Developing Lumped-Parameter Models for Porcine-to-Human Cardiac Xenotransplantation

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An interim report for above thesis project submitted to University College Dublin in the fulfilment of the requirements for the degree of

ME in Mechanical Engineering

College of Engineering and Architecture

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January 2024

Contents

Glossary

Allograft

A tissue graft from a donor of the same species as the recipient but not genetically identical.

Allotransplantation

The transplantation of cells, tissues, or organs to a recipient from a genetically non-identical donor of the same species.

Aortic dissection

A condition caused by the formation of tears in the innermost layer of the aortic wall, causing the division of the lumen into two lumina with separate flow.

Aortic regurgitation

A condition in which aortic valve fails to fully close, allowing some of the blood that was pumped out of the left ventricle to leak back in.

Coagulopathy

A condition in which the blood's ability to coagulate (form clots) is impaired.

Complement regulation

Regulation of the complement system by complement control proteins.

Diastole

The phase of the cardiac cycle when the ventricles relax and fill with blood.

Dilated cardiomyopathy

A condition in which heart chamber walls stretch and thin, causing the chambers to become larger.

Haemodynamics

Relating to the flow of blood within the organs and tissues of the body.

Hyperacute rejection

Rejection that occurs a few minutes after the transplant, when the antigens are completely unmatched.

Hypoplastic left heart syndrome

A birth defect that affects normal blood flow through the heart.

Mitral stenosis

A condition in which the mitral valve narrows.

Non-ischemic cardiomyopathy

A generic term which includes all causes of decreased heart function other than those caused by heart attacks or blockages in the arteries of the heart.

Photoplethysmography

An optical measurement method often used for heart rate monitoring purposes.

Stenosis

The abnormal narrowing of a passage in the body.

Systole

The phase of the cardiac cycle when the ventricles contract and eject blood.

Xenograft

A tissue graft or organ transplant from a donor of a different species from the recipient.

Xenotransplantation

A procedure that involves the cross-species transplantation, implantation, or infusion of live cells, tissues or organs..

Xenozoonosis

The transmission of infectious agents between species via xenograft.

Zero-dimensional model

A model that varies only with time, and has no spatial variance.

Symbols used in mathematical equations

R	Resistance of vessel
μ	Fluid dynamic viscosity
l	Vessel length
r	Vessel radius
C	Compliance of vessel
E	Young's modulus of vessel wall; Elastance
h	Vessel wall thickness
ρ	Density of blood
V	Voltage; Volume of blood in vessel/chamber
I	Current
ΔP	Pressure drop across component
Q	Blood flow rate through component
P	Pressure in a vessel/chamber
T	Time; Heart period
CQ	Flow coefficient

Subscripts

0	Initial value; Offset value; Value for unstressed condition
in	At inlet
out	At outlet
max	Maximum value
min	Minimum value
$s1$	Peak of systolic phase
$s2$	End of systolic phase
s	Systemic circulation
p	Pulmonary circulation
as	Aortic sinus
at	Arteries
ar	Arterioles
cp	Capillaries
vn	Veins

1 Introduction

Porcine-to-human cardiac xenotransplantation is hoped to offer a viable alternative to human-to-human heart transplants. The shortage of human donor organs is currently the limiting factor to successfully completing organ transplants, including heart transplants, in many countries. In Ireland there is currently approximately 600 people on waiting lists for organ transplants [5]. Although human-to-human allotransplantation will always be the preferred option, in the absence of human donor organs, xenotransplantation could revolutionise the world of organ transplantation, significantly increasing the number of transplants performed by using organs from animals bred specifically for xenotransplantation.

After overcoming the issues of immediate rejection and barriers of immunity and infection, factors affecting the long-term success of a xenotransplantation must be considered. In order to determine these factors, a clear understanding of mechanical challenges introduced by the anatomical difference between pig and human hearts must be understood. Differences such as chamber volumes and elastances, as well as valve flow parameters, must be considered when attempting to determine the influence of the xenotransplant on the overall cardiovascular system.

Lumped-parameter modelling is used to model and monitor key performance indicators such as blood pressure and flow rates at different points in the circulatory system. Due to their relatively inexpensive computational cost, they offer a good starting point for gaining an understanding of the circulatory system before more complex geometric models are employed. Lumped-parameter models (LPMs) of the circulatory system exploit the commonly used hydraulic-electric analogy to model the system as an electrical circuit, with voltage representing pressure, and current representing blood flow.

This report contains details of the work done to date on this project as follows:

- Section 2 sets out the overall aim of the project along with specific aims for this phase of the project.
- Section 3 covers the literature review undertaken to date, under the topics of xenotransplantation, and lumped-parameter models of the circulatory system.

- Section 4 details the key mathematical modelling undertaken to date, and the governing equations used in the model of the circulatory system.
- Section 5 of the report provides details of the progress made on the project to date, including models of the systemic and pulmonary system, and the heart.
- Sections 6, 7 and 8 respectively set out plans for continuation of the project, a Gantt chart of this plan, and a risk matrix detailing risks to the project's progression, and possible mitigations.

2 Specific Aims

The overall aim of this project is to investigate the effect that the anatomical differences between pig and human hearts have on the mechanics of the cardiovascular system, and the long-term success of the xenograft.

The specific aims for this phase of the project, undertaken during the Autumn trimester 2023 included:

- Undertaking a literature review to learn about the history of xenotransplantation, and the current state of cardiac xenotransplantation research. This was done to develop an understanding of LPMs and how they are used to model the circulatory system, and to learn about how LPMs have previously been used to investigate different pathological conditions.
- Becoming comfortable with the Julia programming language, and the packages that will be useful in the development of a LPM of the circulatory system.
- Developing a fully functioning LPM of the human circulatory system that can be easily tailored to represent a porcine circulatory system, or human circulation with a transplanted pig heart, by the changing of model parameters.

3 Literature Review

3.1 Background to xenotransplantation

Xenotransplantation can be defined as any procedure that involves the transplantation, implantation, or infusion into a human recipient of live cells, tissues or organs from a non-human animal source [20]. Xenotransplantation is hoped to offer an alternative to allotransplantation, or human-to-human transplantation. The first record of any form of xenotransplantation dates back to the seventeenth century where lamb's blood was used in blood transfusions. One of the first documented organ xenotransplants was a kidney transplant in 1909, in which a macaque kidney was transplanted into a woman, who survived for 32 hours before dying from organ rejection. The invention of effective immunosuppressants in the 1960s saw a renewed interest in organ transplantation, including xenotransplantation.

