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**REAL HEART VALVE
OPERATION IN CARDIOVASCULAR
MODEL WITH SIMULATIONS FOR
MITRAL REGURGITATION AND
AORTIC STENOSIS**

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ABSTRACT

Heart valves control the heart function; which is the responsible for blood distribution through the lungs and the body.

Modeling valves' function may provide a tool for studying the heart's performance, as well as, it helps to represent some of the most common heart's abnormalities such as mitral valve regurgitation and aortic stenosis. Cardiovascular system models using electrical systems do not model chambers and the valves are ideal.

This study proposes a model for heart valves based on the seven cardiac cycle phases, and representing times and shapes for the three real valve operation stages: opening, slow closing and quick closing. It is possible to simulate different slopes in the systolic and diastolic stages, in addition to their time duration depending on the heart rate. Additionally, one can use parameters to represent different hearts sizes.

The model is used for mitral valve regurgitation and aortic stenosis conditions and tested three severity conditions. For testing purposes the model was implemented in VHDL-AMS for the electrical analog circuit of the valves, for both diseases. To simulate dynamic blood flow model, it was implemented in VENSIM, which allow for generation of blood flow velocity profiles and volumes.

This model will be helpful for independent valve's parameters change, so that each heart valve is independently represented; also giving medical personnel to simulate several conditions in heart valves and observe the ultrasound derived blood flow velocity profile for severity level of regurgitation.

RESUMEN

Las válvulas cardiacas controlan la función del corazón, el cual es responsable por la distribución de sangre a través de los pulmones y el cuerpo.

El modelo de la función de las válvulas provee una herramienta para estudiar el comportamiento del corazón; así como también, ayuda a representar algunos de las anomalías más comunes como pueden ser la regurgitación mitral y la estenosis aórtica. Los modelos cardiovasculares basados en sistemas eléctricos no modelan las cavidades como elementos independientes y las válvulas en estos sistemas son ideales.

Este estudio propone un modelo para las válvulas cardiacas basado en las siete fases del ciclo cardiaco, y representa tiempos y formas para las tres etapas de la operación real para las válvulas: apertura, cierre lento y cierre rápido. Es posible simular diferentes pendientes en las etapas de sístole y diástole, además de que su duración depende del ciclo cardiaco. Adicionalmente, se puede usar parámetros para representar diferentes tamaños del corazón.

El modelo es usado para condiciones de regurgitación mitral y estenosis aortica y probado bajo tres condiciones de severidad. Para propósitos de prueba, el modelo fue implementado en módulos de VHDL-AMS usando los circuitos eléctricos análogos de las válvulas para ambas enfermedades. Para simular el modelo dinámico de flujo sanguíneo, se implementó en VENSIM, lo cual nos permitió la generación de los perfiles de velocidad del flujo sanguíneo y volúmenes.

Este modelo puede ser útil para el cambio de parámetros independientes de las válvulas, ya que cada válvula cardiaca del corazón es representada independientemente; del mismo modo permite al personal médico simular varias condiciones en las válvulas cardiacas y observar los perfiles de flujo sanguíneo derivados de los ultrasonidos para la clasificación de la severidad de la regurgitación y estenosis.

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TO THE REASON OF MY EXISTENCE, ALEXA

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Chapter 1

INTRODUCTION

Human physiology can be described by cells and organs that form different systems which make life possible [1]. The cardiovascular (CV) system is responsible for blood oxygenation and nutrient distribution, which makes it one of the most relevant systems of the human body. The cardiovascular system has two major components: the vascular system (circulatory) and the heart.

The heart is the organ which pumps the blood around the body and it is formed by 4 cavities: the left and right atria and the left and right ventricles. These parts are involved with the cardiac cycle, that is the period from the end of one contraction to the end of the next contraction of the heart. The cardiac cycle activity can be monitored by signals like

Electrocardiogram (ECG), the recordings sound produced by the heart as it pumps and the pressure changes in the aorta, the left atrium and the left ventricle [1].

Conditions such as: obstructions in the arterial tree, abnormalities characteristic of the heart, valvular diseases, lead to several cardiovascular diseases that cause most of the deaths every year, according to The World Health Organization.

With the purpose to analyze and better understand interactions and effects of cardiovascular diseases/abnormalities; different models and artifacts have been used such as lumped models, dimensional modeling and experimental methods [2].

Modeling physiological systems is in general a multidisciplinary task that may include areas such as mechanical, electrical, computer and biomedical engineering. It sometimes requires knowledge in mathematical model formulation, numerical simulation and statistical data analysis. Furthermore, modeling and simulation can give qualitative and quantitative information that help to predict specific conditions and develop new experiments or theories. Besides, models can explain how abnormalities or diseases affect the cardiovascular system, avoiding waste of effort, time and human experimentation; these models should be simple enough so that key parameters can be changed using the available clinical data, and at the same time capture fundamental system dynamics [3].

1.1 Problem definition

In particular, the electrical analog models are extensively used for vascular representation of the cardiovascular system; these are based on the Windkessel models, these models present different output signals depending on their components; passive or active, but they are limited to pressure and blood flow signals, analog to current and voltage. These models have the limitation of using ideal valves and the lack of representation for heart chambers [4]. Furthermore, these models are commonly developed for research purposes, so far only concepts of vascular impedance and pulse

wave velocity are widely used to assist clinical diagnosis and treatment; currently few models comprising the complete description of heart composition have seen used in clinical practice [4].

Hence, it is notable the need of an enhanced human cardiovascular system model which contains the valves and the chambers modeling and personalize the models in order to achieve the patient-specific modeling; this can contribute with information that help to predict and develop new experiments in order to improve the understanding of the cardiovascular system and how valvular abnormalities/diseases affect it, in particular the heart performance, which is reflected in velocity and volume signals, and this could bring innovations to the cardiovascular clinical practice.

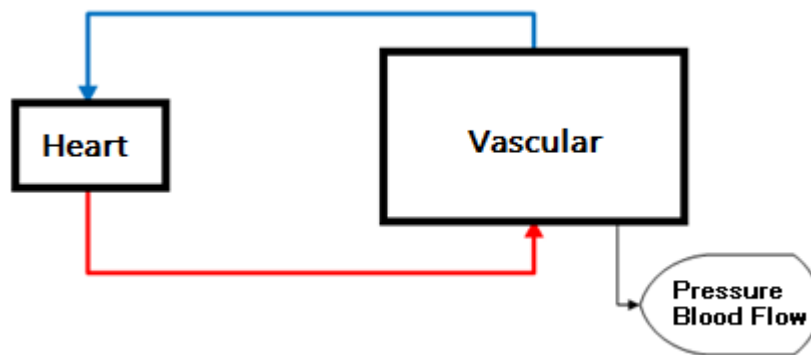


Figure 1. Typical human Cardiovascular System Model.

1.1.1 Thesis statement

Does a heart valve model using parameterized multi-segmented curve for blood flow and heart cycle phases for time synchronization represent normal/abnormal valve operation of real heart's?

Does heart chambers size can be parameterized to represent person's distinct anatomy characteristics and parameterized heart cycle phases to represent distinct activities for blood flow dynamics?

A flexible parameterizable model for heart valves based on the seven cardiac cycle phases, and representing times and shapes for the three operation stages: opening, slow closing and quick closing can help to improve valvular diagnoses and control timing for representing activities, in addition to a flow dynamics based model, it is possible to represent some body dimensions by changing parameters of every compartment of the model.

1.2 Objectives

1.2.1 General

Design a cardiovascular model that includes the heart dynamics, and its valves in order to represent some valve's abnormalities and improve the understanding of their performance in a non-invasive way.

1.2.2 Particular

- i. Design a cardiovascular system model (Heart and Vasculature) based on the seven phases of the cardiac cycle.
- ii. Design a heart model with all its elements and add it to the first one.
- iii. Modeling of the heart valves with the real performance by controlling the opening and closing and use it in the four valves of the previous heart model design.

- iv. Inclusion of the valve model into an electrical analog model to test the functionality.
- v. Modeling mitral regurgitation, mitral and aortic stenosis as an abnormalities of the heart.

1.3 State of the art

1.3.1 Modeling the cardiovascular system

Models are developed to achieve specific research purposes in each individual study, thus the complexity of the models should fit the purposes of the study. An over-simplified model will produce inadequate accuracy in the study. However, this does not mean that a more complex model will always produce more accurate results [4].

Relevant literature reviewed, referred that modeling and simulation is a standard way for deepening on the understanding of cardiovascular system operation. Different existing models were found for the cardiovascular system, such as: Heart Models, Vascular models and cardiovascular models.

There are some models that represent the morphology and the structure of heart using finite elements and images to design 2-D and 3-D models [5], [6]. And they are used to develop artificial structures.

Vascular modeling can be divided in three main parts: vessel-tree, microcirculation and blood flow. Vessel tree modeling includes functional physiologic and anatomic models; the functional models use mathematical methods for modeling [7], and the anatomic models represent the characteristics of vessel tree using images and 3-D graphics [8]. The microcirculation modeling uses chaos

theorems and some blood flow modeling includes oxygen supply and systemic circulation [9]; all these details according to model's purpose.

In Cardiovascular modeling some models contain the two previously mentioned parts; heart and vascular system, literature mentions functional physiologic models that represents the systemic circulation and the cardiac cycle [10], [11], [12], [13], [14]. Most of the cardiovascular models are based into the Windkessel model for the modeling of specific vascular segments, [15], [16] . There are models of circuits equivalents to cardiovascular system dynamics with 6 or 21 [17], and 43 components [18] modeling by differential equations and space-state equations [19]. These models are electrical analogs and their number of components are dependent on the purpose and the level of detail; their principal outputs are the pressure and volume signals. Some of these models are design for represent and study a specific disease [20], [21].

Other works about hemodynamics simulation have models that study the flow dynamics of the systemic circulatory system [22], simulate the normal operation of the systemic and pulmonary circulation [18], and some others describe the pressure, volume and flow dynamics of the systemic circulatory system over the full physiological range of human pressures and volumes [23]. Table 1, shows a summary of the main models mentioned before.

