev = 1 + cos((tcar-Tme)*pi/(Tce-Tme));
else
    ev = 0;
end

% Specify Elastances
Ela_max = 0.25;
Ela_min = 0.15;

% Elv_max = 2.5;
% Elv_max = 0.5; %%%%% HEART FAILURE !!!!
% Elv_min = 0.07;

%%%%% NEW PARAMETERS FOR LOWER INITIAL BP
global tempfac2
Elv_max = tempfac2; %0.45; %0.5; %2.5;
%Elv_max = 0.5; %%%%% HEART FAILURE !!!!
Elv_min = 0.085; %0.07;

Era_max = 0.25;
Era_min = 0.15;

Erv_max = 1.15;
Erv_min = 0.07;

%%%%% Incorporating Baroreceptor response
```

```
% testing sum of sine fit
% clear map norm_press
% map = y(15);
% setpoint = 70;
% norm_press = map/setpoint;
res_factor = 1;

% 2 sine terms fit
%res_factor = 1.434*sin(0.3968*norm_press + 1.93) +
0.2048*sin(3.33*norm_press - 0.1073);

% 3 sine terms fit
%res_factor = 3.336*sin(0.1352*norm_press + 2.694) +
0.1806*sin(3.424*norm_press - 0.3021) + 0.04048*sin(6.943*norm_press +
2.633);

% fid = fopen('baroresponse_trial.txt','a');
% fprintf(fid,'%6.2f \t %6.2f \t %6.2f\n',t,map,res_factor);
% fclose(fid);

%%%%% NEW PARAMETERS FOR LOWER INITIAL BP
% Arterial Resistances

%Specify patient resistance based on cath measurements
global tempfac1
external_factor = tempfac1;

%scale_factor = 0.58*res_factor;

scale_factor = external_factor*res_factor;

modf = 1.0; %%% FOR REDUCING INITIAL BP
Rsat = 0.05*modf*scale_factor;
Rsar = 0.5*modf*scale_factor;
Rscp = 0.52*modf*scale_factor;
Rsvn = 0.075*modf*scale_factor;

% Modeling pulmonary hypertension
pscale = 1.0;
Rpat = 0.01*pscale;
Rpar = 0.05*pscale;
Rpcp = 0.07*pscale;



% Specify all system constants
B = zeros(38,1);

B(1) = 1;
B(2) = Ela_min + 0.5*(Ela_max - Ela_min)*ea;
```

```
B(3) = 4;
B(4) = 350; %400; %%%%% NEW PARAMETERS FOR LOWER INITIAL BP
B(5) = 1;
B(6) = Elv_min + 0.5*(Elv_max -Elv_min)*ev;
B(7) = 5;
B(8) = 300; %350; %%%%% NEW PARAMETERS FOR LOWER INITIAL BP
B(9) = 1;
B(10) = Era_min + 0.5*(Era_max - Era_min)*ea;
B(11) = 4;
B(12) = 400;
B(13) = 1;
B(14) = Erv_min + 0.5*(Erv_max - Erv_min)*ev;
B(15) = 10;
B(16) = 350;
B(17) = 0.08;
B(18) = 0.003;
B(19) = 0.000062;
B(20) = 1.4; %1.6; %%%%% NEW PARAMETERS FOR LOWER INITIAL BP
%B(20) = 0.8; % LOWERING Csat to raise MAP - DOES NOT WORK, ONLY
INCREASES RANGE, NOT MEAN
%B(21) = 1.07;
B(21) = Rsat + Rsar + Rscp;
B(22) = 0.0017;
B(23) = 20.5;
B(24) = Rsvn; %0.075;
B(25) = 0.18;
B(26) = 0.002;
B(27) = 0.000052;
B(28) = 3.8;
B(29) = Rpat+Rpar+Rpcp; %0.13;
B(30) = 0.0017;
B(31) = 20.5;
B(32) = 0.006;

B(33) = 0.08; % Capacitance for outflow graft
B(34) = 0.06; % Resistance for outflow graft
B(35) = 0.000062; % Inductance for outflow graft

% % Constants for LVAD H-Q curve
% % ----- TYPE OF LVAD -----
% % 1: HVAD
% % 2: HM3
% % ------------------------
% % ----- RPM for HVAD -----
% % 1: 2200 (HVAD)
% % 2: 2400 (HVAD)
% % 3: 2600 (HVAD)
% % 4: 2800 (HVAD)
% % 5: 3000 (HVAD)
% % ------------------------
```

```
% % ----- RPM for HM3 -----
% % 1: 3000 (HM3)
% % 2: 3400 (HM3)
% % 3: 4000 (HM3)
% % 4: 5000 (HM3)
% % 5: 5400 (HM3)
% % 6: 6000 (HM3)
% % 7: 7400 (HM3)

global SpeedOG poly
OGspeed = SpeedOG;
poly = PC_HM3(OGspeed,3);

                B(36) = 0;
                B(37) =0;
                B(38) = poly(1)*16.67;
                B(39) = poly(2)*16.67;
                B(40) = poly(3)*16.67;
                B(41) = poly(4)*16.67;
end
```

```
function fdata = temp_factor(fdata)

tempf = newval;

end
```

```
function cost = dae_optimize_SO(MAP_target, Q_target,
tspan,y0new,init,num_iter,half_iter,tempval,t_final)
format long G
global tempfac1 tempfac2
tempfac1 = tempval(1);
tempfac2 = tempval(2);

y = calldae(tempval,tspan,y0new,init);

MAP = mean(y(15,half_iter:num_iter))

st = 1;
fin = num_iter;

Mean_Qvad = trapz(tspan(st:fin),y(26,st:fin))*(60/t_final)*1e-3

Mean_Qav = trapz(tspan(st:fin),y(6,st:fin))*(60/t_final)*1e-3

fileID = fopen('Patient1.txt','a')
fprintf(fileID,'%1d %2d %3d %4d %5d\n', MAP, Mean_Qvad,
Mean_Qav,tempfac1,tempfac2);
fclose(fileID);

cost(1) = MAP - MAP_target;
cost(2) = Mean_Qvad - Q_target;

end
```

```
MassPatientInput_SO
clear all
    clc
    format long G
    %call patientData Excel file
    patientData = readtable('HM3_PatientData.xlsx');

    Optvals = readtable('PatientsOptvals.xlsx');

%% Pre-optimized Function Work

    %seperate tables into arrays
    PI = (table2array(patientData(:,1)))';
    Q_target = 77 %(table2array(patientData(:,2)))';
    Speed = (table2array( patientData(:,3) ) )';
    MAP_target = 5 %(table2array(patientData(:,4)))';
    pat_optval2 = (table2array(Optvals(:,2)))';

    %initialize global variables
    global tempfac1 tempfac2 elv_max poly
    tempfac1 = 0.58;
    poly = 1;