The first cardiac transplantation was a xenotransplantation of a chimpanzee heart into an human adult male in 1964 [11], and occurred before the first human-to-human cardiac transplantation. The patient unfortunately only survived for 90 minutes due to the chimpanzee heart being too small to handle the large venous return. Three other cardiac xenotransplantations occurred in the late twentieth century, two of which resulted in immediate failure of the xenograft [10]. The third - in 1984 - was to a prematurely born baby with hypoplastic left heart syndrome, who received a baboon heart in the absence of of a human infant donor heart. "Baby Fae" survived for 20 days after the operation before sadly passing away. Her case gained a lot of media attention, sparking an ongoing ethical debate on the subject of xenotransplantation [24].

Although early xenotransplantations utilised non-human-primate (NHP) xenografts, several limitations including cost and ethical concerns mean the use of NHPs as source animals for xenotransplantations is unsustainable [10]. Pigs have been identified as a source animal for cardiac xenotransplantations due to low breeding and raising costs, lower xenozoonosis risk, and fewer ethical constraints. Current trials are using 10-gene edited pigs which are genetically engineered to prevent hyperacute rejection, coagulopathy and xenograft overgrowth, and improve inflammation and complement regulation [11].

Since January of 2022, two porcine-to-human cardiac xenotransplantations have taken place, both at the University of Maryland Medical Centre, USA. The first of these was on 57-year-old David Bennet, a patient with non-ischemic cardiomyopathy (abnormal heart function), who was not a candidate for a traditional allograft [9]. A biopsy taken on post-operative day 34 showed no evidence of rejection, and the xenograft was functioning normally. The patient was even able to leave his bed for the first time in 109 days. However on post-operative day 49, sudden deterioration of cardiac function occurred [11], and the patient passed away on post operative day 60. Post-mortem examination revealed that the heart had almost doubled in weight, along with a number of other failure mechanisms not normally seen in human allotransplantation [9]. The second of such operations occurred in September of 2023 on 59-year-old Lawrence Faucette, a patient with terminal heart disease. Although researchers agreed that he was a more appropriate candidate for such a novel procedure [14], he sadly passed away just under six weeks after the operation.

Three main challenges exist that need to be overcome by researchers before xenotransplantation becomes a viable alternative to allotransplantation [20].

- The first is immunological rejection. Rejection still remains an issue in allotransplantation, and is even more difficult to address in xenotransplantation due to the evolutionary differences between the two species. Cloning, gene knockout and gene transfer are being utilised to try and overcome this issue.
- The second challenge is the risk of xenozoonosis and infectious diseases, which could possibly lead to risking the health of more than just the xenograft recipient, but also the wider population if a zoonotic disease is infectious.
- The final challenge, and that which relates to the project in question, is the physiological and anatomical differences between humans and source animals.

3.2 Lumped-parameter models of the cardiovascular system

Lumped-parameter models, or zero-dimensional models, of the cardiovascular system assume a uniform distribution of the fundamental variables (pressure, flow and volume) within any particular compartment (organ, vessel or part of vessel) of the model at any

instant in time [21]. They can be described by ordinary differential equations. Lumped parameter models (LPMs) of the cardiovascular system offer a concise and computationally inexpensive way to evaluate the haemodynamic interactions among the heart and vasculature [21]. They use the common hydraulic-to-electric analogy to represent the cardiovascular system as an electric circuit, where a change in blood pressure is represented by voltage, and blood flow is represented by current flow. The theory and modelling behind this will be discussed further in Section 4.1.1.

The earliest representation of systemic circulation as an electrical system was by Otto Frank in 1899 with his two-element Windkessel model [23]. The Windkessel (loosely translating to 'air chamber' in English) effect draws a comparison between the compliance of the large arteries with the Windkessel present in fire engines, which is illustrated in Figure 3.1. Blood vessel compliance is the ability of the vessel to expand to accommodate a larger volume of blood without increased resistance or blood pressure [8]. The two-element Windkessel models the time-delay effect that compliance of large arteries has on blood-pressure fluctuation.

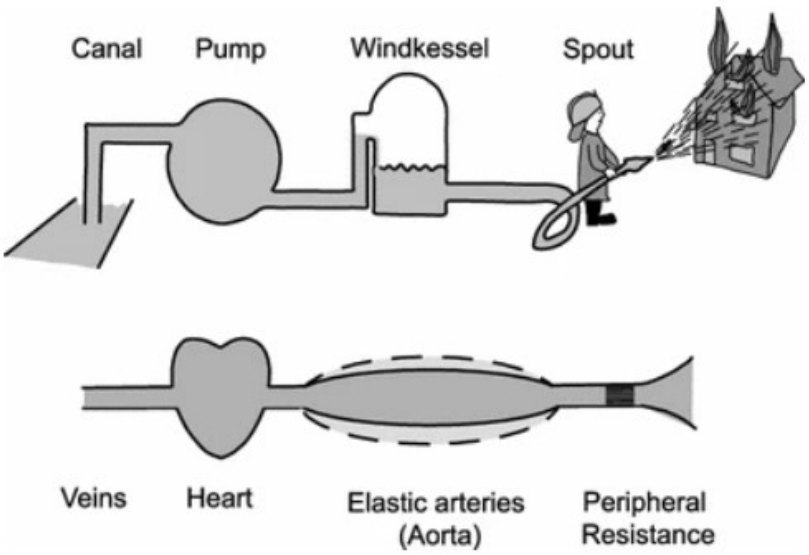


Figure 3.1: Windkessel effect [23].

The two-element Windkessel consists of a resistor and capacitor in series. The resistance represents the resistance of peripheral blood vessels to blood flow, determined by the vessel dimensions. The capacitance represents the compliance of the blood vessels. Similar to a capacitor connected in parallel which acts to smooth spikes in voltage, the

compliance of a vessel means it can act as a "blood resevoir", and can smooth out spikes in pressure.

This early model was improved upon in the three-element Windkessel model, in which a resistance is added in series to represent the characteristic impedance of the aorta [23]. This resulted in a more accurate pressure-flow relationship predicted by the model during systole.

This three-element model was further improved upon by adding an inductance to the model to represent inertia of blood flow in the arteries. This inductance has been modelled both in series and parallel with the characteristic impedance. A study by Burattini and Bini [4] used a generalised sensitivity function analysis to gain insight into the physiological meaning of the inductance for both models. They determined that the model containing an inductance in series (shown in figure 3.2) provided a better representation of blood flow inertia than a model with inductance in parallel. This circuit is commonly referred to as the four-element Windkessel model.

Diagrams of the two, three and four-element Windkessels are illustrated below.