Table 1. Summary of main models reviewed

Ref.	Models	Type	Contribution	Purpose
[2]	CV	Functional physiologic	It describes a 36-vessel model and cardiac system of human body with details that could show hydrodynamic parameters of cardiovascular system.	Simulate obstruction in the aorta of the cardiovascular system model.
[5]	Heart	Anatomic	This model, develop an efficient and robust	Propose a novel four-chamber surface

			<p>approach for automatic heart chamber segmentation in 3-D CT volumes.</p>	<p>mesh model for a heart.</p>
[6]	Heart	Functional Physiologic	<p>A beating heart model was constructed and 12-lead ECG was simulated based on this model.</p> <p>Compared with the simulated ECG based on the static heart model, the simulated ECG based on beating heart model is more accordant with clinical recorded ECG.</p>	<p>Present a method of beating heart modeling and ECG simulation.</p>
[8]	Vascular	Anatomic	<p>The developed model is used to extract the liver and lung vessel tree as well as the coronary artery from high-resolution volumetric computed tomography images. Comparisons are made with several classical active contour models and manual extraction.</p>	<p>A novel active contour model is proposed for vessel tree segmentation</p>
[9]	Vascular	Functional physiologic	<p>A model of the coronary circulation was presented.</p>	<p>This model is integrated with a model of the systemic circulation, and contains models for</p>

				oxygen supply and demand.
[13]	CV	Functional physiologic	An active learning tool that demonstrates the interactions between the functions of the heart and peripheral circulation. This learning package consists of a Lab Book, a Model, and an Information file.	Learners are guided to predict the direction and relative magnitude of changes of key variables in the cardiovascular system, evaluate the accuracy of their predictions, and describe the cause-and-effect mechanisms involved.
[14]	CV	Functional Physiologic	The forward model, on which the theoretical validation is based, provides a convenient test bed of data, which may facilitate the development of new methods that could be incorporated with the cardiovascular system identification method so as to provide a more detailed picture of cardiovascular state.	This study supports system identification as a powerful approach for the intelligent patient monitoring of cardiovascular function.
[15]	Heart	Functional physiologic	This work proposed a hydraulic-electric analogy model solely estimated from non-invasive blood flow, blood pressure, and temporal activation of	The purpose of this work is to investigate regional behavior of the heart under normal conditions.

			ventricular muscle.	
[17]	CV	Functional Physiologic	Elaborated versions consisting of 6- and 21-compartment computational models implemented in C.	Educational simulator.
[18]	CV	Functional physiologic	Describing the system based on the vessel diameters, and simulating the mathematical equations with active electrical elements. 43 compartments.	The objective of this study is to develop a model of the cardiovascular system capable of simulating the normal operation of the systemic and pulmonary circulation.
[21]	Heart	Functional Physiologic	Comprehensive state-space model for a Left Ventricular Assistant Device connected to the cardiovascular system.	Developed a patient adaptive feedback controller for the pump speed in the LVAD which insures that the patient's blood flow requirements are met as a function of the patient's activity level and at the same time avoid the occurrence of suction.
[23]	CV	Functional physiologic	The mathematical model developed for this study is capable of accurately describing the pressure, volume and flow dynamics of the systemic	This is in large part due to new mathematical representations for the ANS and CNS reflexes which maintain arterial

			circulatory system over the full physiological range of human pressures and volumes.	pressure, cardiac output and cerebral blood flow as well as a new approach to modeling the pressure.
[24]	Heart	Functional physiologic	This paper presents a new mathematical model of the human heart.	The objective of this research was to adapt the complexity of the model but can represent the cardiac activity of the heart.
[25]	Heart	Functional physiologic	The models discussed here are all derived from the systems of physical equations underlying the heartbeat.	The models of cardiac function discussed here are integrative models based on the anatomy, biophysics, and biochemistry of the heart.
[26]	Heart	Functional physiologic	The model presented was designed at a macroscopic level with a limited number of internal parameters. Given the high complexity of cardiac motion, composed of different twisting rotations and radial and axial contractions.	This paper presents a new three-dimensional electromechanical model of the two cardiac ventricles designed both for the simulation of their electrical and mechanical activity, and for the segmentation of time series of medical images.
[27]	CV	Functional	This article highlights	The purpose of this

		physiologic	the influence of sensory-visual input upon the function of the autonomic nervous system and the coherent function of the various organ networks.	article is to discuss a novel cognitive, top-down, mathematical model of the physiological systems, in particular its application to the neuro-regulation of blood pressure.

There are models that only represent the activity of heart [24], others introduce devices like Left Ventricular Assistant Device (LVAD) for the treatment of cardiac diseases [21] and also, investigate regional behavior of the heart under normal conditions, by the use of a hydraulic-electric analogy model [15]. Besides there is a cardiovascular model that includes the mitral valve dynamics applied to the ischemic mitral insufficiency [28] and one applied to study the global hemodynamic influences of an atrioventricular stenosis and arterial stenosis located in various regions [29]. Table 2, summarizes main electrical models reviewed.

The principal limitations of these models are the parameters; the number of parameters for these models depend on the level of detail, see Figure 2 and 5; that is, if we need a maximum detail for modeling, the number of parameters will be very extensive. Another characteristic is the valves, which in this type of model are representing as ideal diodes, so a lack of a real representation of the heart function is notable as Paeme, et al. mentioned in [28], and the capacity to represent are valvular diseases is reduced.

Furthermore, these models are commonly developed for very specific research purposes, so far only concepts of vascular impedance and pulse wave velocity are widely used to assist clinical diagnosis and treatment and few models comprising the complete description of heart composition have seen used in clinical practice [4].

Table 2. Main Electrical models reviewed

Ref	Type of function	# components	Outputs	Properties
[16]	Normal	Left heart and circulatory impedance	Aortic pressure and blood flow	Computer model of the left heart and systemic circulation in LabVIEW TM , the program developed employs Windkessel-type impedance models
[14]	Normal	6	Pressures	Computational model of the cardiovascular system capable of generating realistic beat-to-beat variability (forward modeling).
[18]	Normal	43	Pressures	
[20]	Abnormal	Left and right heart, pulmonary circulation, systemic circulation, cerebral circulation	Pressures	This model accurately represents the cardiopulmonary system and can explain how the heart, lung, and autonomic tone interact during the Valsalva maneuver disease.

[17]	Normal	6, 21	Volume, pressures	Cvmsim
[21]	Abnormal	Left heart	Pressures	Comprehensive state-space model for a LVAD connected to the cardiovascular system.
[15]	Normal	Heart	Pressure and flow	This work proposed a hydraulic-electric analogy model solely estimated from non-invasive blood flow, blood pressure, and temporal activation of ventricular muscle.

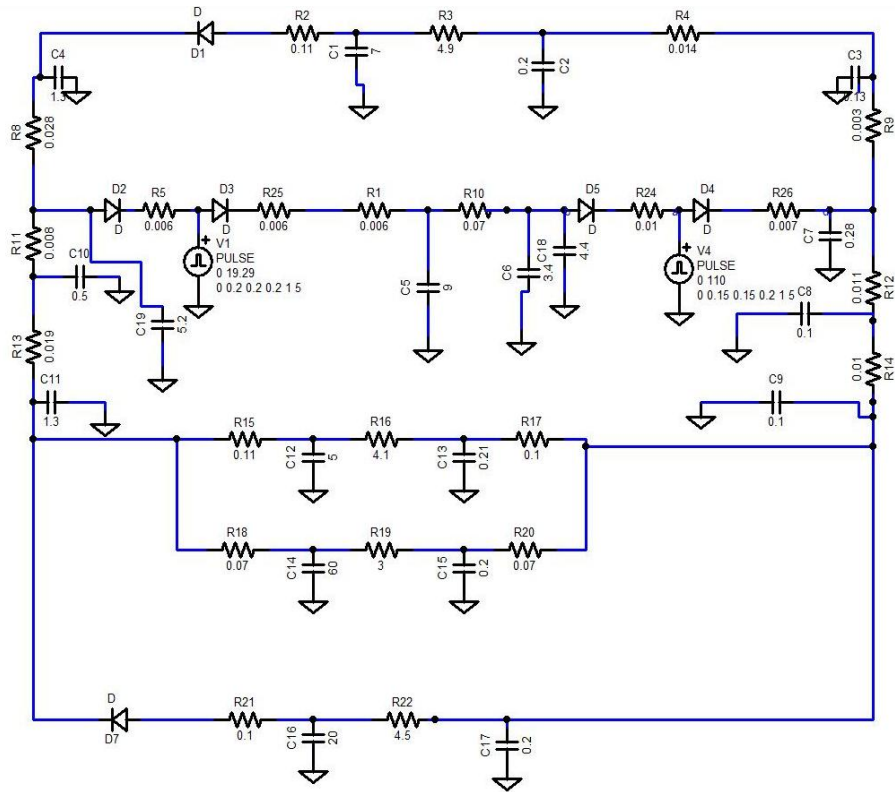


Figure 2. Circuit for cardiovascular system with 21 elements, extracted from [17].

In spite of the wide range of studies, there is a notable lack of flexibility in changing parameters for the models used on all these works. Regarding output, it is limited to volume and pressure analysis and there is no modeling of heart valves dynamics for early symptoms detection of specific diseases such as; mitral regurgitation or valvular stenosis.

Another opportunity area in the modeling of this type of models it is important to personalize the models in order to achieve the patient- specific modeling, and this will bring innovations to the cardiovascular clinical practice. To reduce the difficulty in parameter setting, models for patient-specific analysis may have reduced complexity as compared to those for research purposes.

In this work we develop a flexible and parameterized cardiovascular system model that eases the modification on its structure and gives output signals for velocity profile and volume analysis; that will ease learning on symptoms' detection on heart's valves operation and/or variation on cardiac cycle phases.

1.4 Thesis Organization

This thesis is organized as follows: Chapter 2 presents the basic concepts for developing this work. Chapter 3 presents the cardiovascular system modeling process. Chapter 4 describes the simulations and results and finally Chapter 5 presents the conclusions and future work.

Chapter 2

THE CARDIOVASCULAR SYSTEM

This chapter explains the required elements to understand the Cardiovascular System function. It starts by describing the cardiovascular system elements; the vascular system and heart and finally the description of the cardiac cycle phases is presented.

2.1 The Cardiovascular System

The cardiovascular system is a closed hydraulic system. The circulation of blood is maintained within the blood vessels by the rhythmic pressure in the trunk vessels exerted by the contraction and expansion of the heart. The heart acts as a pump whose elastic muscular walls contract rhythmically to develop pressure to push the blood through the vascular system. The heart contracts continuously and rhythmically, without rest, about

1,000,000 times per day [30]. The cardiovascular system consists of two main parts; the vascular system or vasculature and the heart.

2.1.1 Vascular System

The vascular system of the body consists of the complete system of arteries, veins and the capillary networks. This system is the responsible for directing blood to the networks spread throughout the body and for returning it to the heart [31, 32].

The vessels of the blood circulatory system are:

- **Arteries.** Blood vessels that carry oxygenated blood away from the heart to the body.
- **Veins.** Blood vessels that carry blood from the body back into the heart.
- **Capillaries.** Tiny blood vessels between arteries and veins that distribute oxygen-rich blood to the body.

Blood moves through the circulatory system as a result of being pumped out by the heart. Blood leaving the heart through the arteries is saturated with oxygen. The arteries break down into smaller and smaller branches in order to bring oxygen and other nutrients to the cells of the body's tissues and organs. As blood moves through the capillaries, the oxygen and other nutrients move out into the cells, and waste matter from the cells moves into the capillaries. As the blood leaves the capillaries, it moves through the veins, which become larger and larger to carry the blood back to the heart [32].

2.1.2 Heart

The heart is in charge of pumping blood into the aorta and the pulmonary veins, and it is formed by

- Left and right atria

- Left and right ventricles
- Semilunar valves
- Atrioventricular valves

The heart can be considered as a pair of two stage pumps working in series with each stage of the pumps arranged physically in parallel. However; the circulating blood passes through from first stage to second stage. The heart has two parts; the right heart and the left heart, Figure 3 shows a right part. The right heart is a low pressure pump while the left heart is a high pressure pump. The right heart receives blood from inferior vena cava and superior vena cava veins and pumps it to the lungs. The blood flow through the lungs is called the pulmonary circulation. The left heart receives blood from the pulmonary vein. The left heart acts as a pressure pump and it pumps the blood for the systemic circulation which has a high circuit resistance with a large pressure gradient between the arteries and veins. The muscle contraction of the left heart is larger and stronger as it is a pressure pump while the right heart is a volume pump with lesser contraction [30].