    %What patient to run?
    PatIndex = input('Which patient(s) would you like to run?\n (single
patient: 3)\n(patients 3 thru 5: 3 5)\n', 's');

    x = str2num(PatIndex);
    if length(x) == 1
        x(2)= x(1);
    end

%% Run Patient(s) and Put information into Structure; Save Structure
    ctr = 0;
    tic
    for i = x(1):x(2)
        tic
        %find tempfac2 for the patient(s) you are running, to initialize
        %starting point speed
        tempfac2 = Speed(i);

        %find polynomials for patient i
        OGspeed = tempfac2;
        poly = PC_HM3(OGspeed,3);

        %get elv_max for patient i which is gotten from optval2 taken
from
        %the previous step
        elv_max = pat_optval2(i);
```

```
        [data] = optimizedMain_SO(MAP_target,Q_target);%Change
optimizedMain to optimizeMain_Loop to run a matrix of tempfac values
        % save data in a new structure
        % opt speed, MAP at opt speed, flows at opt speed, solution data
(y)
        new_pat(i).y = data.y;
        new_pat(i).optval1 = data.optval_1;
        new_pat(i).optval2 = data.optval_2;
        new_pat(i).FinalMAP = data.FinalMAP;
        new_pat(i).FinalQvad = data.FinalQvad;
        new_pat(i).FinalQav = data.FinalQav;

%             SpeedOpt(i).Solution = Solution;
%
        %Save Patient File
%         filename =
strcat('PatientData/HVAD/Patient_',num2str(i),'.mat');
%         save(filename,'patient');

        %filename =
strcat('PatientData/HVAD/Patient_Matrix_Optval2constant/PatMat_opt2cons_'
,num2str(i),'.mat');
        filename =
strcat('SpeedOptimization_Results/SpeedOpt_',num2str(i),'.mat');
        save(filename,'data');

        toc
    end

    % Save all patient data
      filename =
strcat('SpeedOptimization_Results/SpeedOpt_allpatients.mat');
        save(filename,'new_pat');
```

```
OptimizationPlotting
clear all
clc

OG = readtable('HM3_PatientData.xlsx');
% OptimizationData = readtable('OptimizationResults.xlsx');
% NegOptimData = readtable('NegativeOptimizationResults.xlsx');
 PI = (table2array(OG(:,1)));
 MAP =(table2array(OG(:,4)));
 Q =(table2array(OG(:,2)));
 Speed =(table2array(OG(:,3)));
 %DiffSpeed = (table2array(OptimizationData(:,5)))';

%  Neg_PI = (table2array(NegOptimData(:,1)))';
%  Neg_MAP =(table2array(NegOptimData(:,2)))';
%  Neg_Q =(table2array(NegOptimData(:,3)))';
%  Neg_Speed =(table2array(NegOptimData(:,4)))';
%  Neg_DiffSpeed = (table2array(NegOptimData(:,5)))';
%

% MAP vs Fick CO
figure
ms = 100; % makersize
fs = 20; %Font Size
lw = 10; %Line Width
% szPos = reshape(abs(DiffSpeed),numel(DiffSpeed),1);
% szNeg = reshape(abs(Neg_DiffSpeed),numel(Neg_DiffSpeed),1);
% szPosBig = szPos*10;
% szNegBig = szNeg*10;
hold on
%Boundaries for targets/Green Bars
xp1 = [3 9 9 3];
%yp1 = [69 69 71 71];
yp1 = [75 75 79 79];
patch(xp1,yp1,'g','Facealpha',0.3)
%Boundaries for targets/Green Bars
xp2 = [4.9 5.1 5.1 4.9];
yp2 = [55 55 115 115];
patch(xp2,yp2,'g','Facealpha',0.3)

scatter(Q,MAP,ms,Speed,'filled','MarkeredgeColor','k','MarkerFaceAlpha',.
9)
%scatter(Neg_Q,Neg_MAP,szNegBig,Neg_Speed,'filled','MarkeredgeColor','k')

grid on
xlabel('Q [L/min]')
ylabel('MAP [mmHg]')
set(gca,'FontSize',fs,'FontWeight','bold')
colorbar
colormap cool
```

```
caxis([3000 7500])
ylim([55 115])

%%

% %Plotting other graphs
% figure
% fs = 20; %Font Size
% lw = 5; %Line Width
% hold on
%
% subplot(221) %Q vs DiffSpeed
% plot(Q,DiffSpeed,'o','MarkerFaceColor','b')
% xp2 = [4.9 5.1 5.1 4.9];
% yp2 = [-800 -800 200 200];
% patch(xp2,yp2,'g','Facealpha',0.3)
% xlabel('Q [L/min]')
% ylabel('Difference in Speed [RPM]')
% set(gca, 'Fontsize',fs)
% ylim([-800 200])
% grid on
%
% subplot(222) %MAP vs DiffSpeed
% plot(MAP,DiffSpeed,'o','MarkerFaceColor','b')
% xp1 = [69 71 71 69];
% yp1 = [-800 -800 200 200];
% patch(xp1,yp1,'g','Facealpha',0.3)
% xlabel('MAP [mmHg]')
% ylabel('Difference in Speed [RPM]')
% set(gca,'FontSize',fs)
% ylim([-800 200])
% grid on
```

```
function [data] = optimizedMain_SO(MAP_input,Q_input)
%
**********************************************************************
% Testing 2006 shi et al model (no valve angle, no reverse flow)
% Included HVAD at 2600RPM
% using DAE function written by Tony Roberts (found online)
% CVKeshav
% May 2017
%**********************************************************************
**

global tempfac1 tempfac2

% Read initial conditions for original set of equations
fileID = fopen('Cardiac_Initial_Conditions_Shi_et_al_wVAD.txt');
init_c = textscan(fileID,'%f');
fclose(fileID);

ic_guess = init_c{1,1};

y0est = ic_guess;

% Use fsolve to obtain better guess for ICs
%X = fsolve(@symbolic_DAE_v3_ALG_only,ic_guess);
X = fsolve(@cardiac_lpn_system_Shi_et_al_ALG_ONLY_wVAD,ic_guess);


yp0 = zeros(length(ic_guess),1);

[y0new,yp0new] =
decic(@cardiac_lpn_system_Shi_et_al_Implicit_wVAD,0,X,ic_guess,yp0,yp0);


% determine tspan
t_final = 10;
num_iter = 10000;
half_iter = num_iter/2;

tspan = linspace(0,t_final,num_iter);
init = 10;

%tic

% call DAE solver for 1st solve
%y = dae4o('shi_dae_wVAD',tspan,y0new,init);

y = dae4('shi_dae_wVAD',tspan,y0new,init);

MAP = mean(y(15,half_iter:num_iter))
```

```
% plot_params(tspan,y);

st = 1;
fin = num_iter;

