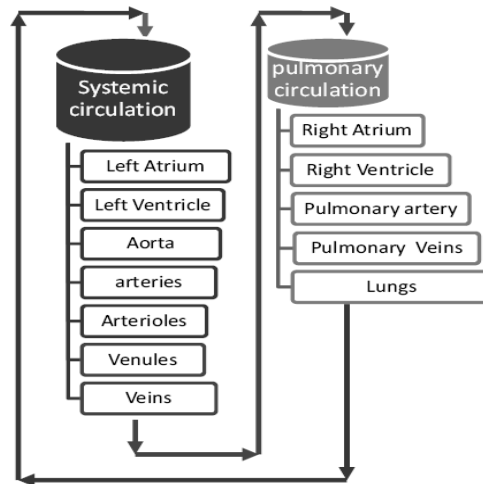


Investigation in the Simulation of the Human's Heart Structure from the Mathematical Perspective



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Thesis by

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Abstract:

The present work has been done after a question defined by the author about the approaches of the human's heart simulation. In this way, the structure and function of the heart have been investigated to understand the anatomy and physiology of the heart. Then, a literature study about the heart simulation has been done to figure out which modeling approaches have been applied in this way and how they have been implemented to represent the heart function. We have realized that lumped parameter, two dimensional and three dimensional models have been applied for this purpose and the Immersed Boundary Method introduced by C.S.Peksin has been considered as a powerful numerical method for simulation of the nonlinear fluid-structure interactions which is the base of one of the advanced three dimensional modeling approaches of the heart function. Besides, some of the applicable tools for the simulation of heart function are addressed.

Keywords:

Cardiovascular system, Heart function, Mathematical Simulation, Numerical methods, Immersed Boundary Method (IMB), Heart muscles (Myocardium)

Acknowledgement

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1 Notations

D	differential operator
d	diameter
E	Yong's modulus
E	elastance
F	force
f	Viscous friction coefficient
i	index of node
J	Momment of inertia
j	index of node
k	node number
k	Spring coefficient
L	Inductance
L	length
M	Mass
M_Q	current generator
P	pressure
P_{ext}	external pressure
Q	Flow rate
q	curvilinear coordinates
R	length
R	Radius
R	Resistance
r	curvilinear coordinates
s	curvilinear coordinates
T	Temperature
T	Torque
t	thickness
t	time
u	displacement

V	Velocity
V	Voltage
V	volume
w	width
X	displacement vector
x	Cartesian coordinate
x	Displacement
y	Cartesian coordinate
z	Cartesian coordinate
α	quality factor
δ	segment
η	viscosity
λ	length
ϕ	auxiliary function
ψ	flow rate density distribution
∇	divergence

Abbreviations

AC	aortic valve closure
AO	aortic valve closure
AV	Aortic Valve
CO	Cardiac output
CT	X-ray computed tomography
ECG	electrocardiogram
EDV	end of diastole volume
ESV	end of systole volume
HR	heart rate
IBM	immersed boundary method
LA	Left Atrium
LV	Left Ventricle
MC	Mitral valve closure

MO Mitral valve opening
MRI Magnetic resonance imaging
MV Bicuspid Valve (Mitral Valve)
PCG phonocardiogram
PV Pulmonary Valve
RA Right Atrium
RV Right Ventricle
SA Sino-Atrial
SDOF single degree of freedom
SV stroke volume
TV Tricuspid Valve
US Ultra-sonic

2 Introduction

The present thesis is about the different aspects of simulation of the human's heart function from mechanical perspective and application of numerical methods in this way. Within the introduction we present some background about the importance of the simulation of human's heart function and describe the motivations that have encouraged us to step in this way. And then we define our aims for the present work and give an overview on the accomplished work.

2.1. Background

During the last years, the methods and tools of data collecting have been developed very fast. And this gives us the opportunity to investigate more unknown aspects of natural systems because we can observe that many of the human-made materials and tools have been created based on the inspiration from the nature; "Learning from Nature [1]", [2, 3]. On the other side, many aspects of nature have vital roles in the human life such as medical information about the human body. With the spite of this fact, a lot of aspects of the nature are still unknown for us and should be scrutinized. Hence, in the present thesis we deal with one of the most vital and complicated natural systems; the human's heart function. It's vital because the heart failure is the leading cause of mortality, during the last years, in the word, with comparison to the other types of diseases [4, 5]. And its complex because it has complex geometry [6], nonlinearity in behavior of its structure and function [7, 8, 9], fluid-structure interactions [10, 11, 12, 13], mass transfer in the vascular walls [14, 15, 16], chemical-electrical reactions during controlling of heart rate [17, 18, 19] and so on.