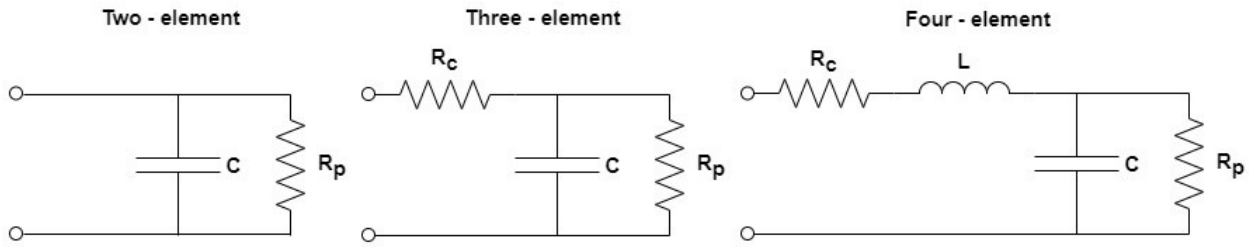


Figure 3.2: Two, three and four-element Windkessel models.

Combinations of these RCL circuits are often used to describe sections of the systemic and pulmonary circulation.

3.2.1 Uses of LPMs for investigating pathological conditions

Lumped parameter models have been widely use to simulate pathological conditions, in order to investigate the effect of these conditions on the performance of the cardiovascular system.

Bozkurt et al [3] used three patient-specific LPMs of the circulatory system to simulate

three cases of mild to severe dilated cardiomyopathy in children, a condition in which heart chamber walls stretch and thin, causing the chambers to become larger. Their study gave insights into which characteristics of the circulatory system had the greatest influence on cardiovascular performance of children with this condition.

Korakianitis and Shi [12] proposed a new model of heart valve dynamics, where the valve opening is decided by the angular position of the valve leaflets, instead of the pressure difference between the two chambers that each individual valve connects. They used this valve model in an LPM of the circulatory system to investigate the response of key performance parameters to two separate heart valve diseases, mitral stenosis and aortic regurgitation.

Laubscher et al [13] aimed to improve on the valve model presented by Korakianitis and Shi, by proposing a new valve model where pressure loss and motion models are based on basic valve parameters, instead of valvular flow and force coefficients that need to be manually tuned, limiting Korakianitis and Shi's model in terms of patient-specific modelling. They compare their model to Korakianitis and Shi's model in five different cases of increasing valve stenosis.

Rudenick et al [18] use a LPM of aortic dissection - a condition caused by the formation of tears in the innermost layer of the aortic wall - causing division of the lumen into two lumina with separate flow - to investigate the effect of wall elasticity on several blood flow characteristics within the aortic dissection.

3.2.2 Making LPMs patient-specific

In order for lumped parameter models to be useful in clinical practice, it is important that they are customisable, so that patient specific models can be made, ideally without the need for invasive measurements that could cause stress or discomfort to the patient. A number of researchers have tackled the problem of customising LPMs.

Dash et al [6] investigated the feasibility of using non-invasive photoplethysmography (PPG) signals to estimate model parameters for an LPM of the cardiovascular system, as opposed to more commonly, used but invasive and difficult to obtain, arterial blood pres-

sure (ABP) measurements. They found strong correlation between parameter estimates from both signals, giving credibility to the hope of using this model for a wide-reaching screening programme for coronary artery disease.

Duanmu et al [7] used CT images from a patient to measure vessel length and diameter in order to personalise their LPM of the coronary circulation, which they then used to investigate the effect that head loss at vessel inlets has on blood flow characteristics.

Bozkurt et al [3] used an optimisation process to fit parameters in order to minimise the difference in mean arterial pressure and cardiac output between clinical data and the output of their LPM. They then used this model to investigate the effect that individual parameters have on cardiovascular performance in patients with mild to severe dilated cardiomyopathy.

Bjørdalsbakke et al [1] developed a number of cost functions to estimate LPM parameter subsets using synthesized data. Their aim is to develop an algorithm for parameter estimation with the goal of easily-personalised LPMs.

A review of the literature outlined has given an understanding of how LPMs of the cardiovascular system have previously been used, along with methods that could be used to investigate porcine-to-human cardiac xenotransplantation using LPMs.

4 Proposed Methodology

4.1 Mathematical model

4.1.1 Hydraulic-electrical analogy for blood vessel behaviour

In this section, the underlying theory behind the hydraulic-electric analogy, allowing the circulatory system to be modelled as an electrical circuit, will be discussed. The basic parameters of voltage and current represent pressure drop and blood flow respectively. There are three basic electrical elements, the resistor, capacitor, and inductor, which are used to model both systemic and pulmonary circulation. They represent blood vessel resistance, blood vessel compliance, and blood flow inertia respectively. Both of Kirchhoff's circuit laws apply to circuits created using these elements. Resistance, capacitance and inductance values can be obtained through the following formulae based on physical properties of the blood vessels.

$$R = \frac{8\mu l}{\pi r^4} \qquad C = \frac{3\pi r^3 l}{2Eh} \qquad L = \frac{\rho l}{\pi r^2} \tag{4.1}$$

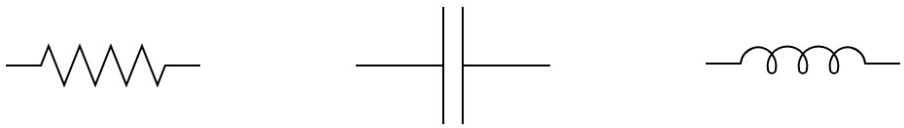


Figure 4.1: Electrical Components used to describe blood vessel characteristics

The governing equations of each of these electrical elements, along with their corresponding hydraulic equation can be seen in Table 4.1

	Electrical	**Hydraulic**
Resistor	Ohm's Law: $V = IR$	Poiseuille's Equation: $\Delta P = RQ$
Capacitor	$I = C\frac{dV}{dt}$	$Q = C\frac{d\Delta P}{dt}$
Inductor	$V = L\frac{dI}{dt}$	$\Delta P = L\frac{dQ}{dt}$

Table 4.1: Lumped-parameter components governing equations.

4.1.2 Redefining compliance

As mentioned previously, blood vessel compliance is the ability of the vessel to expand under an applied mechanical load to accommodate a larger volume of blood without increased resistance or blood pressure [8]. In order for a capacitor to represent a "blood reservoir", it must be connected in parallel with the other components of the circulation, to a reference pressure (often represented as ground in literature). Examples of this configuration are common in literature where the whole circulatory system is being modelled. An example of this configuration for a simple two-element Windkessel is shown below.