Mean_Qvad = trapz(tspan(st:fin),y(26,st:fin))*(60/t_final)*1e-3

Mean_Qav = trapz(tspan(st:fin),y(6,st:fin))*(60/t_final)*1e-3


%% Set up optimization
close all
temp_init = [tempfac1,tempfac2];
MAP_target = 77;
Q_target = 5;
fdata.temp_init = temp_init;

cost = @(tempval) dae_optimize_SO(MAP_target,
Q_target,tspan,y0new,init,num_iter,half_iter,tempval,t_final);
lb = [0.05, 3400];
ub = [0.9, 7400];

[best_res1] = lsqnonlin(cost,temp_init,lb,ub);
best_res1

%best_res = fminunc(cost,temp_init);
%best_res = fminsearch(cost,temp_init);

%% Test optimal value
tempfac1 = best_res1(1);%(0.1-0.9)
tempfac2 = best_res1(2);%(3400-7400)

y = dae4('shi_dae_wVAD',tspan,y0new,init);

MAP = mean(y(15,half_iter:num_iter))

st = 1;
fin = num_iter;

Mean_Qvad = trapz(tspan(st:fin),y(26,st:fin))*(60/t_final)*1e-3

Mean_Qav = trapz(tspan(st:fin),y(6,st:fin))*(60/t_final)*1e-3

clear data
data.tspan = tspan;
data.y = y;
data.optval_1= tempfac1;
data.optval_2= tempfac2;
data.FinalMAP = MAP;
data.FinalQvad = Mean_Qvad;
```

```
data.FinalQav = Mean_Qav;

% Solution = [data.y; data.optvals; data.FinalMAP; data.FinalQvad;
data.FinalQav];


end
```

```
function B = system_constants_Shi_et_al_wVAD_SO(t,y)

% Determine cardiac cycle time
RR = 0.8;                       % Length of cardiac cycle = 0.8 s
tcar = mod(t,RR);

% Specify time thresholds for activation functions
Tac = 0.875*RR;
Tme = 0.3*sqrt(RR);
Tce = 1.5*Tme;

% Determmine activation function for atrium
if(tcar >= 0 && tcar <= Tac)
    ea = 0;
else
    ea = 1 - cos((tcar-Tac)*2*pi/(RR-Tac));
end

% Determine activation function for ventricle
if(tcar >=0 && tcar < Tme)
    ev = 1 - cos(tcar*pi/Tme);
elseif(tcar >= Tme && tcar < Tce)
    ev = 1 + cos((tcar-Tme)*pi/(Tce-Tme));
else
    ev = 0;
end

% Specify Elastances
Ela_max = 0.25;
Ela_min = 0.15;

% Elv_max = 2.5;
% Elv_max = 0.5; %%%%% HEART FAILURE !!!!
% Elv_min = 0.07;

%%%%% NEW PARAMETERS FOR LOWER INITIAL BP
global elv_max
Elv_max = elv_max; %0.45; %0.5; %2.5;
%Elv_max = 0.5; %%%%% HEART FAILURE !!!!
Elv_min = 0.085; %0.07;

Era_max = 0.25;
Era_min = 0.15;

Erv_max = 1.15;
Erv_min = 0.07;

%%%%% Incorporating Baroreceptor response
% testing sum of sine fit
% clear map norm_press
```

```
% map = y(15);
% setpoint = 70;
% norm_press = map/setpoint;
res_factor = 1;

% 2 sine terms fit
%res_factor = 1.434*sin(0.3968*norm_press + 1.93) +
0.2048*sin(3.33*norm_press - 0.1073);

% 3 sine terms fit
%res_factor = 3.336*sin(0.1352*norm_press + 2.694) +
0.1806*sin(3.424*norm_press - 0.3021) + 0.04048*sin(6.943*norm_press +
2.633);

% fid = fopen('baroresponse_trial.txt','a');
% fprintf(fid,'%6.2f \t %6.2f \t %6.2f\n',t,map,res_factor);
% fclose(fid);

%%%%% NEW PARAMETERS FOR LOWER INITIAL BP
% Arterial Resistances

%Specify patient resistance based on cath measurements
global tempfac1
external_factor = tempfac1;

%scale_factor = 0.58*res_factor;

scale_factor = external_factor*res_factor;

modf = 1.0; %%% FOR REDUCING INITIAL BP
Rsat = 0.05*modf*scale_factor;
Rsar = 0.5*modf*scale_factor;
Rscp = 0.52*modf*scale_factor;
Rsvn = 0.075*modf*scale_factor;

% Modeling pulmonary hypertension
pscale = 1.0;
Rpat = 0.01*pscale;
Rpar = 0.05*pscale;
Rpcp = 0.07*pscale;



% Specify all system constants
B = zeros(38,1);

B(1) = 1;
B(2) = Ela_min + 0.5*(Ela_max - Ela_min)*ea;
B(3) = 4;
B(4) = 350; %400; %%%%% NEW PARAMETERS FOR LOWER INITIAL BP
```

```
B(5) = 1;
B(6) = Elv_min + 0.5*(Elv_max -Elv_min)*ev;
B(7) = 5;
B(8) = 300; %350; %%%%% NEW PARAMETERS FOR LOWER INITIAL BP
B(9) = 1;
B(10) = Era_min + 0.5*(Era_max - Era_min)*ea;
B(11) = 4;
B(12) = 400;
B(13) = 1;
B(14) = Erv_min + 0.5*(Erv_max - Erv_min)*ev;
B(15) = 10;
B(16) = 350;
B(17) = 0.08;
B(18) = 0.003;
B(19) = 0.000062;
B(20) = 1.4; %1.6; %%%%% NEW PARAMETERS FOR LOWER INITIAL BP
%B(20) = 0.8; % LOWERING Csat to raise MAP - DOES NOT WORK, ONLY
INCREASES RANGE, NOT MEAN
%B(21) = 1.07;
B(21) = Rsat + Rsar + Rscp;
B(22) = 0.0017;
B(23) = 20.5;
B(24) = Rsvn; %0.075;
B(25) = 0.18;
B(26) = 0.002;
B(27) = 0.000052;
B(28) = 3.8;
B(29) = Rpat+Rpar+Rpcp; %0.13;
B(30) = 0.0017;
B(31) = 20.5;
B(32) = 0.006;

B(33) = 0.08; % Capacitance for outflow graft
B(34) = 0.06; % Resistance for outflow graft
B(35) = 0.000062; % Inductance for outflow graft

% % Constants for LVAD H-Q curve
% % ----- TYPE OF LVAD -----
% % 1: HVAD
% % 2: HM3
% % ------------------------
% % ----- RPM for HVAD -----
% % 1: 2200 (HVAD)
% % 2: 2400 (HVAD)
% % 3: 2600 (HVAD)
% % 4: 2800 (HVAD)
% % 5: 3000 (HVAD)
% % ------------------------
% % ----- RPM for HM3 -----
% % 1: 3000 (HM3)
```

```
% % 2: 3400 (HM3)
% % 3: 4000 (HM3)
% % 4: 5000 (HM3)
% % 5: 5400 (HM3)
% % 6: 6000 (HM3)
% % 7: 7400 (HM3)

global tempfac2 poly
OGspeed = tempfac2;
poly = PC_HM3(OGspeed,3);