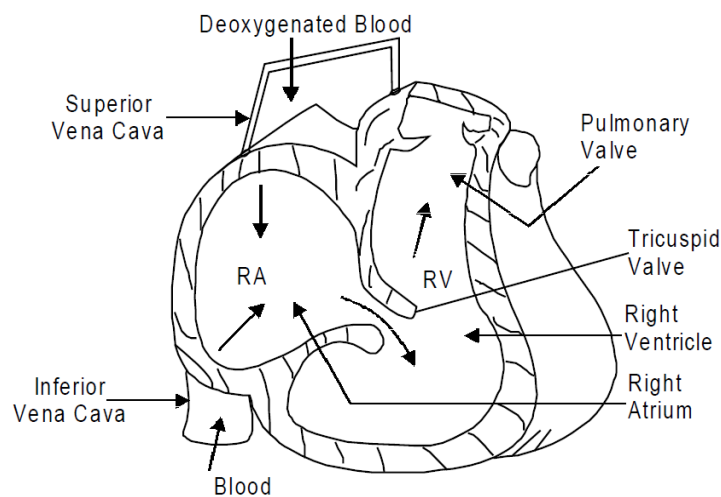


Figure 3. Right Heart Structure. Figure by Sawhney, "Fundamentals of Biomedical Engineering", [Ed.] New Age International (P) Ltd., Publishers, 2007.

It has four cardiac valves, at the entrance and the exit of each chamber. Such valves prevent blood backflow when chambers contract.

These valves are [1] [32]:

- Atrioventricular (AV), tricuspid and mitral valves regulate the blood flow from ventricles to atria, when ventricles are contracting.
- Semilunar valves, the pulmonary and aortic valves regulate the blood flow from ventricles to lungs and the aorta.

These valves control the blood flow at systole and diastole of the heart.

2.1.2.1 Cardiac Cycle Phases

A general form of the cardiac cycle gives the timing for a pumping heart. It is formed by 7 phases [32]:

A. *Atrial systole*: Prior to atrial systole, blood has been flowing passively from the atrium into the ventricle through the open AV valve. During atrial systole the atrium contracts and tops off the volume in the ventricle with only a small amount of blood. Atrial contraction is complete before the ventricle begins to contract.

B. *Isovolumetric ventricular contraction*: The atrioventricular (AV) valves close at the beginning of this phase. Electrically, ventricular systole is defined as the interval between the QRS complex and the end of the T wave (the Q-T interval). Mechanically, the isovolumetric phase of ventricular systole is defined as the interval between the closing of the AV valves and the opening of the semilunar valves (aortic and pulmonary valves).

C. *Rapid ventricular ejection*: The semilunar (aortic and pulmonary) valves open at the beginning of this phase of ventricular systole.

D. *Reduced ventricular ejection*: At the end of this phase the semilunar (aortic and pulmonary) valves close.

E. *Isovolumetric ventricular relaxation*: At the beginning of this phase the AV valves are closed.

F. *Rapid ventricular filling*: Once the AV valves open, blood that has accumulated in the atria flows rapidly into the ventricles

G. *Reduced ventricular filling*: Ventricular filling continues, but at a slower rate.

2.2 Valvular diseases diagnosis.

The valvular diseases are commonly diagnosed by using the Doppler echocardiography, this not only detects the presence of abnormalities but also permits to understand mechanisms of them, quantification of their severity and repercussions [33].

An example of this kind of diseases is the mitral regurgitation (MR), which is the most prevalent cause of valvular heart disease in western countries. Mitral Regurgitation was the second most common heart valve disease requiring surgery [34].

Accurate quantification of MR is, very important for decisions regarding surgery. Due to its relatively low cost and extensive availability, echocardiography is a key imaging method for the diagnosis of MR severity [33]. Current guidelines propose integration of qualitative, semi-quantitative, and quantitative criteria for grading the severity.

The Proximal Isovelocity Surface Area (PISA) method is currently the main quantitative method for MR grading. Figure 4 shows an example of the quantitative assessment of mitral regurgitation.

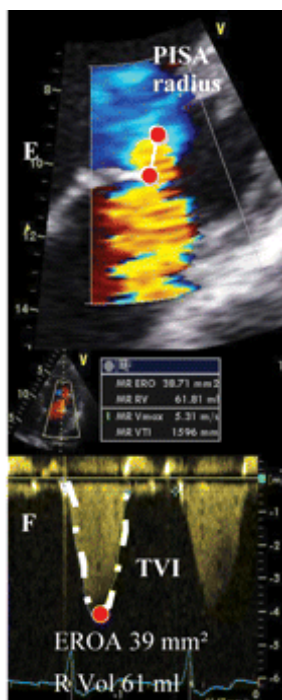


Figure 4 Quantitative assessment of mitral regurgitation (MR) severity using the proximal isovelocity surface area method [33].

2.3 Summary

The cardiovascular system is the vehicle for transportation of oxygen and nutrients through the body, this system is composed for some parts such as:

- Heart
- Veins
- Arteries

Each part has a specific function that can be represented by using some kind of models, in order to improve the modeling design.

In this chapter the function characteristics of the cardiovascular system were explained, these features were used in the development of this thesis, for the design of a new model, the next chapter will be focused in to describe the stages of the cardiovascular model design.

Chapter 3

CARDIOVASCULAR MODEL DESIGN

A model is an abstract representation of a system or process, which helps to explore, or predict the performance of elements of interest for such systems. This chapter explains the principal stages for developing a new flexible and configurable cardiovascular model that includes the valves dynamics.

3.1 Current cardiovascular system modeling

The principal limitations of existing models are the non-specific-patient parameterization, and also the notable lack of flexibility in changing parameter values for the models used on all these works, in Figure 5. Circuit for left Heart representation, extracted from, which makes impractical use of it for medical personnel. Models' outputs are limited to

volume and pressure signals for analysis and there is not a modeling on heart valves dynamics.

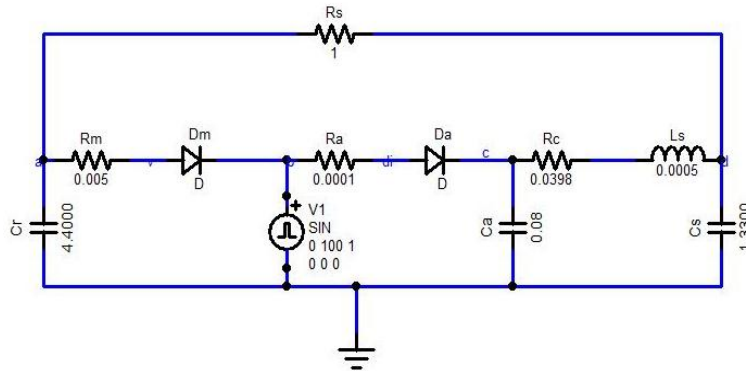


Figure 5. Circuit for left Heart representation, extracted from [21]

3.2 Cardiovascular model in Vensim

In order to improve the understanding about heart's dynamics numerous cardiovascular models have been developed to different levels of detail [17, 15, 24, 21, 18]. Most of the previously published models are difficult to modify when a user wants to reflect a given person's body dimension or activity; thus, for these cases the design of a flexible and customizable model comes to order.

In order to show blood flow, and volume information that will enable visualization of velocity profiles, the valve model was implemented, simulated and presented results that are consistent with medical diagnosis techniques of some abnormal conditions in valves. For this we used Vensim from Ventana Systems, Inc.

Our proposed model subdivides the human cardiovascular system into three subsystems; the pulmonary, heart and body's vascular system. The heart's model includes

its four valves; the complete model has six compartments: four for heart chambers, one for lungs and one for the rest of the body. We assume that the vascular and pulmonary systems are healthy and normal. The model can reproduce the hemodynamics of the heart based on volume analysis and the phases of the cardiac cycle.

Each cardiac chamber is described by volume and blood flow dynamics synchronized by cardiac cycle phases; this will be further developed in next section. Four cardiac valves are located in the heart, at the input and the output of each ventricle.

All parts of the model are customizable by parameters; giving that we can represent different sizes of heart's chambers, some activities and even some heart's valves diseases on a simulation by simulation basis.

As previously mentioned the design is based in the cardiac cycle phases. The cardiac cycle is a sequence of events that occur for each heart beat; this has the following 7 phases:

- A) Atrial systole*
- B) Isovolumetric ventricular contraction*
- C) Rapid ventricular ejection*
- D) Reduced ventricular ejection*
- E) Isovolumetric ventricular relaxation*
- F) Rapid ventricular filling*
- G) Reduced ventricular filling*

Each phase occurs at a time within each heartbeat, and all together the phases sum up to the heart's pulse timing; these phases are repeated every heart beat and they define the

timing function of valves i.e. the opening and closing times for each valve. In the next sections, we describe each part of the proposed model.

3.2.1 Modeling Heart Chambers

The heart is an organ responsible for pumping blood throughout the body; this organ is formed by four chambers, two atria and two ventricles. The atria receive blood from lungs and body and pass it into the ventricles. During each cardiac cycle, the atria contract first, ejecting blood into their respective ventricles, then the ventricles contract, ejecting blood into the pulmonary and systemic circuits [35].

It is important to mention that the two ventricles contract at the same time and eject equal volumes of blood to the lungs and body.

Our proposed model subdivides the human cardiovascular system into six blocks or compartments, four of these compartments are the heart chambers representation; the remaining two are for pulmonary's and body's vascular systems. All compartments are inter-connected and hold to the volume conservation law.

Each cardiac chamber is described by volume and blood flow dynamics and cardiac cycle phases. Four chambers (right atria, left atria, right ventricle and left ventricle) are modeled as container compartments. Each one has an initial volume value, which is given by the user, depending on the heart's size. Their dynamics are regulated by the opening, and closing times for valves, in turn controlled by the cardiac cycle phases.

Each chamber has two valves controlling input and output blood flow; these valves allow the diastole (filling) and systole (draining) for each chamber, these actions (diastole and systole) represent the complete cardiac cycle and are used to estimate the stroke volume; that is, the volume of blood pumped from one ventricle of the heart for each beat. Its value is obtained by subtracting end-systolic volume (ESV) from end-diastolic volume (EDV) for a given ventricle [32].

$$SV = EDV - ESV \quad (1)$$

The cardiac output (CO) as the volume of blood being pumped by the heart in one minute, either the left or right ventricle, is given by the following formula

$$CO = SV * HR \quad (2)$$

Where HR is the heart rate and SV is the stroke volume. These values are used for the volume analysis, and are used to verify that the model is working properly.

As previously mentioned the volume in each chamber is controlled by their input and output valves. The chamber volume is the accumulation of the difference of blood flow through the valves.