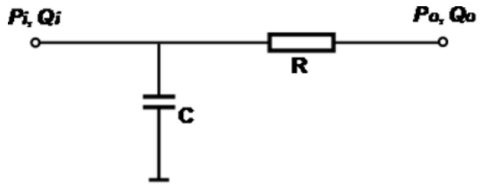


Figure 4.2: Two-Element Windkessel [21].

While this model can be used to evaluate the pressure difference across models of the circulation (Sections 5.1 and 5.2), calculations become complex and more difficult to define when using this model to describe the entire circulatory system, including the variable-volume heart chambers. An alternative model to represent the compliance of a blood vessel is defining it as a vessel or chamber with constant pressure across it (no pressure drop), and varying volume. In this way, it can be connected in series with the other elements of the circulation, making subsequent calculations less complex. Such a vessel can be described by the following governing equations:

$$P = P_0 + \frac{(V - V_0)}{C} \tag{4.2}$$

$$\frac{dV}{dt} = Q_{in} + Q_{out} \tag{4.3}$$

4.1.3 Heart chambers

Similar to the model for blood vessel compliance, the four heart chambers are modelled as chambers with constant pressure across them (no pressure drop), and varying volume. Therefore, the equations governing the behaviour of the chambers closely resemble

Equations 4.2 and 4.3:

$$P = P_0 + E(t)(V - V_0) \tag{4.4}$$

$$\frac{dV}{dt} = Q_{in} + Q_{out} \tag{4.5}$$

The function for $E(t)$ represents the elastance of the ventricle walls over the heart's cycle. Elastance represents the ability of the heart walls to resist a change in shape when a mechanical load is applied, and is the reciprocal of compliance. This can clearly be seen when comparing Equations 4.2 and 4.4. The time-varying elastance of the heart chamber walls is as follows:

$$E(t) = E_{min} + \frac{E_{max} - E_{min}}{2}\, e(t) \tag{4.6}$$

where $e(t)$ is the following activation function [2]:

$$e(t) = \begin{cases} 1 - cos\left(\dfrac{t}{T_{s1}}\pi\right) & 0 \leq t < T_{s1} \\ 1 - cos\left(\dfrac{t - T_{s1}}{T_{s2} - T_{s1}}\pi\right) & T_{s1} \leq t < T_{s2} \\ 0 & T_{s2} \leq t < T \end{cases} \tag{4.7}$$

Although the elastance function for the ventricles and atria have the same activation function, they occur at different times in the heart cycle. Therefore a time shift must be applied to t in Equation 4.6 when representing elastance of the atria, which occurs later in the cycle. The period of the heart cycle in which the ventricles contract (i.e. the ventricle elastance increases above minimum value) is referred to as systole, while diastole refers to the period of the heart cycle when the ventricles are at rest (i.e. ventricle elastance is at its minimum) [16].

4.1.4 Heart valves

The heart valves are to be modelled as orifice valves in series with diodes. The diodes model the closing of the valves to prevent backflow through it. When the valves are open, flow characteristics are modelled as an orifice valve. The combination of these two

elements has the following governing equation:

$$Q = \begin{cases} CQ\sqrt{-\Delta P} & \Delta P < 0 \\ 0 & \Delta P > 0 \end{cases} \tag{4.8}$$

4.1.5 Making an LPM of the human circulatory system

The theory behind the individual components discussed above can be used to create a lumped parameter model of the entire circulatory system, seen in Figure 4.3 below. This model is based on the model of the circulatory system suggested by Korakianitis and Shi [12] in their investigation of heart valve models.

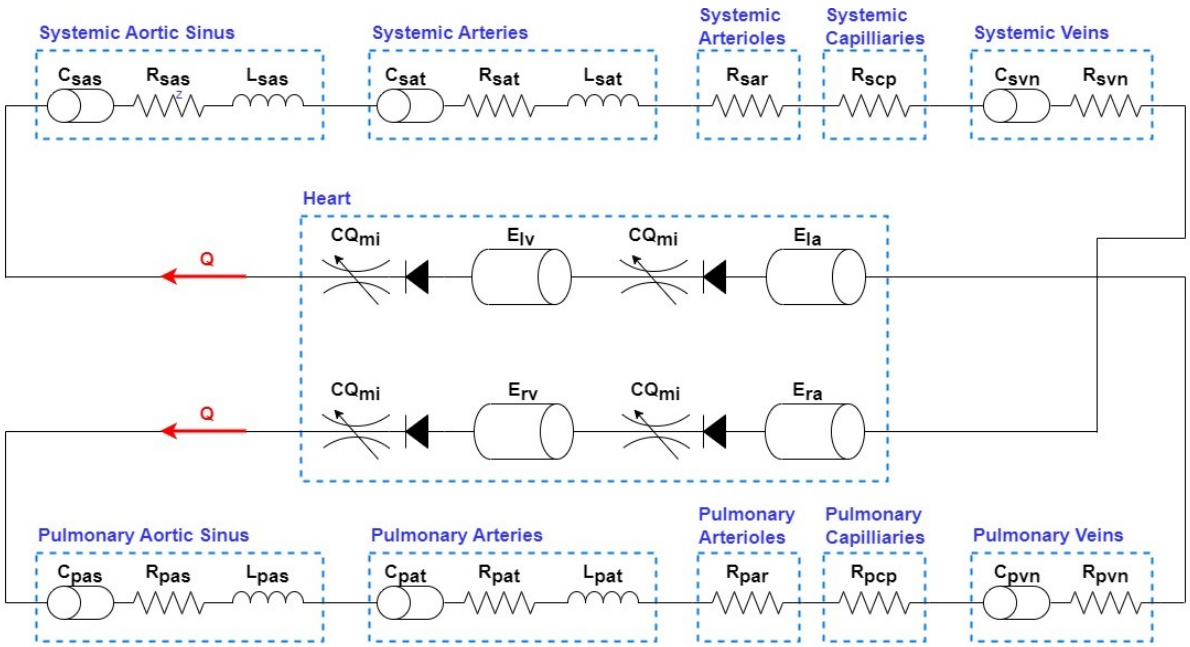


Figure 4.3: LPM of circulatory system

4.2 Model parameters

The parameters used to define the model in Figure 4.3 are taken from Korakianitis and Shi [12], and are listed in Appendix A.

5 Progress to Date

All models have been created in the Julia programming language using *ModelingToolkit.jl* [15], a high-performance symbolic-numeric equation-based modeling package. The systems of differential equations associated with these models are solved using *DifferentialEquations.jl* [17], using the fourth-order Runge-Kutta method. Many components of the circulatory system are based on models in *CirculatorySystemModels.jl* [19] with modifications to suit this specific project.