        B(36) = 0;
        B(37) =0;
        B(38) = poly(1)*16.67;
        B(39) = poly(2)*16.67;
        B(40) = poly(3)*16.67;
        B(41) = poly(4)*16.67;



end
```

```
UpdateOptPlotting
clear all
clc

OptimizationData = readtable('HM3_OptimizationResults.xlsx');
NegOptimData = readtable('HM3NegativeOptimizationResults.xlsx');
 PI = (table2array(OptimizationData(:,1)))';
 MAP =(table2array(OptimizationData(:,4)))';
 Q =(table2array(OptimizationData(:,2)))';
 Speed =(table2array(OptimizationData(:,3)))';
 DiffSpeed = (table2array(OptimizationData(:,5)))';

 Neg_PI = (table2array(NegOptimData(:,1)))';
 Neg_MAP =(table2array(NegOptimData(:,4)))';
 Neg_Q =(table2array(NegOptimData(:,2)))';
 Neg_Speed =(table2array(NegOptimData(:,3)))';
 Neg_DiffSpeed = (table2array(NegOptimData(:,5)))';


% MAP vs Fick CO
figure
%ms = 5;
fs = 20; %Font Size
lw = 10; %Line Width
szPos = reshape(abs(DiffSpeed),numel(DiffSpeed),1);
szNeg = reshape(abs(Neg_DiffSpeed),numel(Neg_DiffSpeed),1);
szPosBig = szPos*8;
szNegBig = szNeg*5;
hold on
%Boundaries for targets/Green Bars
xp1 = [3 9 9 3];
%yp1 = [69 69 71 71];
yp1 = [75 75 79 79];
patch(xp1,yp1,'g','Facealpha',0.3)
%Boundaries for targets/Green Bars
xp2 = [4.9 5.1 5.1 4.9];
yp2 = [55 55 115 115];
patch(xp2,yp2,'g','Facealpha',0.3)

scatter(Q,MAP,szPosBig,Speed,'filled','MarkeredgeColor','r')
scatter(Neg_Q,Neg_MAP,szNegBig,Neg_Speed,'filled','MarkeredgeColor','k')
grid on
xlabel('Q [L/min]')
ylabel('MAP [mmHg]')
set(gca,'FontSize',fs,'FontWeight','bold')
colorbar
colormap cool
caxis([3000 9000])
ylim([55 115])
```

```
%%

%Plotting other graphs
figure
fs = 20; %Font Size
lw = 5; %Line Width
hold on

subplot(221) %Q vs DiffSpeed
plot(Q,DiffSpeed,'o','MarkerFaceColor','b')
xp2 = [4.9 5.1 5.1 4.9];
yp2 = [-800 -800 200 200];
patch(xp2,yp2,'g','Facealpha',0.3)
xlabel('Q [L/min]')
ylabel('Difference in Speed [RPM]')
set(gca, 'Fontsize',fs)
ylim([-800 200])
grid on

subplot(222) %MAP vs DiffSpeed
plot(MAP,DiffSpeed,'o','MarkerFaceColor','b')
xp1 = [65 79 79 75];
yp1 = [-800 -800 200 200];
patch(xp1,yp1,'g','Facealpha',0.3)
xlabel('MAP [mmHg]')
ylabel('Difference in Speed [RPM]')
set(gca,'FontSize',fs)
ylim([-800 200])
grid on
```

A.4 Code for Speed Modulation

```
function AV_open = aortic_valve_count(y)
C = y(6,:);
C_round = round(C,2);
W = zeros(1,length(C_round));
    for j = 1:length(C_round)
        W(j) = C_round(j) > 0;
    end
    var = 0;
    for i = 1:length(W)-1
        if W(i) ~= W(i+1)
            var = var + 1;
        end
        AV_open = var/2;
    end
end
```

```
function create_table(file_location,Excel_sheet_name)


    Sub_file = table(0,0,0,0,0,0,0,0,0,0,0,'VariableNames',
{'date/time','tempfac1', 'ReducedtoSpeed', 'tempfac3', 'Num_AV_open',
'Mean_Qvad_SM', 'Mean_Qvad', 'Mean_Qav', 'Mean_Qav_SM', 'MAP_SM',
'MAP'});
    cd(file_location);
    writetable(Sub_file,Excel_sheet_name)
end
```

```
function H = creating_MainFile(tempfac1, tempfac3, Num_AV_open,
Mean_Qvad_SM, Mean_Qvad, Mean_Qav, Mean_Qav_SM, MAP_SM, MAP)


    %Get Values to be save
    ReducedtoSpeed = tempfac1*tempfac3;
    t =string(datetime('now'));
    % Save values in table
    H(1,:) = [t, tempfac1, ReducedtoSpeed, tempfac3, Num_AV_open,
Mean_Qvad_SM, Mean_Qvad, Mean_Qav, Mean_Qav_SM, MAP_SM, MAP];
    % write table to Excel sheet
cd('C:\Users\jmart\Documents\Research\Speed
Modulation\LPM_Parallel\SpeedModulationResults');
   %filename = 'Test.xlsx';
    %Range = ['A',num2str(i)];
   writematrix(H,'Output_filename.xlsx','Sheet',1,'WriteMode', 'append')
end
```

```
function
[y,MAP,Mean_Qvad,h,tspan,Mean_Qvad_SM,MAP_SM,Mean_Qav_SM,Mean_Qav,Elapsed
time,Num_AV_open,data] = Main_file_Test_JM

tic
tic
global order  tempfac1 tempfac2 tempfac3 %Case
%Case = 1; %Case to run from system constants file
order = 3; %performance curves order
% Read initial conditions for original set of equations
fileID = fopen('Cardiac_Initial_Conditions_Shi_et_al_wVAD.txt');
init_c = textscan(fileID,'%f');
fclose(fileID);
ic_guess = init_c{1,1};
y0est = ic_guess;
% Use fsolve to obtain better guess for ICs
%X = fsolve(@symbolic_DAE_v3_ALG_only,ic_guess);
X = fsolve(@cardiac_lpn_system_Shi_et_al_ALG_ONLY_wVAD,ic_guess);
yp0 = zeros(length(ic_guess),1);
[y0new,yp0new] =
decic(@cardiac_lpn_system_Shi_et_al_Implicit_wVAD,0,X,ic_guess,yp0,yp0);
toc
%%
% determine tspan
number_cycles = 25;
total_steps = 10000;
tspan = linspace(0,number_cycles,total_steps);
init = 10; % iterations per time step
tic
% call DAE solver
y = dae4o('shi_dae_wVAD',tspan,y0new,init);
toc
%%
% plot solution
[h] = plot_params_v2(tspan,y);
st = 6000; %Start
fin = 10000; %Finish
st_SM = 4000; %Speed Modulation Starts
fin_SM = 6000; %Speed Modulation Finishes
MAP = mean(y(15,st:fin))
MAP_SM = mean(y(15,st_SM:fin_SM))
t_elap = tspan(fin) - tspan(st);
t_elap_SM= tspan(fin_SM)-tspan(st_SM);
Mean_Qav = trapz(tspan(st:fin),y(6,st:fin))*(60/t_elap)*1e-3
Mean_Qav_SM =
trapz(tspan(st_SM:fin_SM),y(6,st_SM:fin_SM))*(60/t_elap_SM)*1e-3
Mean_Qvad = trapz(tspan(st:fin),y(27,st:fin))*(60/t_elap)*1e-3
Mean_Qvad_SM =
trapz(tspan(st_SM:fin_SM),y(27,st_SM:fin_SM))*(60/t_elap_SM)*1e-3
```