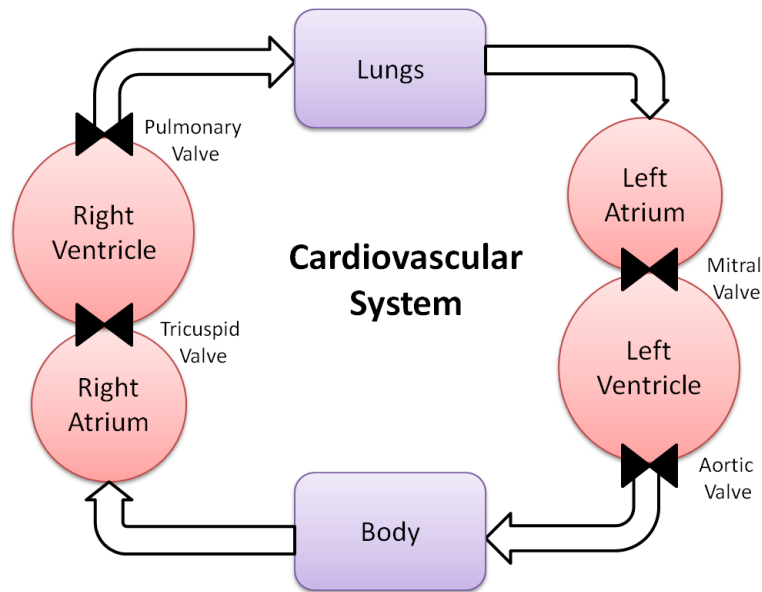


Figure 6. Proposed Cardiovascular Model

From, Figure 6, we can see the representation of each heart's chamber with their input and output valves, the valves' dynamics control the accumulation in the heart's chamber, and both of them are regulated by the seven phases of the cardiac cycle. The chamber's volume is given by an accumulation that can be modeled as follows:

$$V_C = \int_0^t (f_{IV} - f_{OV}) dt + V_0 \quad (3)$$

Where V_C is the chamber's volume, t is the simulation time, f_{IV} is the blood flow through the input valve, f_{OV} is the blood flow through the aortic valve and V_0 is the initial volume value.

The initial volume value is dependent on the heart's size. This is the remaining volume for each chamber. In the ventricles case this value is named as End-Systolic-Volume (ESV); that is, the volume of blood in ventricles at the end of the contraction [32].

For the designed model, see Figure 8, we use some parameters that help to adjust the capacity of the heart and the blood flow through the valves. Those parameters can be modified by the user in order to simulate different heart's sizes.

With these parameters the left ventricle volume is given by the expression,

$$V_{LV} = \int_0^T [f_M(t) - f_A(t)] dt + V_{LV}(t_0) \quad (4)$$

Where V_{LV} is the left ventricle volume, f_A is the flow through the aortic valve, f_M is the flow through the mitral valve and T is the beat time.

For each chamber we use the same formula to represent the volume and the difference of flows through the valves, for example for the left atrium we use the flow through the mitral valve and the pulmonary artery, in Figure 8 are presented all the chambers and their valves.

In the next section, we describe the design of the valves model to represent the blood flow and a real operation for the valves.

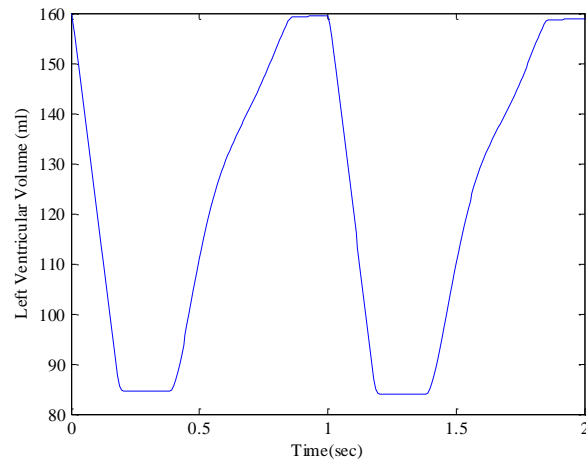


Figure 7. Left Ventricular volume

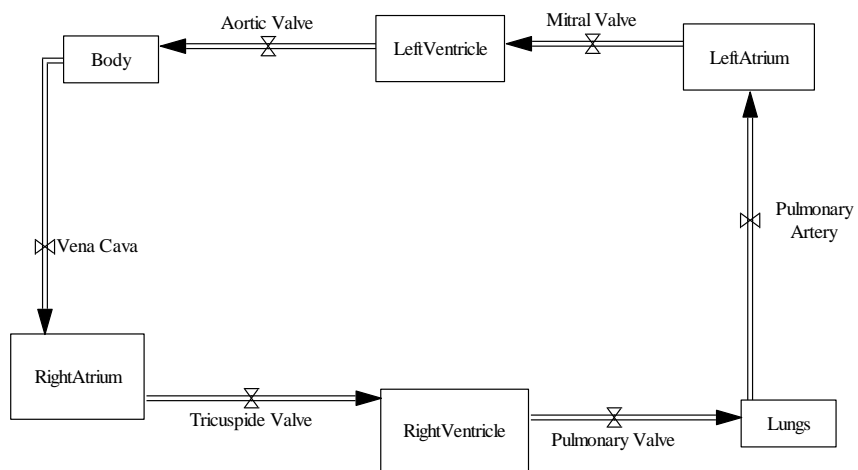


Figure 8. Cardiovascular model in Vensim

3.2.2 Modeling Heart Valves

Four cardiac valves are located in the heart, at the entrance and the exit of each chamber. Such valves prevent backflow of blood when chambers contract. These valves are [35]:

a) Atrioventricular (AV) valves, tricuspid and mitral valves regulate the blood flow from ventricles to atria, when ventricles are contracting.

b) Semilunar valves, the pulmonary and aortic valves regulate the blood flow from ventricles to lungs and the aorta.

As mentioned before each chamber in model has two valves, one for input and one for output blood flow; these valves allow the filling and draining for every chamber.

The valves' model considered by this work uses the 7 phases of cardiac cycle for time control, see Figure 9, every phase has a duration time depending on the heart's rate; thus, this model can vary cardiac cycles phases times by changing the heart's rate parameter.

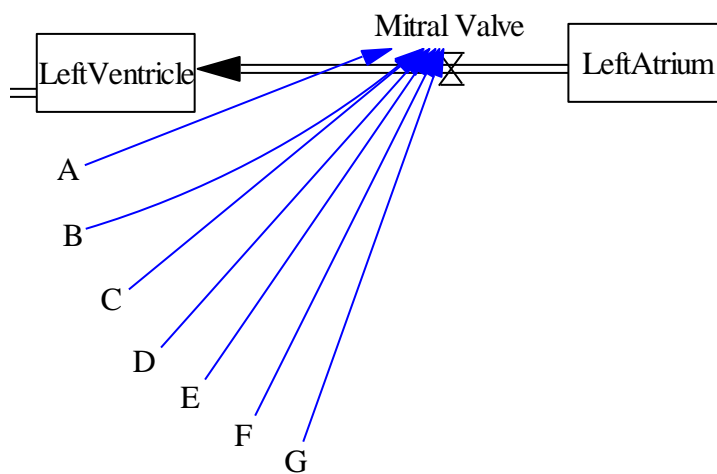


Figure 9. Cardiac cycle Phases in Mitral Valve

Cardiac cycle phases define the time when the AV and semilunar valves open and close at every heartbeat.

Considering a heart rate of 60 bpm it is possible to obtain the times for valves' opening and closing. These times are obtained from the relation of volume and pressure with the phases of cardiac cycle [32], see Figure 105 for valves' timing.

This work presents a heart valves' design based on the cardiac cycle phases, which represents the normal heart's beat operation; the cardiac cycle phases are used as markers for controlling valves' shape and time.

The valves' modeling was made by using blood flow dynamics. This modeling has the following three stages: opening, slow closing and quick closing for each valve. These stages are taken from [36] as the real operation for heart's valves.

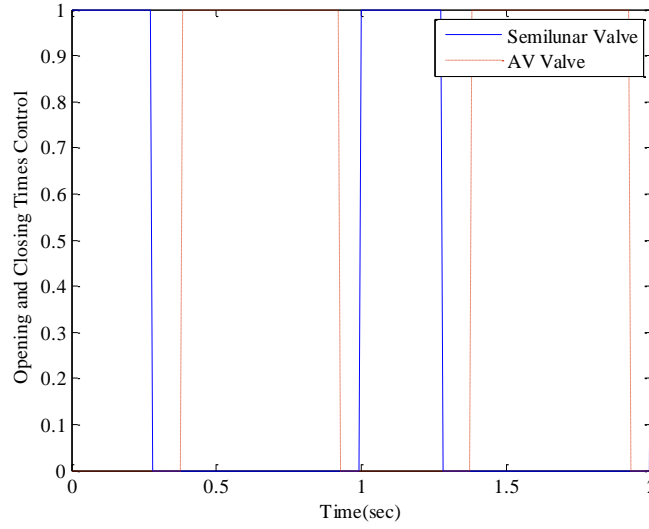


Figure 10. Heart valves' timing

A. Opening Stage

The opening stage refers to the time and shape when the valve opens. And is given by,

$$f_{ov}(t) = \frac{f_v}{1 + \rho_o^{-(t_0 * f_v)}} \quad (5)$$

Where, $f_{ov}(t)$ is the opening function, f_v is the flow through the valve (when completely open), ρ_o models how fast is the rate of growth while opening the valve, t_0 is the opening time of the valve.

B. Slow closing stage

Is when the valve reaches the fully open state, followed by a slow closing period.

$$f_{SC}(t) = \frac{f_v}{1 + \rho_{SC}^{(t_s * f_v)}} \quad (6)$$

Where, f_v is the blood flow through the valve, ρ_{SC} gives slope of the slow closing function, this parameter is in the range of 0.7 to 1 for the slow closing, t_s the period of time, from where the valve reaches the fully open state, until the valve starts the quick closing, this parameter is given by the cardiac cycle phases.

C. Quick closing stage

It occurs when the valve closes from the time the valve starts closing until the valve is fully closed. The closing function's shape is given by

$$f_{QC}(t) = \frac{f_v}{1 + \rho_{QC}^{(t_c * f_v)}} \quad (7)$$

Where, f_v is the blood flow through the valve, ρ_{QC} gives slope of the closing function, this parameter has to be greater than 2, t_c is the closing time of the valve, this parameter is given by the cardiac cycle phases.

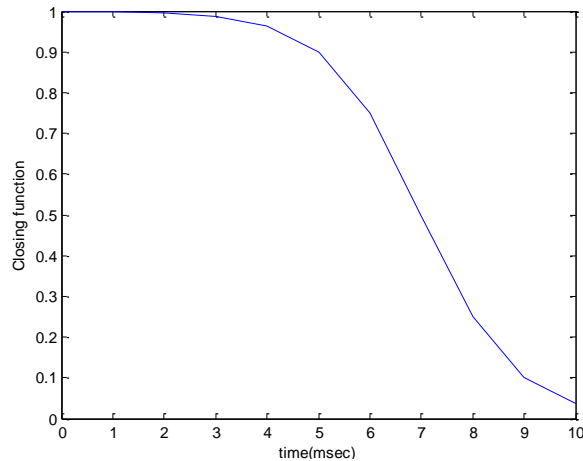


Figure 11. Closing function

Time parameters t_0 , t_s and t_c are the control periods, and their sum is the period of one beat. The time t_0 starts when the valve starts to open until this is fully open, t_s is when the valve reaches the fully open state, until the valve starts the quick closing and t_c is the period of time since valve starts to close until it is fully closed. From these models, one can readily see that each stage is modeled independently, which means that opening and closing forms can be different.