5.1 Initial investigations of Windkessel circuits

The basic two, three and four element Windkessel representations of the systemic circulation have been used to investigate the effect of each element on the total pressure difference across the circulation. These simple circuits have also been used to validate results from *ModelingToolkit.jl* against results from first-principle derivations of pressure differences.

This validation was carried out by using a simple sine wave as an input for blood flow into the systemic circulation. This sine wave was defined through the stroke volume of the heart. The stroke volume is defined as the volume of blood pumped out of the left ventricle of the heart during each systolic cardiac contraction [22] and the normal range is 50-100 ml. A stroke volume of 90 ml was assumed for the investigation of Windkessel circuits. This is represented by the area under the blood flow rate curve for each cardiac cycle of one second in Figure 5.1.

Figure 5.1 below shows the aortic pressure derived using two, three, and four element Windkessel models, with the simple sine wave input for blood flow shown for reference. The following circuit parameters were used:

	Value	Unit
R_p	0.9	mmHg s/ml
C	1.1	ml/mmHg
R_c	0.05	mmHg s/ml
L	0.0045	mmHg s^2/ml

Table 5.1: Parameters used to define Windkessel circuits [21].

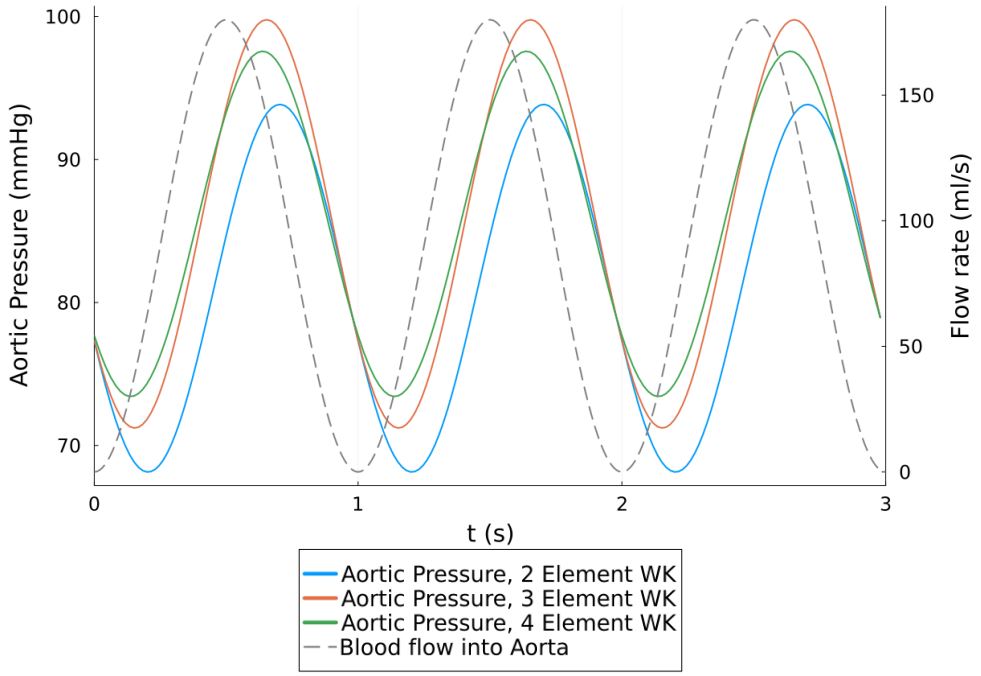


Figure 5.1: Aortic pressure for 2, 3 and 4 element Windkessel circuits.

As can be seen from this image, the peak pressure for each of the three different Windkessel circuit configurations occurs after the peak of the blood flow into the aorta. This is a result of the compliance of the blood vessels, which causes a time delay between blood flow and pressure increase in the aorta through teh expanding of blood vessels. The pressure across the three element Windkessel is greater than that of the two-element Windkessel due to the added resistive element. An inductive element is added to form the four-element Windkessel in order to account for the inertia of blood flow through the circulatory system. Inertia acts to resist change in motion or velocity of a body (in this case the blood), having a damping effect on the overall mechanical system. This explains why the magnitude of the pressure wave of the four-element Windkessel (circa 24 mmHg) is smaller than that of the three-element circuit (circa 28 mmHg).

5.2 Modelling systemic and pulmonary circulation

After validation of *ModelingToolkit.jl* using the simple Windkessel circuits, *ModelingToolkit.jl* can be used with confidence to model more intricate models of the systemic and pulmonary circulations. An LPM that can be tailored to represent either the systemic or pulmonary circulation through changing model parameters can be seen in Figure 5.2. As mentioned in Section 4.1.2, the capcatitor-in-parallel model of compliance can be used to model the systemic and pulmonary circulations with prescribed blood flow inputs.

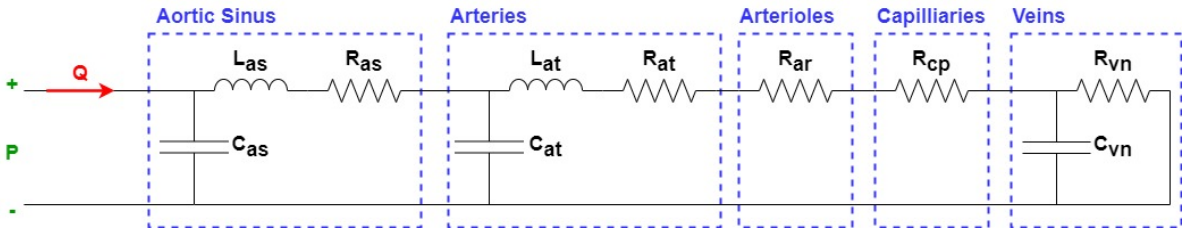


Figure 5.2: LPM of systemic and pulmonary circulation.

Similar to the analysis of the Windkessel models, the aortic pressure is investigated for an inputted blood flow rate signal. In this investigation, a truncated sine wave is used to give a more realistic input to the system, taking into account the fact that blood only flows into the aorta during systole, when the aortic valve is open. This signal still lacks many of the intricacies of realistic blood flow through the aorta, and again can only give a general idea of the pressure range in the systemic and pulmonary aortic sinuses. Again, a stroke volume of 90 ml is assumed for both the right and left ventricles in this investigation. The results can be seen below in Figure 5.3.