```
Mean_Qvad_tot =
trapz(tspan(st_SM:fin),y(27,st_SM:fin))*(60/(t_elap+t_elap_SM))*1e-3
Elapsedtime = toc;
%Counting number of times aortic valve opens
Num_AV_open = aortic_valve_count(y);

%%
% Write simulation data to file
clear data
data.BaselineSpeed = tempfac1;
data.Change_T = tempfac2;
data.Rratio = tempfac3;
data.tspan = tspan;
data.y = y;
data.Mean_Qvad = Mean_Qvad;
data.Mean_Qvad_SM = Mean_Qvad_SM;
data.Mean_Qav = Mean_Qav;
data.Mean_Qav_SM = Mean_Qav_SM;
data.MAP = MAP;
data.MAP_SM = MAP_SM;
data.Elapsedtime = toc;
data.Num_AV_open= Num_AV_open;
end
```

```
function [poly] = PC_EVAHEART(Speed,order)
%EVAHEART H_Q Curves
oldspeed = 2000;
newspeed = Speed;

Q = [0 2 4 6.04 8 10 12 14 16.01 18.02];
P = [91.4 89.5 90.2 82.9 76.7 69.2 60.7 49.9 36.4 19.1];

ratio = newspeed/oldspeed;

ratiosquared = ratio^2;

NewQ = Q*ratio;
NewP = P*ratiosquared;
poly = zeros(1,6);

if order == 3
    poly(1,3:6) = polyfit(NewP,NewQ,order);
elseif order == 4
    poly(1,2:6) = polyfit(NewP,NewQ,order);
elseif order == 5
    poly = polyfit(NewP,NewQ,order);
end

 end
```

```
function [h] = plot_params_v2(tspan,y)


h(1) = figure;
subplot(211)
plot(tspan,y(5,:))
hold on
plot(tspan,y(15,:),'r')
plot(tspan,y(2,:),'k')
legend('Plv','Psat','Pla')
xlabel('Time(s)')
ylabel('Pressure (mmHg)')

subplot(212)
plot(tspan,y(4,:))
hold on
plot(tspan,y(1,:),'r')
legend('Vlv','Vla')
xlabel('Time(s)')
ylabel('Volume (ml)')

%---------------------------------

h(2) = figure;
subplot(221)
plot(y(4,:),y(5,:))
xlabel('Volume (ml)')
ylabel('Pressure (mmHg)')
title('LV P-V loop')

subplot(222)
plot(y(1,:),y(2,:))
xlabel('Volume (ml)')
ylabel('Pressure (mmHg)')
title('LA P-V loop')

subplot(223)
plot(y(10,:),y(11,:))
xlabel('Volume (ml)')
ylabel('Pressure (mmHg)')
title('RV P-V loop')

subplot(224)
plot(y(7,:),y(8,:))
xlabel('Volume (ml)')
ylabel('Pressure (mmHg)')
title('RA P-V loop')

%---------------------------------
```

```
h(3) = figure;
subplot(211)
plot(tspan,y(8,:))
hold on
plot(tspan,y(11,:))
plot(tspan,y(19,:))
legend('Pra','Prv','Ppas')
xlabel('Time(s)')
ylabel('Pressure (mmHg)')

subplot(212)
plot(tspan,y(10,:))
hold on
plot(tspan,y(7,:),'r')
legend('Vrv','Vra')
xlabel('Time(s)')
ylabel('Volume (ml)')

%-----------------------------------

h(4) = figure;
subplot(211)
plot(tspan,y(3,:))
hold on
plot(tspan,y(6,:))
legend('Qmi','Qao')
xlabel('Time(s)')
ylabel('Flow (ml/s)')

subplot(212)
plot(tspan,y(9,:))
hold on
plot(tspan,y(12,:))
legend('Qti','Qpa')
xlabel('Time(s)')
ylabel('Flow (ml/s)')

%-----------------------------------

h(5) = figure;
plot(tspan,y(27,:))
hold on
plot(tspan,y(6,:))
legend('Qlvad','Qao')
xlabel('Time(s)')
ylabel('Flow (ml/s)')

%-----------------------------------

h(6) = figure;
```

```
plot(tspan,y(5,:),'b')
hold on
plot(tspan,y(15,:),'r')
plot(tspan,y(25,:),'k')
legend('Plv','Psat','Pog')
xlabel('Time(s)')
ylabel('Pressure (mmHg)')

%-----------------------------------

h(7) = figure;
plot(tspan,(y(25,:)-y(5,:)),'r')
xlabel('Time(s)')
ylabel('Pressure Drop Across LVAD (mmHg)')


end
```

```
SpeedMod_Main_file
clear
clc
clear all

global tempfac1 tempfac2 tempfac3 Case tempfac4
%CaseListEvaheart = readtable('CaseListEvaheart_mod.xlsx');
CaseListEvaheart_mod = xlsread('CaseListEvaheart_mod','extended case
list');

CaseIndex = CaseListEvaheart_mod(:,1);
BaselineSpeed = CaseListEvaheart_mod(:,2);
Rratio = CaseListEvaheart_mod(:,4);
Change_T = CaseListEvaheart_mod(:,5);
waveform = CaseListEvaheart_mod(:,6);
ScaleFactor = CaseListEvaheart_mod(:,7);
%MAP/VR
%Contractility/Elv_max
NumberofCases = input('how many cases to run?\n','s');
x = str2num(NumberofCases);
if length(x) == 1
   x(2)= x(1);
end

%creating Excel sheet for mainfile
    file_location = 'C:\Users\jmart\Documents\Research\Speed
Modulation\LPM_Parallel\SpeedModulationResults';
    Excel_sheet_name = 'Output_filename.xlsx';
   create_table(file_location,Excel_sheet_name)


for i = x(1):x(2)
    %Global Variables
        tempfac1 = BaselineSpeed(i);
        tempfac2 = Change_T(i);
        tempfac3 = Rratio(i);
        Case = waveform(i);
        tempfac4 = ScaleFactor(i);
        addpath 'C:\Users\jmart\Documents\Research\Speed
Modulation\LPM_Parallel\SpeedModulationResults\'