2.2 Motivation

Generally speaking, functional quality of the heart as one of the vital organs of the body has non-negligible role in the human life. From medical point of view, the importance of the human health, has attracted many attentions towards researching about the organs of the human's body in order to find more effective methods of diagnosing, treatment and preventing the diseases and furthermore, creating the artificial organs. Nevertheless, the complexity of this organ in the structure and function (as mentioned) still causes some difficulties in understanding of its structure and function. Hence, a comprehensive model of the heart not only can help the researchers and medical students to understand this complexity but also can be applied for treatment of the heart failure or considering the effects of medicines. In this way, the mathematical simulation is a powerful tool which can cover different

aspects of the heart function [17, 20], and can help the researchers to consider mechanical-electrical-chemical reactions of the heart function. But, consequently, simulation of such a coupled systems by the mathematical approaches results in a complicated mathematical problem with a system of differential equations. So, after overcoming the challenge of simulation, the challenge of solving the system of coupled nonlinear differential equations would appear.

On the other side, by the rapid advancement in the computing technologies, the new powerful techniques of computations such as numerical methods have been presented to solve the vast majority of differential equations which is very difficult to find analytical solutions for them.

So, after study in some courses about the numerical methods within the mechanical field, we have tried to open our angle of view about the application of these methods and consider the role of the numerical methods in other branches of science. Since the numerical methods have been applied in many other fields as well, so we have to narrow our case study and as it was mentioned the human heart's function is the chosen field in this way which requires much attention because of its role in the human life.

Although, during the last years, many efforts have been done to apply the numerical methods to simulate the heart function, but after searching in the recent works related to this subject, the answer of one question is not completely clear for us and the question is how the numerical methods can be applied to simulate the human heart function?

2.3. Aim and scope

The aim of the present work is to realize the heart structure and function with the review of the modeling approaches and consider the role of numerical methods in this way. During this work we try to find some answers for the following questions:

1. Which components form the human's heart structure and how they are interconnected to each other?
2. What are the mechanical characteristics of the heart's muscles?
3. By which approaches can the mechanical characteristics of the heart function been simulated?
4. And in which way the numerical methods facilitate the simulation approaches?

It should be mentioned that because of limitations in the time and also extent of required knowledge and data for presenting a new model, the purpose of this work is not to present a new model of the heart function by the writer or new methods of analyzing the heart function.

In the Figure 2.1, the structure of the following chapters has been outlined.