3.2.3 Normal Valve Model

By changing the heart rate parameter, it is possible to simulate different activity levels. Figure 12, shows the mitral valve function for a heart rate of 72bpm, where with a very small variation of the time parameters we can obtain a different shape of the mitral valve function, this with the purpose of experiment with the valve dynamics

The profile of the transmitral flow velocity is modeled observing the representative stages E and A, the E wave (early filling), the diastasis and the A wave (atrial contraction) [34]. These stages are shown in Figure 13.

This profile is analyzed in order to determine the severity of many diseases and this is normally obtained from the echocardiogram, so it is a novelty that we have include this type result for analysis as output of our model.

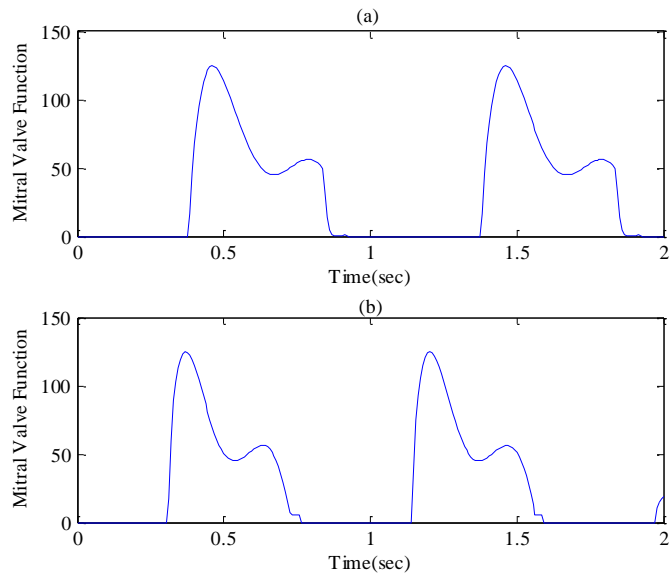


Figure 12. Mitral Valve Function for a)60bpm b) 72bpm

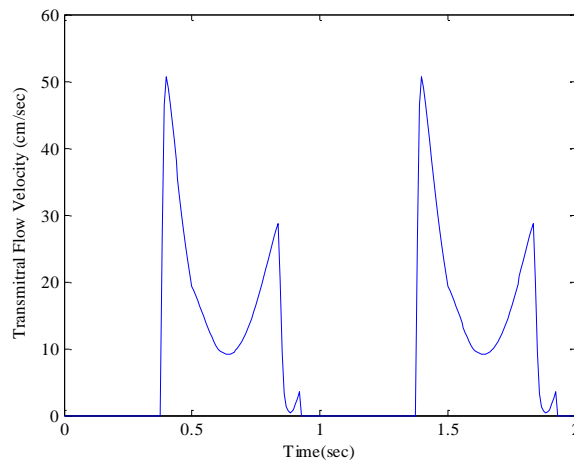


Figure 13. Flow Velocity Profile.

The E/A ratio at this instance of our model has 1.7; that is in the normal range for Doppler-derived diastolic measurement [37].

Additionally, to the graphs presented in this work for the mitral valve, the model was changed for the aortic valve Figure 14, confirming that it is possible to apply the same model for both types of valves (AV and semilunar), by modifying the dimensions and the opening and closing times.

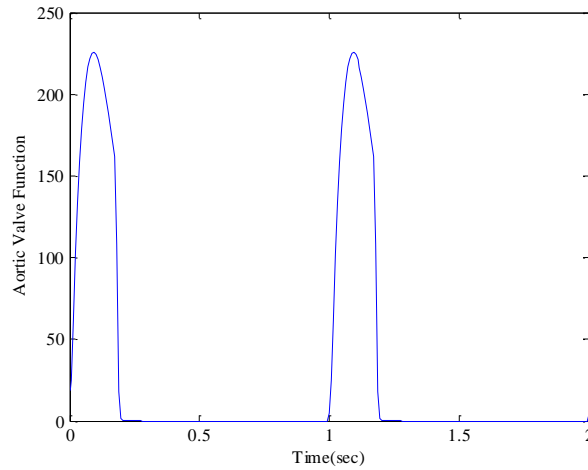


Figure 14. Aortic Valve Function

The function for both valves are showed in Figure 15, with a heart rate of 60 bpm. The timing of the valves is regulated by the duration of the seven cardiac cycle phases.

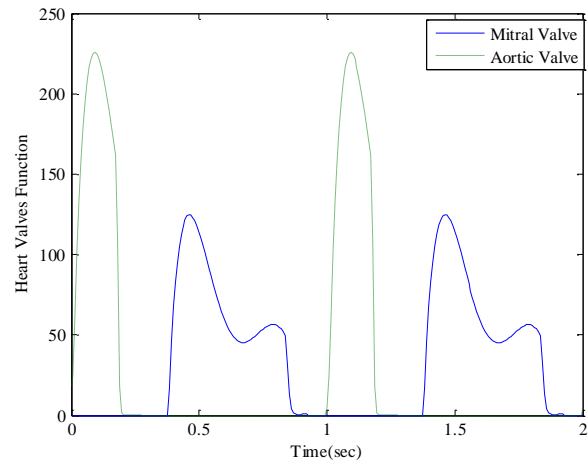


Figure 15. Heart Valves' Function

3.2.4 Modeling Valves' diseases

3.2.4.1 Mitral Regurgitation

The mitral regurgitation is modeled by introducing to the normal valve's model different parameters and timing control (reversed opening and closing times), in order to hold the valve partially open (during closing stage), when the mitral valve has to be fully closed, we introduce a backflow into the atria that represents the regurgitation flow. From (1), the f_M parameter, can be changed by a regurgitant blood flow as is shown in Figure 16.

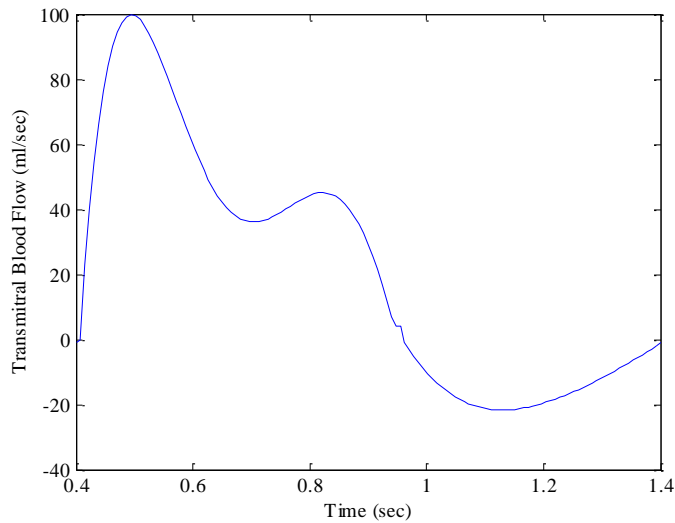


Figure 16. Transmittal blood flow with regurgitation

The velocity profile was calculated by using the aperture area, and the regurgitant blood flow; these parameters are customizable in order to modify the severity of the regurgitation, the relation used for the velocity is given,

$$v(t) = \frac{f_{MV}(t)}{A} \quad (8)$$

Where, v is the velocity, $f_{MV}(t)$ is the blood flow through the valve, and A is the aperture area of the valve.

To compute the regurgitant volume, we use the Proximal Isovelocity Surface Area or PISA method where the regurgitant volume is given by,

$$Rvol = EROA \times MR_VTI \quad (9)$$

Where $Rvol$ is the regurgitant volume, $EROA$ is the Effective Regurgitant Orifice Area and MR_VTI is the Velocity Time Integral of the regurgitation. Model's parameters are given in Table 3.

Table 3. Model Parameters

General Parameters		
Parameter	Normal sample value	Test range
Heart rate (HR) (bpm)	60	60–180
$V_{RV}(t_0)$ (ml)	160	100-160
$V_{LV}(t_0)$ (ml)	165	100-165
$V_{RA}(t_0)$ (ml)	34	14-56
$V_{LA}(t_0)$ (ml)	35	15-58
Valve Parameters		
f_M (ml/sec)	100	50-100
ρ_{MV}	3	0-5

MR TVI (m)	0	10-500
<i>Aperture area</i> (cm^2)	1.6	0-2

3.2.4.2 Aortic Stenosis

The aortic stenosis is modeled by introducing to the normal valve's model different parameters and timing control (valvular area parameter), when the aortic valve has to be fully open, we introduce a parameter to reduce the valvular aperture area, which reduces the blood flow into the aorta.

The velocity profile was calculated by using the aperture area, and the blood flow; these parameters are customizable in order to modify the severity of the stenosis, the relation used for the velocity is given in (8).

3.3 Valves' Substitution

From the cardiovascular system study and reviewed literature, it is clear that real valve operation to allow blood flow is a more complex procedure than a simple change of status between open and closed as described by the idealized diode model [1]. This work tackles the idealized model by using three stages, based on real opening and closing characteristics [13].

The ideal diode in [2] model was replaced in Figure 17 with our model and tested for performance of the cardiovascular model as shown in Figure 18.

With the purpose to demonstrate the functionality of our model we use the cardiovascular model from [2] and replaced the ideal valve model of valves with ours as illustrated in Figure 18.

3.3.1 VHDL-AMS Modules

With the purpose to test our model in an electrical model of the cardiovascular system, and due to its nature, VHDL-AMS is a platform to implement it and replace the diodes of the common cardiovascular system electrical model. VHDL-AMS is a convenient choice, by using parameterized modules, and its flexibility in modifying the design and components connection, that comes with the VHDL environment.

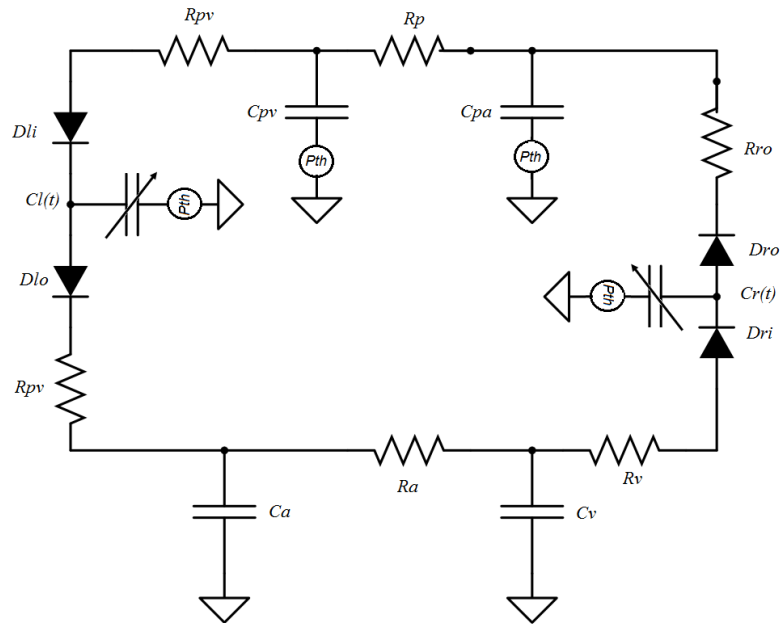


Figure 17. Electrical circuit analog of the human cardiovascular system. Figure redraw from [2].