[y,MAP,Mean_Qvad,h,tspan,Mean_Qvad_SM,MAP_SM,Mean_Qav_SM,Mean_Qav,Elapsed
time,Num_AV_open,data] = Main_file_Test_JM;
   % dir = 'E:\Jasmine Martinez\Speed
Modulation\EVAHEART_Data_Current\LPM_Parallel';
        dir = 'C:\Users\jmart\Documents\Research\Speed
Modulation\LPM_Parallel';
        F = 'SpeedModulationResults';
    %Speed Folder
        SpeedFolder = fullfile(dir,F,num2str(BaselineSpeed(i)));
```

```
        if ~exist(SpeedFolder,'dir')
            mkdir(SpeedFolder)
            addpath 'C:\Users\jmart\Documents\Research\Speed
Modulation\LPM_Parallel'
        else
            cd(SpeedFolder)
            addpath 'C:\Users\jmart\Documents\Research\Speed
Modulation\LPM_Parallel'
           % butt = 5;
            %filename = strcat('E:\Jasmine Martinez\Speed
Modulation\EVAHEART_Data_Current\LPM_Parallel\SpeedModulationResults\',nu
m2str(BaselineSpeed(i)));
       %      save('butt')
        end

    %Change in time folders
         ChangeTFolder =
fullfile(dir,F,num2str(BaselineSpeed(i)),num2str(Change_T(i)));
        if ~exist(ChangeTFolder,'dir') %&& Change_T(i) ~= 0
            mkdir(ChangeTFolder)
            addpath 'C:\Users\jmart\Documents\Research\Speed
Modulation\LPM_Parallel'
%          elseif Change_T(i) == 0
%              cd(SpeedFolder)
        else
            cd(ChangeTFolder)
            addpath 'C:\Users\jmart\Documents\Research\Speed
Modulation\LPM_Parallel'
        end
    %Change in Rratio folders
          rRatioFolder =
fullfile(dir,F,num2str(BaselineSpeed(i)),num2str(Change_T(i)),num2str(Rra
tio(i)));
        if ~exist(rRatioFolder,'dir') %&& Change_T(i) ~=0
            mkdir(rRatioFolder)
            addpath 'C:\Users\jmart\Documents\Research\Speed
Modulation\LPM_Parallel'
%          elseif Change_T(i) == 0
%              cd(SpeedFolder)
        else
            cd(rRatioFolder)
            addpath 'C:\Users\jmart\Documents\Research\Speed
Modulation\LPM_Parallel'
        end
    %Saving figures
       % filename =
strcat('SpeedModulationResults',num2str(BaselineSpeed(i)),num2str(Change_
T(i)),num2str(Rratio(i)),'figures')
```

```
       filename =
strcat(dir,'/','SpeedModulationResults/',num2str(BaselineSpeed(i)),'/',nu
m2str(Change_T(i)),'/',num2str(Rratio(i)),'/','Fig_',num2str(i));
     saveas(h,filename,'fig');
        close all
     %Saving Rratio data in pre-created folders
        clear Finaldata
        Finaldata(i).BaselineSpeed = data.BaselineSpeed;
        Finaldata(i).Change_T = data.Change_T;
        Finaldata(i).Rratio = data.Rratio;
        Finaldata(i).tspan = data.tspan;
        Finaldata(i).y = data.y;
        Finaldata(i).Mean_Qvad = data.Mean_Qvad;
        Finaldata(i).Mean_Qvad_SM = data.Mean_Qvad_SM;
        Finaldata(i).Mean_Qav = data.Mean_Qav;
        Finaldata(i).Mean_Qav_SM = data.Mean_Qav_SM;
        Finaldata(i).MAP = data.MAP;
        Finaldata(i).MAP_SM = data.MAP_SM;
        Finaldata(i).Num_AV_open = data.Num_AV_open;
        Finaldata(i).Elapsedtime = data.Elapsedtime;

        %Saving Rratio structure (Data)
       filename_data =
strcat(dir,'/','SpeedModulationResults/',num2str(BaselineSpeed(i)),'/',nu
m2str(Change_T(i)),'/',num2str(Rratio(i)),'/','Data_', num2str(i));
        save(filename_data,'Finaldata');

          %create Excel sheet for all of the data
      H = creating_MainFile(tempfac1, tempfac3, Num_AV_open,
Mean_Qvad_SM, Mean_Qvad, Mean_Qav, Mean_Qav_SM, MAP_SM, MAP);

      %creating another Excel sheet for individual speeds
      x = [num2str(BaselineSpeed(i)),'.xlsx'];
      if ~exist(x,'dir')
    file_location = ['C:\Users\jmart\Documents\Research\Speed
Modulation\LPM_Parallel\SpeedModulationResults\'num2str(BaselineSpeed(i))
,'\'];
    Excel_sheet_name = [num2str(BaselineSpeed(i)),'.xlsx'];
    create_table(file_location,Excel_sheet_name);
      end
      Sheet = 1;
     M = creating_Excel_file(i,tempfac1, tempfac3, Num_AV_open,
Mean_Qvad_SM, Mean_Qvad, Mean_Qav, Mean_Qav_SM, MAP_SM, MAP,Sheet);

%      %Creating subsheet for rRatio data
%      Sub_file = table(0,0,0,0,0,0,0,0,0,0,0,'VariableNames',
{'date/time','tempfac1', 'ReducedtoSpeed', 'tempfac3', 'Num_AV_open',
'Mean_Qvad_SM', 'Mean_Qvad', 'Mean_Qav', 'Mean_Qav_SM', 'MAP_SM',
'MAP'});
%      cd(file_location)
```

```
%      writetable(Sub_file,Excel_sheet_name,'Sheet',2)
%      Sheet = 2;
%      M = creating_Excel_file(i,tempfac1, tempfac3, Num_AV_open,
Mean_Qvad_SM, Mean_Qvad, Mean_Qav, Mean_Qav_SM, MAP_SM, MAP,Sheet);
end


    %%
%     %Change in MAP files
%      mkdir('SpeedModulationResults',
Speed(i),Change_T(i),Rratio(i),MAP)
%     %Saving MAP data
%     clear data
%     All_MAP(i).tspan = data.tspan;
%     All_MAP(i).y = data.y;
%     All_MAP(i).Mean_Qvad = data.Mean_Qvad;
%     All_MAP(i).Mean_Qvad_SM = data.Mean_Qvad_SM;
%     All_MAP(i).Mean_Qav = data.Mean_Qav;
%     All_MAP(i).Mean_Qav_SM = data.Mean_Qav_SM;
%     All_MAP(i).MAP = data.MAP;
%     All_MAP(i).MAP_SM = data.MAP_SM;
%
%     %Save a MAT file per MAP change
%         filename =
strcat('SpeedModulationResults/Speed',num2str(i),'/Rratio',num2str(i),'/M
AP/MAP_',num2str(i),'.mat');
%         save(filename,'Data');
%
%        % Save all MAP data
%       filename =
strcat('SpeedModulationResults/Speed',num2str(i),'/Rratio',num2str(i),'/M
AP/All_MAP_Changes.mat');
%         save(filename,'All_MAP');
%
%    %Change in Contractility files
%          mkdir('SpeedModulationResults',
Speed(i),Change_T(i),Rratio(i),MAP)
%     %Saving MAP data
%     clear data
%     MAP(i).tspan = data.tspan;
%     MAP(i).y = data.y;
%     MAP(i).Mean_Qvad = data.Mean_Qvad;
%     MAP(i).Mean_Qvad_SM = data.Mean_Qvad_SM;
%     MAP(i).Mean_Qav = data.Mean_Qav;
%     MAP(i).Mean_Qav_SM = data.Mean_Qav_SM;
%     MAP(i).MAP = data.MAP;
%     MAP(i).MAP_SM = data.MAP_SM;
%
%     %Save a MAT file per MAP change
```