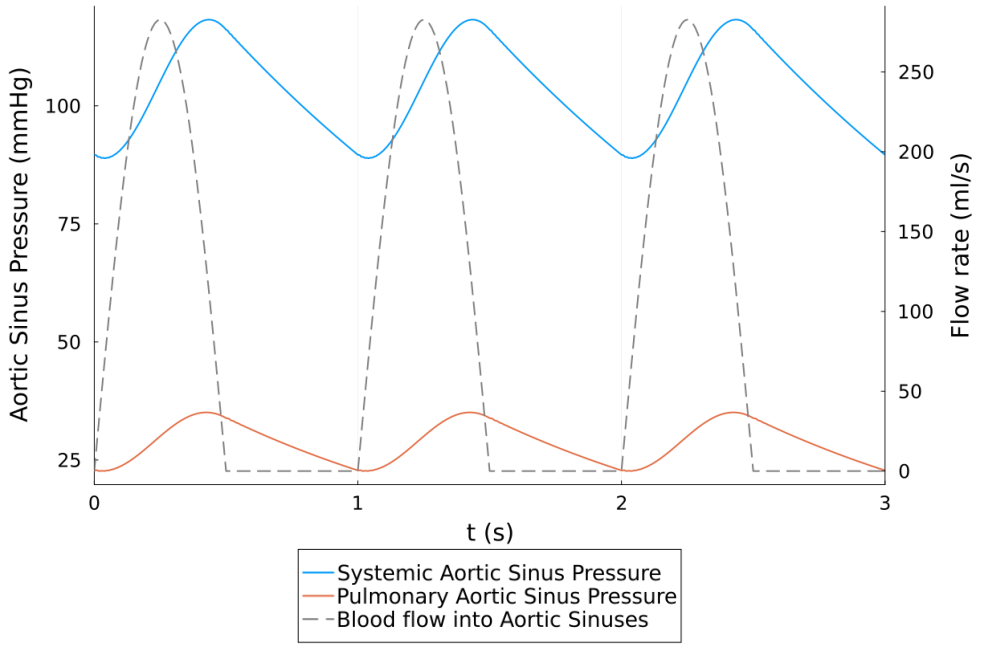
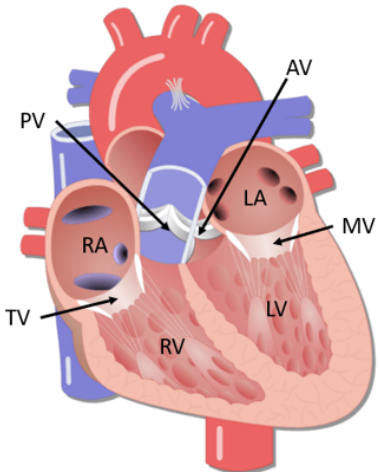


Figure 5.3: Pressure and flow rates in systemic and pulmonary aortic sinuses.

The pressure in the systemic aortic sinus is significantly larger than that in the pulmonary aortic sinus due to the increased resistance of the systemic circulation when compared to that of the pulmonary circulation.

5.3 The Heart

The next step was modelling the heart. Figure 5.4 below illustrates the parts of the heart that were modelled and how they connect to each other.



Abbreviation	Part of Heart
LV	Left Ventricle
LA	Left Atrium
RV	Right Ventricle
RA	Right Atrium
AV	Aortic Valve
MV	Mitral Valve
TV	Tricuspid Valve
PV	Pulmonary Valve

Figure 5.4: Heart diagram.

5.3.1 Heart chambers

The driving force behind the blood flow throughout the cardiovascular system is the time-varying elastance of the heart chambers.

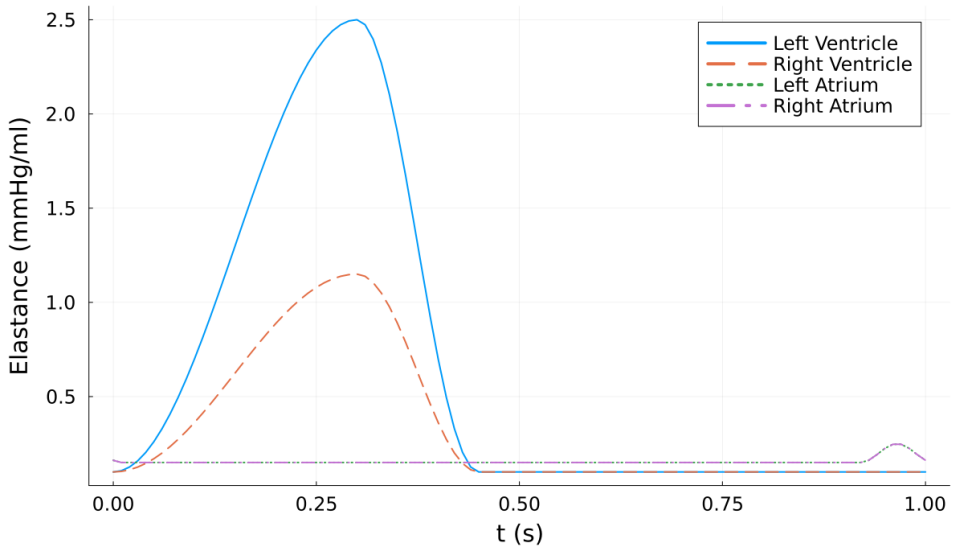


Figure 5.5: Elastance of heart chambers.

The elastance, described by Equation 4.6 in Section 4.1.3, is shown for each of the four heart chambers in Figure 5.5 above, when the appropriate values detailed in Appendix A are inputted for each heart chamber. This image illustrates the large difference between the magnitude of elastance of the ventricles compared to the atria. As can be seen from this graph, in this particular model, the elastance of both atria are identical over the cardiac cycle.

Figure 5.6 illustrates the relationship between chamber elastance, chamber pressure, and the volume of blood in each chamber. The elastance of the ventricles is the primary cause of pressure and volume change in the ventricles during systole, with a large increase in ventricular pressure, and a sharp decrease in volume, as blood is ejected from the ventricles. Similarly, the elastance of the atria also causes a sharp change in both the pressure and volume of the atria, however, significant changes in both of these parameters can also be seen at the end of systole, when the mitral and tricuspid valves open, allowing blood to flow out of the atria.