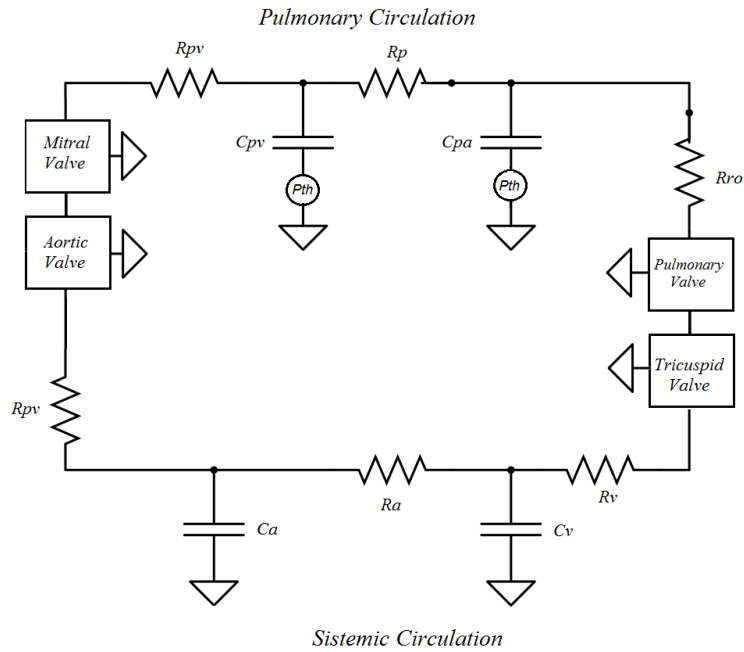


Figure 18. Electrical circuit analog of the human cardiovascular system with valve replacement.

Two modules were developed: one for each type of valve (AV valve and Semilunar Valve) and each one was configured depending on the heart valve replaced. The modules are designed as electrical components with the functions previously presented that model real heart valve operation, and are controlled by the timing given by the cardiac cycle phases; as shown in Appendix B. The design has one module per component: a capacitor, a resistor, an inductor, and a diode. The connection of the electrical model is in Appendix B, including the designed model for the valves.

3.4 Summary

This chapter described the stages for the cardiovascular system design; the physiological dynamics model was proposed and valves' blood flow dynamics were designed, and represented into an electric component using the VHDL-AMS language.

The operation of this design was tested by introducing this model into a selected model from the literature and the results will be presented later in a chapter.

Chapter 4

SIMULATIONS AND RESULTS

The present chapter is focused to explain the results of the different simulations, for different scenarios, using the designed cardiovascular model and the heart valves.

4.1 Cardiovascular System in Vensim simulations

The purpose of this part is verified under the following three conditions:

- Normal heart size with three different activity levels
- Changing Heart sizes
- Valves' abnormalities

these are described on the following sections.

4.1.1 Normal heart size with different activity levels

In order to represent different activity levels, the heart rate parameter was changed for different levels of activity. Two runs were executed and are show in Table 4. The volume parameters were kept for a normal size heart.

Table 4. Setting parameters for activity levels simulation

Parameter	Normal	Activity levels	
	sample value	Moderate activity level	Intensive activity level
Heart rate (HR)	60 bpm	100 bpm	180 bpm
$V_{RV}(t_0)$	160 ml	160 ml	160 ml
$V_{LV}(t_0)$	165 ml	165 ml	165 ml
$V_{RA}(t_0)$	34 ml	34 ml	34 ml
$V_{LA}(t_0)$	35 ml	35 ml	35 ml

Figure 19 , shows the left ventricular volume at 100 bpm, in comparison with output at 60 bpm, there is a notable increment in left ventricular volume.

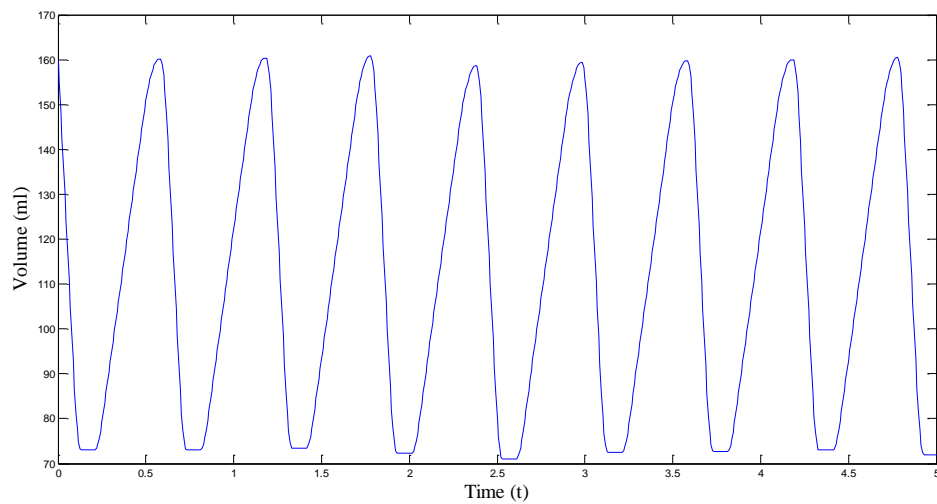


Figure 19. Left Ventricle Output at moderate activity level

4.1.2 Changing heart's size.

Then, the heart rate was kept for representing a rest level of activity and the volume parameters were changed to represent a smaller heart, these parameters are shown in Table 5. This model allows changing the parameters according to the users' purpose, an example of this is in Figure 20, where plot shows the left ventricular volume output at 60 bpm, supposing a small heart. However, this doesn't mean that the simulation is real; given that, the reduction in size of the heart involves a reduction in the Cardiac Output, which is not possible due that the level of blood flow required for the average adult is approximately 5,000 ml per minute; thus in a female case of a smaller heart, the heart rate has to increase to achieve the body's demand for 5,000 ml per minute.

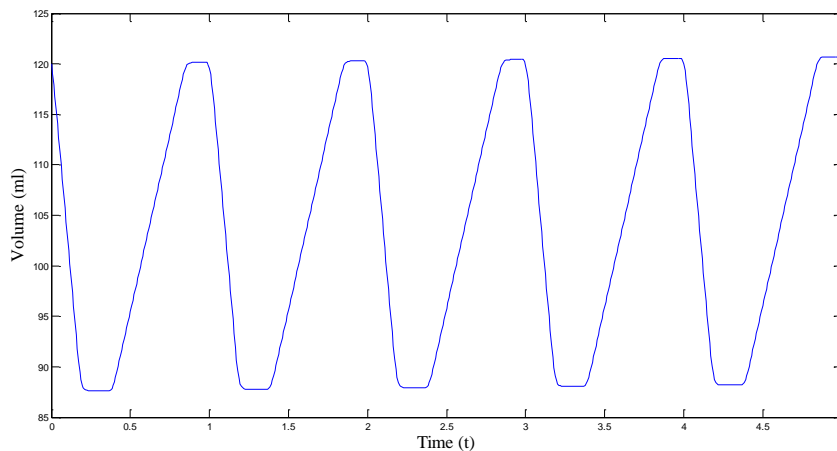


Figure 20. Left ventricle volume at 60bpm with a small heart size

This model allows the parameters' change according to the users' criteria. However, this doesn't mean that the simulation is real. For Table 4 case, the reduction in the size of the heart involves a reduction in the Cardiac Output, which is not possible due to the level of blood flow required for the average adult is approximately 5,000 ml per minute, so that, in a female case the heart rate has to increase in order to achieve this value.

Table 5. Model parameters for different heart sizes

Parameter	Normal sample value	Small heart size
Heart rate (HR)	60 bpm	60 bpm
$V_{RV}(t_0)$	160 ml	120 ml
$V_{LV}(t_0)$	165ml	125 ml
$V_{RA}(t_0)$	34 ml	14 ml
$V_{LA}(t_0)$	35 ml	15 ml

Table 6. Volume and HR parameters changing and their effect to Cardiac Output

Volume	Heart Rate	Cardiac Output
–	–	–
↑	–	↑
↑	↑	↑
–	↑	↑
↓	–	↓
↓	↑	–
↓	↓	↓
–	↓	↓

*↑ increase, ↓ decrease, – hold.

Table 6, gives the relation between volumes and hear rate and their repercussion in the cardiac output. For example, when volume increases and heart rate holds, the cardiac output increases.

4.1.3 Valves' abnormalities simulations

4.1.3.1 Mitral Regurgitation

The mitral regurgitation diagnosis is commonly done by using the echocardiograms which contains information about the dimensions and the circulating blood flow for each valve, Figure 21, shows the continuous wave for a mitral valve with mitral regurgitation.

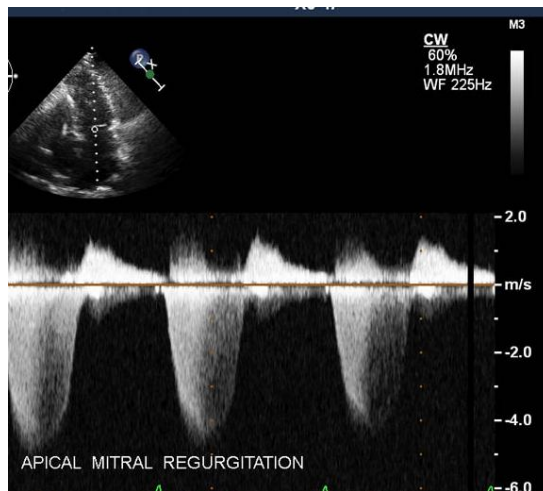


Figure 21. Velocity waveform calculated from the echocardiogram of a mitral valve, with mitral regurgitation [38].

Simulations were made for different severity levels of the regurgitation, mild, moderate and severe regurgitation [33]. The parameter modified for the simulations is the EROA.

The TVI was measured using the velocity profile obtained for each simulation, by calculating the integral of the regurgitant velocity. These values were used to calculate the regurgitant volume using (9). The results are given in Table 7.

Figure 22, shows the velocity profile for a mild, moderate and severe regurgitations, these graphs were used to calculate the TVI from the baseline to the velocity peak wave.

From the results it is observable that the velocity decreases when the EROA increases, this is due to the relation that exists between the area and transmitral blood flow. Validation of the Rvol corresponds with the standard values for the severity classification of mitral regurgitation given in, 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease [37].

Table 7: Simulation parameters and results

Severity	EROA (cm²)	TVI (cm)	Rvol (ml/beat)
Mild	0.05	188	9.4
	0.1	141	14.1
	0.15	147	22.1
	0.18	166	29.9
Moderate	0.2	165	33
	0.25	170	42.5
	0.3	168	50.4
	0.35	166	58.1
Severe	0.5	125	62.5
	0.8	88	70.4
	1	79	79
	1.2	72	86.4

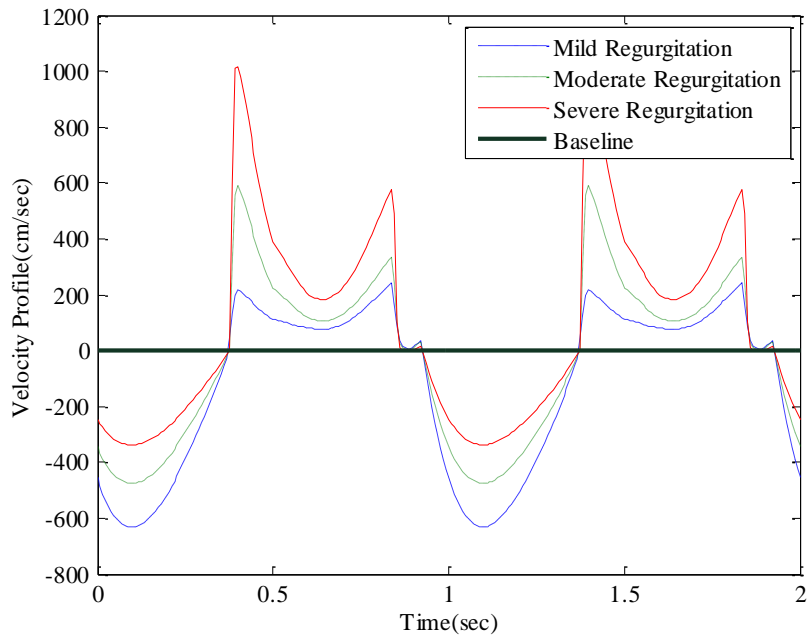


Figure 22. Velocity profile with mitral regurgitation levels.