```
%         filename =
strcat('SpeedModulationResults/Speed',num2str(i),'/Rratio',num2str(i),'/M
AP/MAP_',num2str(i),'.mat');
%         save(filename,'MAP_Change');
%
%        % Save all MAP data
%       filename =
strcat('SpeedModulationResults/Speed',num2str(i),'/Rratio',num2str(i),'/M
AP/All_MAP_Changes.mat');
%         save(filename,'All_MAP_Changes');
% end
```

```
function coef=
square_wave_rpm_JM_v2(Base_line,R,start_time,end_time,order,t)
    % 'A' is the amplitude
    % 'B' is the period
    % 'C' is the horizontal shift
    % 'D' is the vertical shift
    % 'start_time' is the time that you are wanting to implement the
square
    % wave
    % 'end_time' is the time you are wanting to end the square wave
    % 'speed' is the predefind matrix that contains all the coefficient
    % values for any given rpm. Note: In order to index this matrix, you
    % need to determine the order (3rd,4th,5th) and the desired rpm value
    % 't' is the value of time that is being passed in. Note: this is a
    % single value, NOT an array
    % The rpm value that runs before and after the start_time/end_time is
    % equal to the verticle displacement 'D'
    if t <= start_time
        poly= PC_EVAHEART(Base_line,order);
        coef = poly * 16.67;
    elseif t>= end_time
        poly = PC_EVAHEART(Base_line,order);
        coef = poly * 16.67;
    else
        Drop2Speed = R*Base_line;
        poly = PC_EVAHEART(Drop2Speed,order);
        coef = poly * 16.67;
%         speed_rpm_square = A*square(P*t+C)+D %this is a standard
formula for a square wave
%         Resultspeed_10= round10(speed_rpm_square); %rounding all the
values to be in increments of 5
%         poly = PC_EVAHEART(Resultspeed_10,order);
%         coef = poly * 16.67;
    end
end
```

```
function B = system_constants_Shi_et_al_wVAD_JM_v2(t,y)

global tempfac4

% Determine cardiac cycle time
RR = 0.8;                       % Length of cardiac cycle = 0.8 s
tcar = mod(t,RR);

% Specify time thresholds for activation functions
Tac = 0.875*RR;
Tme = 0.3*sqrt(RR);
Tce = 1.5*Tme;

% Determmine activation function for atrium
if(tcar >= 0 && tcar <= Tac)
    ea = 0;
else
    ea = 1 - cos((tcar-Tac)*2*pi/(RR-Tac));
end

% Determine activation function for ventricle
if(tcar >=0 && tcar < Tme)
    ev = 1 - cos(tcar*pi/Tme);
elseif(tcar >= Tme && tcar < Tce)
    ev = 1 + cos((tcar-Tme)*pi/(Tce-Tme));
else
    ev = 0;
end

% Specify Elastances
Ela_max = 0.25;
Ela_min = 0.15;

% Elv_max = 2.5; % normal elastance
Elv_max = 0.5; %%%%% HEART FAILURE !!!!
Elv_min = 0.07;

Era_max = 0.25;
Era_min = 0.15;

Erv_max = 1.15;
Erv_min = 0.07;

% Arterial Resistances
scale_factor = tempfac4;
Rsat = 0.05*scale_factor;
Rsar = 0.5*scale_factor;
Rscp = 0.52*scale_factor;
```

```
% Specify all system constants
B = zeros(41,1);

B(1) = 1;
B(2) = Ela_min + 0.5*(Ela_max - Ela_min)*ea;
B(3) = 4;
B(4) = 400;
B(5) = 1;
B(6) = Elv_min + 0.5*(Elv_max -Elv_min)*ev;
B(7) = 5;
B(8) = 350;
B(9) = 1;
B(10) = Era_min + 0.5*(Era_max - Era_min)*ea;
B(11) = 4;
B(12) = 400;
B(13) = 1;
B(14) = Erv_min + 0.5*(Erv_max - Erv_min)*ev;
B(15) = 10;
B(16) = 350;
B(17) = 0.08;
B(18) = 0.003;
B(19) = 0.000062;
B(20) = 1.6;
%B(20) = 0.8; % LOWERING Csat to raise MAP - DOES NOT WORK, ONLY
INCREASES RANGE, NOT MEAN
%B(21) = 1.07;
B(21) = Rsat + Rsar + Rscp;
B(22) = 0.0017;
B(23) = 20.5;
B(24) = 0.075;
B(25) = 0.18;
B(26) = 0.002;
B(27) = 0.000052;
B(28) = 3.8;
B(29) = 0.13;
B(30) = 0.0017;
B(31) = 20.5;
B(32) = 0.006;

B(33) = 0.08; % Capacitance for outflow graft
B(34) = 0.06; % Resistance for outflow graft
B(35) = 0.000062; % Inductance for outflow graft

global order  Case tempfac1 tempfac2 tempfac3
% Speed Modulation Shape
        switch Case
            case 1 %Constant Speed
                %Speed_x = 1000; %starting speed;
                Base_line = tempfac1; %Speed to be held constant
```

```
                poly = PC_EVAHEART(Base_line,order);
                B(36:41) = poly*16.67;

            case 2 %Square Wave
%                 A = 45; % Amplitude
%                 P = pi/5; % Period
%                 C = 0; % Horizontal Shift
%                 D = 1755; % Vertical Shift aka Baseline speed
                Base_line = tempfac1;
                Duration = tempfac2;
                start_time = 10; %what time square wave will come
in/start
                end_time = start_time + Duration; %when square wave will
finish
                R = tempfac3; % Decimal
                B(36:41) =
square_wave_rpm_JM_v2(Base_line,R,start_time,end_time,order,t);

            case 3 %Ramp?
                poly = PC_EVAHEART(Speed_x,order);
                B(36:41) =
ramp_repeating(0,1,2400,1,3,2400,2600,3,5,2600,5,6,2600,2400,6,7,2400,Spe
ed_x,t);

            case 4
                B(36) = 0;
                B(37) = 0;
                B(38) = -0.0001*16.67;
                B(39) = 0.0076*16.67;
                B(40) = -0.3641*16.67;
                B(41) = 20.4224*16.67;
        end


end
```

```
function ys=dae4o(f,tspan,y0,nint,g)