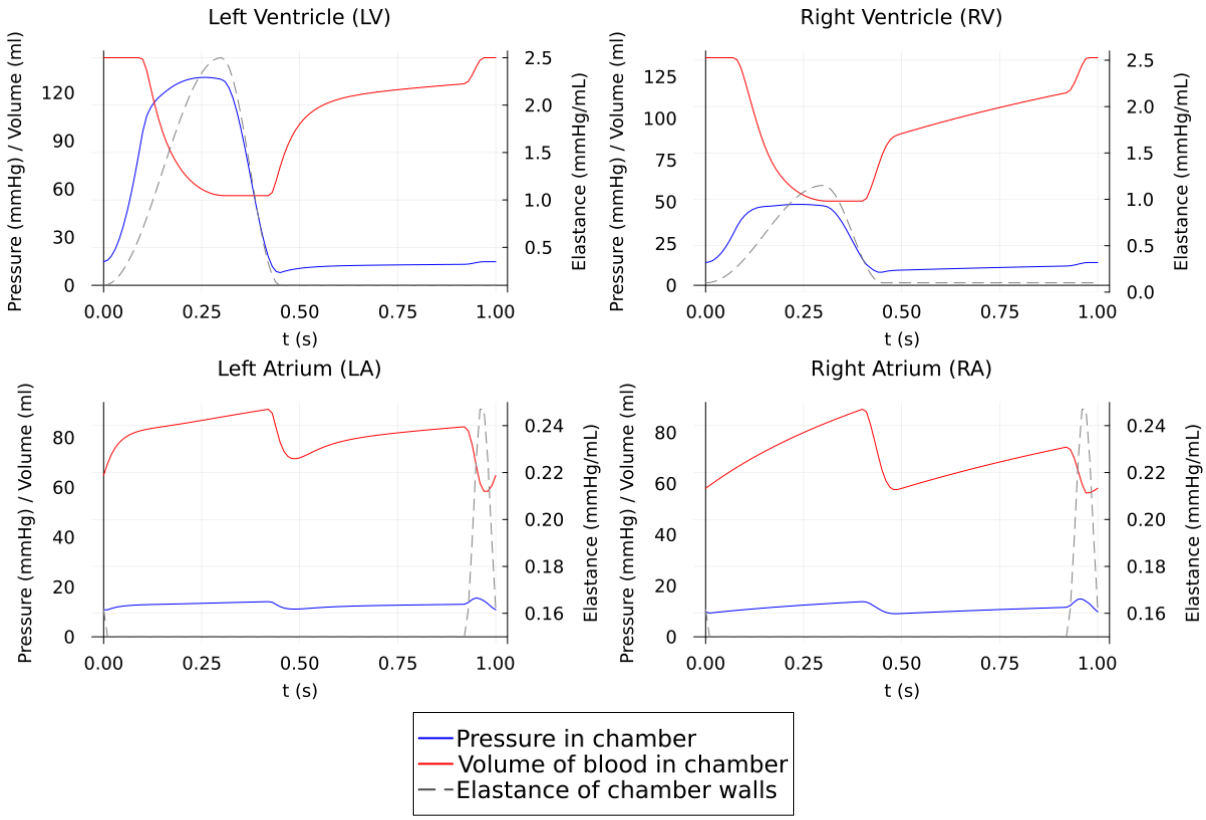


Figure 5.6: Pressure and volume in heart chambers.

5.3.2 Heart valves

The behaviour of the heart valves, described by Equation 4.8 in Section 4.1.4, is illustrated in Figure 5.7 below. From these graphs, it is clear that the valves only allow flow through them when there is a negative pressure gradient across them, and that this flow rate is proportional to the magnitude of this pressure gradient. When comparing these graphs with those in Figure 5.6, the change in chamber volumes can be understood in terms of inflow and outflow of blood to the chambers, through these valves.

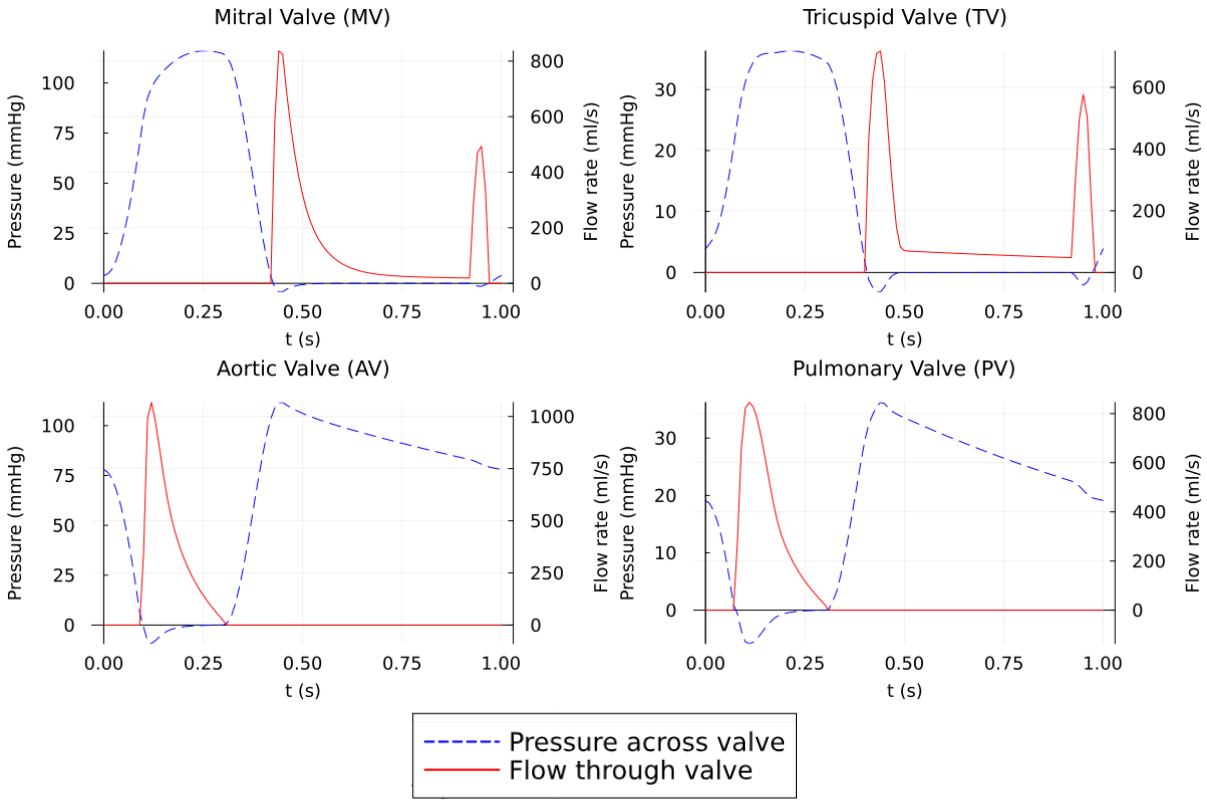


Figure 5.7: Pressure and flow rates across heart valves.