4.1.3.2 Aortic Stenosis

For comparison purposes, we use data presented by Mynard and Smolich [39], their model presents their simulated and in vivo data. Table 8, shows our model results along with those of Mynard and Smolich [39].

From this comparison it is observed that the values of our models' results are within the range of real data, and they were verified with Nishimura, et al. [37].

Simulations were made for different severity levels of stenosis, mild, moderate and severe. For the simulations the parameter modified is the aperture area, and we use the method of peak jet velocity to determine the severity of the disease, see

Figure 23.

By using the velocity profile, we can calculate the Peak Jet Velocity and it was possible to compare the values with the reference guidelines [37]. The results are showed in Table 9.

Table 8. Comparison with in vivo reference data Extracted from [39]

Parameter	Our Model	Mynard, J.P. [10]	In vivo Reference *
Heart rate (beats/min)	75	75	71 (53,89) [16]
Cardiac Output (L/min)	6.6	6.2	6.5 (3.6, 9.4) [16]
Heart chamber volumes			
LV (mL)	144	141	150 (83,218) [17]
RV (mL)	161	156	173 (78,256) [17]
LA (mL)	108	115	97 (± 27) [17]
RA (mL)	97	110	101 (37,177) [17]

**Reference data given as a mean, with range in parentheses [39].*

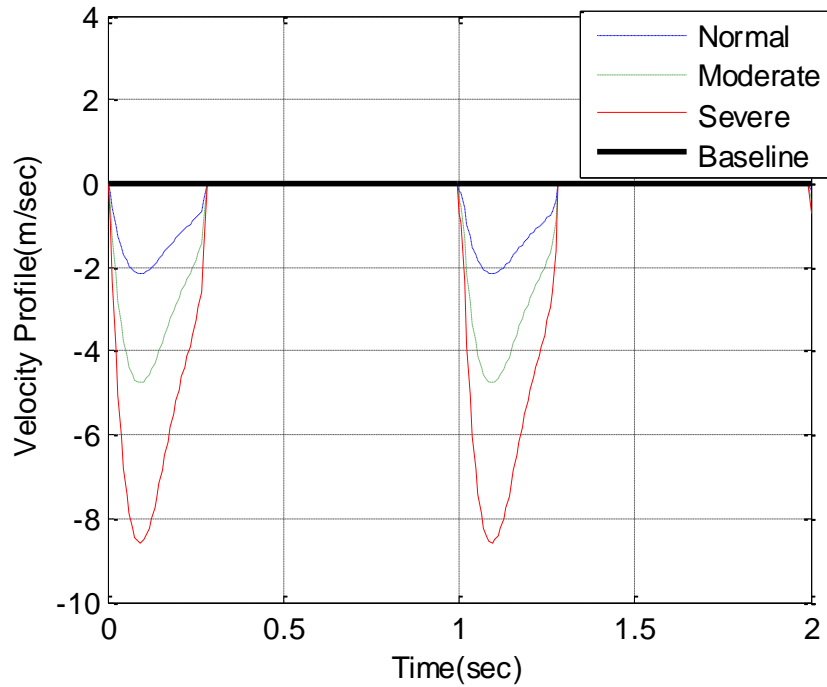


Figure 23. Velocity profile of the Aortic Jet with diferent aortic stenosis levels.

Table 9 Simulation parameters and results

Severity	Valve Area (cm ²)	Peak Jet Velocity (m/s)
Mild	2	2.15
	1.7	2.52
	1.5	2.85
Moderate	1.4	3.1
	1.2	3.55
	1	3.9
Severe	0.9	4.7

	0.5	8.5
	0.2	21.4

4.2 Valves Replacement using VHDL-AMS simulations

As mentioned before our valve model was placed into an electrical analog model in order to test the proper function of the model by using VHDL-AMS for electrical valves' design.

At the first time we introduced our model into a half model of the cardiovascular system from [21], where the electrical analog represents the left part of the heart and we simulated it, the aortic pressure waveform of the electrical analog model with diodes is shown Figure 24. Once we verified the correct function for the model we simulate the performance of it but we introduce our valve model instead of diodes, the simulated Aortic pressure waveform with our proposed model is shown in Figure 25.

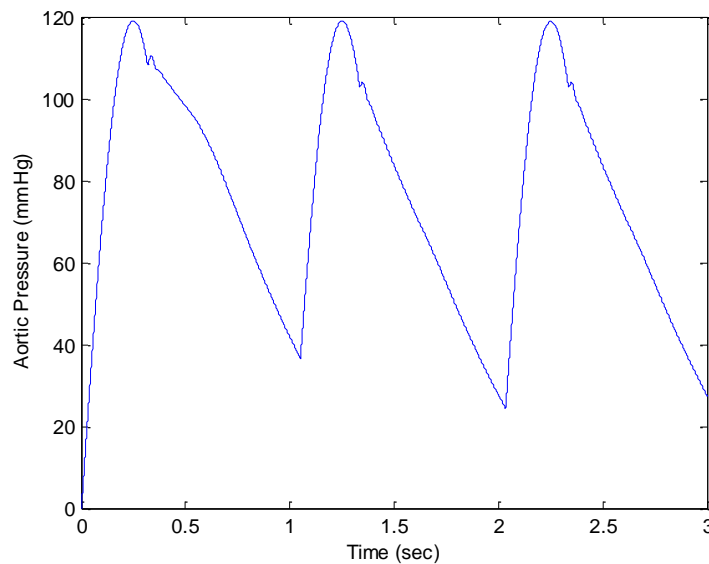


Figure 24. Aortic Pressure waveform for a left heart without modifications [21].

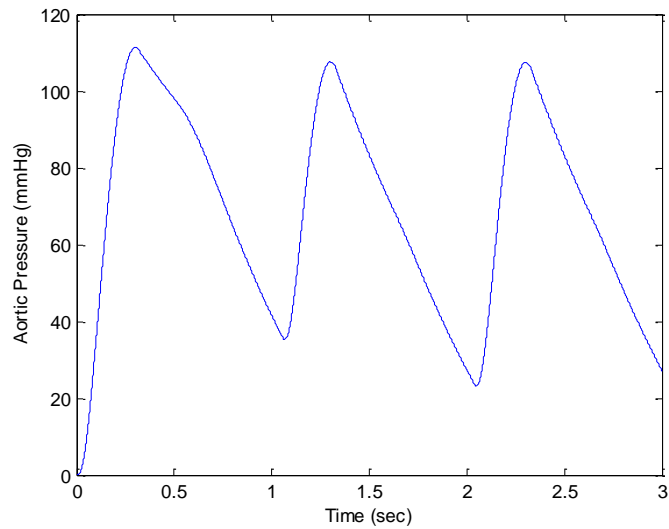


Figure 25. Aortic Pressure waveform for a left heart with our model [21].

Once the first simulation was made, we replace diodes from [14] with our valve model, and the aortic pressure waveforms are shown in Figure 26. The values from the simulations were verified with [37], and we notice that it is possible to represent the hemodynamics by using our proposed model for the valves.

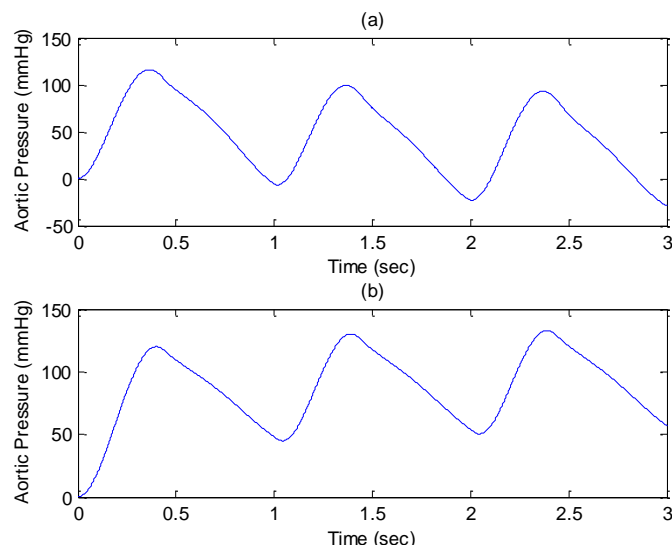


Figure 26. Aortic Pressure Waveform of a) Simulated Aortic Pressure from [14], b) Simulated Aortic Pressure with our valve replaced.

4.3 Summary

In this chapter we presented the main results for the simulations of the model, we can use parameters to represent different hearts sizes and different activity levels. The simulation results present values in the reference ranges for a normal performance of the heart. The valve model was implemented in VHDL-AMS for the electrical analog circuit replacing diodes.

Chapter 5

CONCLUSIONS AND FUTURE WORK

5.1 Conclusions

Using a segmented curve as model for a heart valve gives a real blood flow operation as proved by simulation experiments.

Heart cycle phases provide time synchronization for the valve function model.

System dynamics modeling of heart's chambers allow for anatomy characteristics of specific patient, by setting End-Diastolic, and End-Systolic Volumes of chambers.

Both electrical and flow dynamic models simulate distinct patient activities by changing heart rate value.

Valve blood flow for mitral regurgitation, and aortic stenosis is possible with a segmented curve model.

These models open the possibility for medical personnel to explore distinct conditions for specific patients of: activities, heart sizes, and some valve abnormalities.

5.2 Future work

Abnormalities in heart valves operations could be accounted by modifying the abnormal flow velocity shape, from known medical sources. Valve abnormalities such as: Mitral stenosis, aortic regurgitation, tricuspid regurgitation and stenosis.

The multidisciplinary cardiovascular systems area for research would have to significantly improve multidisciplinary collaboration to advance further and deeper.

Further detailing vasculature sections of interest could be modeled such as: The abdominal aorta. This are becoming in a study object because the abdominal aortic aneurysm is a disease that is increasing as a cause of death in last years, according to the World Health Organization (WHO), so the modeling of these will improve the understanding of the cardiovascular function with such abnormality.

In association with medical researchers' work for early diagnosis for valve abnormalities that could be detailed for a prompt and accurate early diagnostic.