% function ys=dae4o(f,tspan,y0,nint,g)
% solves a set of differential algebraic equations (DAEs)
%        f(t,y,y')=0  where y'=dy/dt
% with a 4th order method starting from y0 at time t0 and
% finishing at time tfin where tspan=[t0 t1 ... tfin].
% y0 is a column vector, tspan is a row vector.
%
% The solution is returned at all the times in tspan.
% The time steps are approx diff(ts)/(3*nint) within the domain.
% Error management is entirely up to the user via tspan & nint.
% If optional nint is omitted, then it is assumed to be 1.
% If matlab warms of matrices with high condition number,
% then increase nint.
%
% The jacobians of f, namely k=df/dy and m=df/dy', must be
% provided by f, at each time compute: [f,k,m]=func(t,y,y').
% Both m and k may be returned as sparse matrices.
% If warnings of poor convergence occur, then the coded
% jacobians probably have errors.
%
% The optional argument g is the name of a user supplied
% function g(t,y,y') that is invoked immediately the
% solution is computed at the times in tspan.
%
% The initial state y0 should be consistent with the
% algebraic part of the DAE, but if not consistent then
% transient oscillations will appear as it works towards
% consistency.
%
% The method will also work well for stiff sets of ODEs.
% This version should work well for problems with significant
% oscillations (waves) as all linear oscillations are stable.
% It is more costly than dae4 as it divides each time step
% into three substeps.  The three substeps are solved
% simultaneously which results in linear systems 3X as big.
% However, each time step may be five times than that for dae4.
% The error in each step is approx 0.411E-3*(h*lambda)^5
% when applied to y'=lambda*y.
%
% See pendrun.m, penddae.m & pendg.m for a pendulum example.
% See also dae2.m and dae4.m for other versions.
%
% (c) Tony Roberts, 18 Aug 1998, aroberts@usq.edu.au

if nargin<4, nint=1; end
gcall=(nargin==5);
nout=length(tspan);
ndim=length(y0);
```

```
ys=zeros(ndim,nout);
newtol=1e-9;
newtmax=10;
newtit=zeros(1,newtmax);
% weights for BDF est of deriv
wd=[0 1 1/2 1/3 1/4];
wds=sum(wd);
step3=[1     0     0     0     0
       3     1     0     0     0
       6     3     1     0     0
      10     6     3     1     0
      15    10     6     3     1];

% to allow for varying spaced output, fit a spline
% and solve in s=[1,nts] rather than in t
% dt is dt/ds at each time s
nint=3*nint; % triple nint for the simultaneous steps
nts=1+nint*(nout-1);
ts=spline(1:nint:nts,tspan,(1:nts));
dt=spline(1:nint:nts,tspan,(1:nts)+1e-7);
dt=(dt-ts)/1e-7;

% initialise by solving first three steps together assuming
% a cubic between them (zero fourth & fifth difference).
yy=zeros(ndim,3); % initial guess
y=[y0 yy zeros(ndim,1)];
for newt=1:newtmax
      % extrapolate
      y2=rot90(cumsum(rot90(y )),-1);
      y3=rot90(cumsum(rot90(y2)),-1);
      y4=rot90(cumsum(rot90(y3)),-1);
      % evaluate residuals
      [f2,k2,m2]=feval(f,ts(2),y2(:,1),y2*wd'/dt(2));
      [f3,k3,m3]=feval(f,ts(3),y3(:,1),y3*wd'/dt(3));
      [f4,k4,m4]=feval(f,ts(4),y4(:,1),y4*wd'/dt(4));
      % solve simultaneous equations
      yy(:)=-[  k2+m2/dt(2)    k2+3/2*m2/dt(2)    k2+11/6*m2/dt(2)
              2*k3+m3/dt(3)  3*k3+5/2*m3/dt(3)  4*k3+13/3*m3/dt(3)
              3*k4+m4/dt(4)  6*k4+7/2*m4/dt(4) 10*k4+47/6*m4/dt(4)
                   ]\[f2;f3;f4];
      y(:,2:4)=y(:,2:4)+yy;
      if max(abs(yy(:)))<newtol*max(abs(y(:))), break, end
end
% output as requested
ys(:,1)=y(:,1);
if gcall, feval(g,ts(1),y(:,1),y*wd'/dt(1)); end
y=y*step3;
if nint==3, ys(:,2)=y(:,1);
if gcall, feval(g,ts(4),y(:,1),y*wd'/dt(4)); end, end
```

```
% take fourth order steps over domain
for n=7:3:nts
       yy=zeros(ndim,3);
       y=[y(:,1:2) yy];
       for newt=1:newtmax
              % extrapolate
              y2=rot90(cumsum(rot90(y )),-1);
              y3=rot90(cumsum(rot90(y2)),-1);
              y4=rot90(cumsum(rot90(y3)),-1);
              % evaluate residuals
              [f2,k2,m2]=feval(f,ts(n-2),y2(:,1),y2*wd'/dt(n-2));
              [f3,k3,m3]=feval(f,ts(n-1),y3(:,1),y3*wd'/dt(n-1));
              [f4,k4,m4]=feval(f,ts(n  ),y4(:,1),y4*wd'/dt(n  ));
              % solve simultaneous equations
              yy(:)=-[  k2+3/2*m2/dt(n-2)    k2+11/6*m2/dt(n-2)
k2+25/12*m2/dt(n-2)
                        3*k3+5/2*m3/dt(n-1)  4*k3+13/3*m3/dt(n-1)
5*k3+77/12*m3/dt(n-1)
                        6*k4+7/2*m4/dt(n  ) 10*k4+47/6*m4/dt(n  )
15*k4+171/12*m4/dt(n )
                                 ]\[f2;f3;f4];
              y(:,3:5)=y(:,3:5)+yy;
              if max(abs(yy(:)))<newtol*max(abs(y(:))), break, end
       end
       newtit(newt)=newtit(newt)+1;
       y=y*step3;
    if rem(n-1,nint)==0, ys(:,1+(n-1)/nint)=y(:,1);
    if gcall, feval(g,ts(n),y(:,1),y*wd'/dt(n)); end, end
end

% check on how many Newtonian iterations were required
newtm=sum((1:newtmax).*newtit)/sum(newtit);
if newtm>newtmax/2,
   disp('WARNING: poor or no convergence in dae4')
   newtit=newtit
end
```

Reused Functions from optimization code are:
CardiacJac _wVAD

Cardiac_Initial_Conditions_Shi_et_al_wVAD.txt

```
Cardiac_lpn_system_Shi_et_al_ALG_ONLY_wVAD
Cardiac_lpn_system_Shi_et_al_Implicit _wVAD
dae4
shi_dae_wVAD
```

refer to Appendix 3 the same functions provided there are utilized for the speed modulation code