6 Plans for Continuation

Up until this point, the focus has been on creating a model of the circulatory system in the Julia programming language where values characterising components of the system can be easily altered. As this has been achieved, focus will now be shifted to the investigation of porcine-to-human xenotransplantation and its effect on the circulatory system, with the following plans for continuation:

- Literature review to determine the differences between pig and human hearts, and how best to translate these differences to changes in the parameters defining the model of the circulatory system.
- Parametric study, using the model already created, to investigate the extent to which each pig-heart parameter affects the pressure and blood flow through different parts of the circulatory system.
- Literature review to determine the possible effects that the changes discovered during the parametric study may have on the overall health and function of the human circulatory system, in the interest of long-term survival of the xenograft.
- Any other necessary or interesting investigations that arise over the course of the project.

7 Gantt Chart

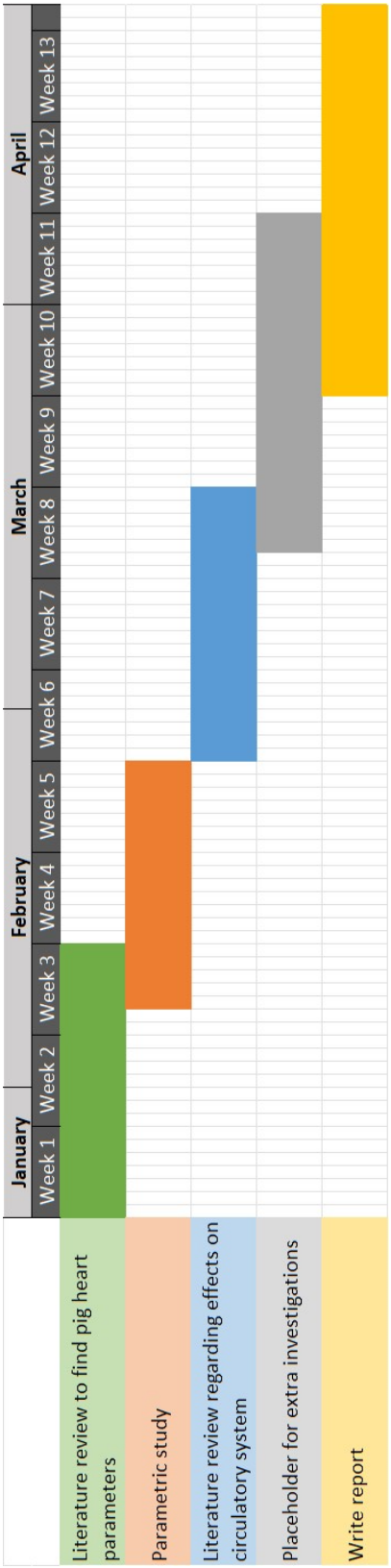


Figure 7.1: Gantt chart detailing expected project progression.

8 Risk Matrix

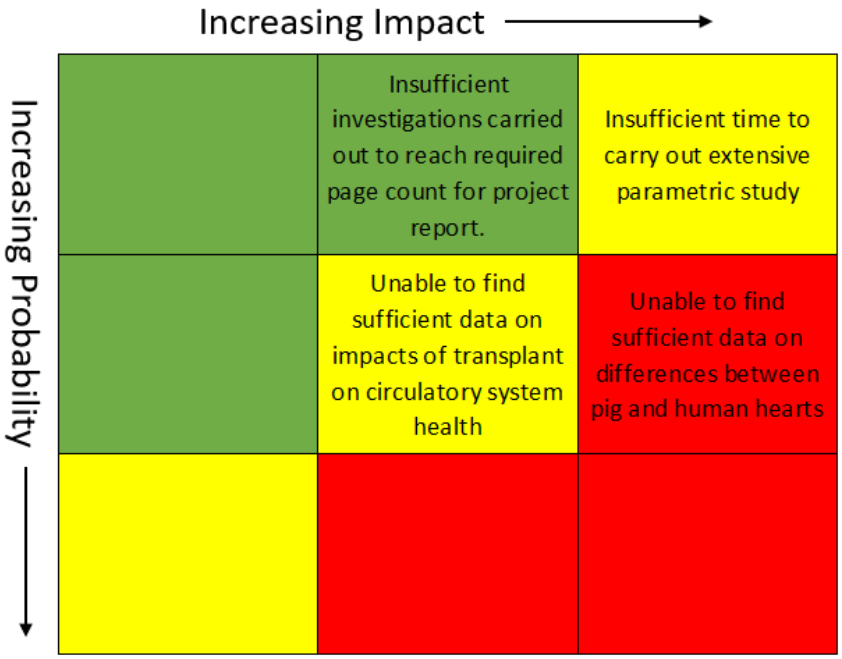


Figure 8.1: Risk matrix detailing risks associated with project progression.

As can be seen from the above risk matrix, the greatest risk to this project's steady progression is the availability of sufficient data regarding the differences between pig and human hearts that can be easily translated into changes in model parameters. In the absence of detailed pig-heart characteristic data, a parametric study can be carried out to investigate the impact on the circulatory system of changing certain heart parameters, providing an insight into how much a parameter can change before circulation characteristics fall into unhealthy or unsustainable ranges.

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Appendices

A Values used in analysis, based on Korakianitis and Shi [12]

		Left Ventricle	Right Ventricle	Left Atrium	Right Atrium
V_0	ml	5	10	4	4
P_0	mmHg	1	1	1	1
E_{min}	mmHg/ml	0.1	0.1	0.15	0.15
E_{max}	mmHg/ml	2.5	1.15	0.25	0.25
T_{s1}	s	0.3	0.3	0.045	0.045
T_{s2}	s	0.45	0.45	0.09	0.09
T_{shift}	s	0	0	0.92	0.92

Table A.1: Parameters used to define heart chambers

		Mitral Valve	Tricuspid Valve	Aortic Valve	Pulmonary Valve
CQ	ml/(s mmHg$^{\frac{1}{2}}$)	400	400	350	350

Table A.2: Parameters used to define heart valves

		Systemic Circulation	Pulmonary Circulation
C_{as}	ml/mmHg	0.08	0.18
R_{as}	mmHg s/ml	0.003	0.002
L_{as}	mmHg s^2/ml	6.2×10^{-5}	5.2×10^{-5}
C_{at}	ml/mmHg	1.6	3.8
R_{at}	mmHg s/ml	0.05	0.01
L_{at}	mmHg s^2/ml	0.0017	0.0017
R_{ar}	mmHg s/ml	0.5	0.05
R_{cp}	mmHg s/ml	0.52	0.25
C_{vn}	ml/mmHg	2.05	20.5
R_{vn}	mmHg s/ml	0.075	0.006

Table A.3: Parameters used to define systemic and pulmonary circulation