APPENDIX A

Valves' Vensim Code

AV VALVES

```
IF THEN ELSE
(Tav=1:AND:ControlTsAV=1 , (FlowAdjustAV*HeartBloodFlow)/(1+Base^(MODULO(
Time-(Period*(C+D+E)) , Period )* -HeartBloodFlow)) ,
IF THEN ELSE(ControlTtAV=1:AND:Tav=1, (HeartBloodFlow*FlowAdjustAV),
IF THEN ELSE
(ControlTbAV=1:AND:Tav=1, (HeartBloodFlow*FlowAdjustAV)
/(1+Base^(MODULO( Time-(Period*(C+D+E)), Period )- (OpenTimeAV+HoldTimeAV
)*Period*(F+G+A ))*HeartBloodFlow)), 0)
))
```

SEMILUNAR VALVES

```
IF THEN ELSE
(Tsv=1:AND:ControlTsSV=1(FlowAdjustSV*(HeartBloodFlow*VolumeAdjust))
/(1+Base^(MODULO( Time , Period )*-HeartBloodFlow )) ,
IF THEN ELSE
(ControlTtSV=1:AND:Tsv=1, (FlowAdjustSV*(HeartBloodFlow*VolumeAdjust)),
IF THEN ELSE
(ControlTbSV=1:AND:Tsv=1,(FlowAdjustSV*(HeartBloodFlow*VolumeAdjust))/(1+Ba
se^((MODULO( Time , Period )-((OpenTimeSV+HoldTimeSV)* Period*(C+D))
)*HeartBloodFlow)), 0)
))
```

COMPARTMENTS

```
= INTEG(AV_Valve- SEMILUNAR_Valve)
Initial value= 150.
```

APPENDIX B

Valves' VHDL-AMS Code

AV- VALVES

```
-----  
LIBRARY DISCIPLINES;  
LIBRARY IEEE;  
  
USE DISCIPLINES.ELECTROMAGNETIC_SYSTEM.ALL;  
USE IEEE.MATH_REAL.ALL;  
  
--Entity declaration.  
ENTITY mit_valve IS  
  GENERIC (Fa : REAL:=0.65;    --0.65  
           HB : REAL :=550.0;  
           Base : REAL:=1.1;  
           Period: real := 1.0;  
           A: real:=0.14;  
           C: real:=0.12;  
           D: real:=0.16;  
           E: real:=0.1;  
           F: real:=0.15;  
           G: real:=0.26);  
  PORT(TERMINAL p,m: ELECTRICAL;SIGNAL input1,input2: in bit); --Interface  
ports.  
END;  
ARCHITECTURE behav OF mit_valve IS  
  QUANTITY v_out across i_out through p TO m;  
  QUANTITY aa: real;  
  SIGNAL io: bit;  
  
BEGIN  
  aa== (C+D+E)*period;  
  io<= input1 or input2;  
  
  IF (input1='1') and (now < 0.93) use  
    v_out== (HB*fa)/(1.0 + base**(-HB * (now - aa)));  
  Elsif (input1='1') and (now >=0.93 and now<= 1.93)use  
    v_out== (HB*fa)/(1.0 + base**(-HB * (now - (1.0 + aa))));  
  Elsif (input1='1') and (now >=1.93 and now<= 2.93)use  
    v_out== (HB*fa)/(1.0 + base**(-HB * (now - (2.0 + aa))));  
  Elsif (input1='1') and (now >=2.93 and now<= 3.93)use  
    v_out== (HB*fa)/(1.0 + base**(-HB * (now - (3.0 + aa))));  
  Elsif (input2='1') and (now < 0.93) use  
    v_out== (HB*fa)/(1.0 + base**(HB * (now - 0.900)));  
  Elsif (input2='1') and (now >=0.93 and now<= 1.93)use  
    v_out== (HB*fa)/(1.0 + base**(HB * (now - 1.900)));  
  Elsif (input2='1') and (now >=1.93 and now<= 2.93)use
```

```

    v_out==(HB*fa)/(1.0 + base**(HB * (now - 2.900)));
Elsif (input2='1') and (now >=2.93 and now<= 3.93)use
    v_out==(HB*fa)/(1.0 + base**(HB * (now - 3.900)));
Else
    v_out==0.0;

    END use;

END;

```

SEMILUNAR VALVES

```

LIBRARY DISCIPLINES;
LIBRARY IEEE;
USE DISCIPLINES.ELECTROMAGNETIC_SYSTEM.ALL;
USE IEEE.MATH_REAL.ALL;

--Entity declaration.
ENTITY ao_valve IS
GENERIC (
    Fa : REAL      := 1.0;  --0.98
    HB : REAL      := 550.0;
    Va: REAL      := 1.0;
    Base : REAL    :=1.1;
    period: REAL  := 1.0;
    A: REAL:=0.14;
    C: REAL:=0.12;
    D: REAL:=0.16;
    E: REAL:=0.1;
    F: REAL:=0.15;
    G: REAL:=0.26);
PORT(TERMINAL p,m: ELECTRICAL;
    SIGNAL input1,input2: in bit); --Interface ports.
END;
ARCHITECTURE behav OF ao_valve IS
    QUANTITY v_out across i_out through p TO m;
BEGIN
    If (input1='1') and (now < 1.0) use
        v_out==(HB*Va*fa)/(1.0 + base**(-HB * (now)));
    Elsif (input1='1') and (now >=1.0 and now<= 2.0)use
        v_out==(HB*Va*fa)/(1.0 + base**(-HB * (now - 1.0)));
    Elsif (input1='1') and (now >=2.0 and now<= 3.0)use
        v_out==(HB*Va*fa)/(1.0 + base**(-HB * (now - 2.0)));
    Elsif (input1='1') and (now >=3.0 and now<= 4.0)use
        v_out==(HB*Va*fa)/(1.0 + base**(-HB * (now - 3.0)));
    elsif (input2='1') and (now < 1.0) use
        v_out==(HB*Va*fa)/(1.0 + base**(HB * (now - 0.25)));
    Elsif (input2='1') and (now >=1.0 and now<= 2.0)use
        v_out==(HB*Va*fa)/(1.0 + base**(HB * (now - 1.25)));
    Elsif (input2='1') and (now >=2.0 and now<= 3.0)use
        v_out==(HB*Va*fa)/(1.0 + base**(HB * (now - 2.25)));
    Elsif (input2='1') and (now >=3.0 and now<= 4.0)use
        v_out==(HB*Va*fa)/(1.0 + base**(HB * (now - 3.25)));
    else

```



```

    v_out==0.0;

    END use;
END;

```

CV SYSTEM CONNECTIONS

```

LIBRARY DISCIPLINES;
USE DISCIPLINES.ELECTROMAGNETIC_SYSTEM.ALL;

```

```

ENTITY cardioVas4 IS
END;

```

```

ARCHITECTURE behav OF cardioVas4 IS
    TERMINAL n1,n2,n3,n4,n5,n6,n7,n8,n9,n10,n11,n12: ELECTRICAL;
    SIGNAL S1,S2,S3,S4: BIT;
BEGIN
    -- Circuit conections
    rpu:ENTITY resistor(behav) GENERIC MAP (0.006) PORT MAP (n1, n2);
    rp:ENTITY resistor(behav) GENERIC MAP (0.07)PORT MAP (n2, n3);
    rm:ENTITY resistor(behav) GENERIC MAP (0.006)PORT MAP (n3, n4);
    rv:ENTITY resistor(behav) GENERIC MAP (0.04)PORT MAP (n7, n8);
    rs:ENTITY resistor(behav) GENERIC MAP (1.0)PORT MAP (n8, n9);
    ra:ENTITY resistor(behav) GENERIC MAP (0.006)PORT MAP (n9, n10);
    -- Capacitors
    cpu: ENTITY c (behav) GENERIC MAP (9.0)PORT MAP (n2, electrical_ground);
    cpa: ENTITY c (behav) GENERIC MAP (7.7)PORT MAP (n3, electrical_ground);
    cv: ENTITY c (behav) GENERIC MAP (100.0)PORT MAP (n8, electrical_ground);
    cs: ENTITY c (behav) GENERIC MAP (2.0)PORT MAP (n9, electrical_ground);
    -- Valves replacement
    rx: ENTITY resistor (behav) GENERIC MAP (1.0) PORT MAP (n4, n5);
    ry: ENTITY resistor (behav) GENERIC MAP (1.0) PORT MAP (n6, n7);
    rz: ENTITY resistor (behav) GENERIC MAP (1.0) PORT MAP (n10, n11);
    rw: ENTITY resistor (behav) GENERIC MAP (1.0) PORT MAP (n12, n1);
    rxx:ENTITY resistor (behav) GENERIC MAP (1.0) PORT MAP (n11, n12);
    ryy:ENTITY resistor (behav) GENERIC MAP (1.0) PORT MAP (n5, n6);
    --Valves
    ao: ENTITY sem_valve (behav) PORT MAP (n11,electrical_ground,S1,S2);
    mit: ENTITY Av_valve (behav) PORT MAP (n12,electrical_ground,S3,S4);
    pul: ENTITY sem_valve (behav) PORT MAP (n5,electrical_ground,S1,S2);
    tric: ENTITY Av_valve (behav) PORT MAP (n6,electrical_ground,S3,S4);

    FF: ENTITY FlipFlop_s_ao (behav) PORT MAP (S1);
    FF1: ENTITY FlipFlop_b_ao (behav) PORT MAP (S2);
    FF2: ENTITY FlipFlop_su (behav) PORT MAP (S3);
    FF3: ENTITY FlipFlop_b (behav) PORT MAP (S4);

END behav;

```

APPENDIX C

Software used for simulations:

- Vensim® (Ventana Systems, Inc.)

Description: Vensim is simulation software for improving the performance of real systems. Vensim is used for developing, analyzing, and packaging dynamic feedback models.

Version: Vensim® Personal Learning Edition (PLE) 6.3 for windows © 2015 Ventana Systems, Inc.

Download: <http://vensim.com/free-download/>

- hAMSTer (Ansoft Corporation)

Description: The hAMSTer tool from SIMEC serves as simulation software. This software is still in development and can be downloaded from the Internet free of charge.

Version: hAMSTer simulation system version 2.0, © Ansoft Corporation, email: support@hamster-ams.com.

Download:

http://www.theoinf.tu-ilmenau.de/~twangl/VHDL-AMS_online_en/download.html

APPENDIX D

The Proximal Isovelocity Surface Area Method

The Proximal Isovelocity Surface Area (PISA) method focuses on the flow convergence proximal to the regurgitant orifice. The proximal flow rate equals the MR flow at the orifice based on the conservation of mass principle. Then, the ERO and RVol can be derived using the following formula [33]:

$$\text{ERO} = \text{PISA flow rate} / \text{MR peak velocity}$$

$$\text{Regurgitant Volume} = \text{ERO} * (\text{MR regurgitant TVI})$$

This method has the advantage of providing a visual confirmation of adequacy based on the shape and size of the observed flow convergence and has become the most widely used method [34].

PUBLICATIONS DERIVED FROM THE THESIS

Rosas-Huerta Carolina and Martinez-Carballido Jorge Fco., "Real Heart Valve Model for Different Severity Level of Mitral Regurgitation", The WORLDCOMP 2015 International Conference on Biomedical Engineering and Science (BIOENG'2015), pp. 16-22 July 2015, Las Vegas, Nevada, ISBN: 1-60132-417-0.

Rosas-Huerta Carolina and Martinez-Carballido Jorge Fco., "Parameterized Real Operations Based Model for Heart's Valves with Aortic Stenosis", 12th IEEE International Conference on Electrical Engineering, Computing Science and Automatic Control (CCE'2015), pp. 212-216, October 2015, México City, México, ISBN: 978-1-4673-7837-6.

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