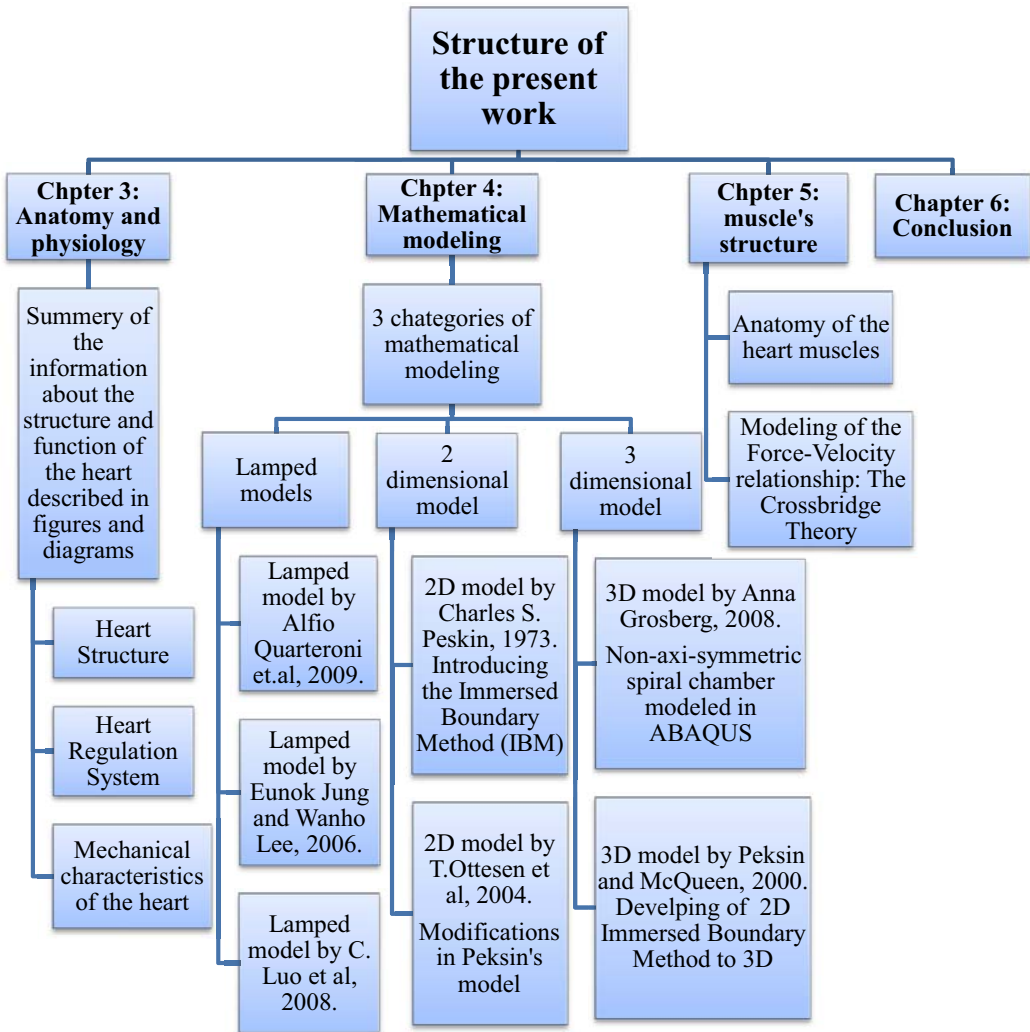


Figure 2.1: Structure of the presented work

3 Anatomy and physiology of the human heart

To study about the simulation of a system, first of all we need to know about the components of that system and how they work and how they are physically connected to each other. We need to consider how these components interact with each other during the function of the system. The more knowledge about a system, the more accurate model of this system will be obtained. Therefore, in the first chapter we deal with this issue and present some information about the anatomy (study of the structure) and physiology (study of the function) of the human's heart. Within this chapter we try to provide necessary and as much as possible complete information for the reader. Since considering all details about the heart's structure and function is not aim of the present work, and also is out of the ability of the writer, we try to introduce necessary information in a comprehensive and understandable way for the reader by means of pictures and diagrams.

In this chapter we introduce the cardiovascular system (blood circulation) and position of the heart in this system (section 3.2). Then we consider the heart's structure (section 3.3) and address some information about the regulation process throughout the cardiovascular system (section 3.4). After that we deal with the conduction system in the heart (section 3.5) and furthermore we provide general information about the cardiac cycle (one heartbeat) and mechanical work of the heart function (section 3.6-8).

3.1. Introduction

All physical systems in the known realm of the science need energy to run. From the similar point of view, blood provides the energy for the human's body. Through the blood, all other parts of the body receive oxygen and nutrients and give back the carbon dioxide and other metabolic wastes. This process is been carried out by the cardiovascular system which consist of three main parts: Blood, Heart and Blood Vessels. The heart runs this system and pumps the blood throughout blood vessels. So it has a vital role in the well functioning of the other organs of the body.

3.2. The cardiovascular system

The blood circulation inside the body is carried out by the cardiovascular system which consists of the two main circulation systems;

1- Systemic circulation: circulation of the oxygen-rich blood from left part of the heart to the upper body (hands and head) and to the lower body to nourish the cells.

2- Pulmonary circulation: circulation of the oxygen-poor blood from right part of the heart to the lungs in order to absorb the oxygen.

Each of these systems has the corresponding heart pump, the arteries, the microcirculation and the veins. In the Figure 3.1, connections of different parts of these two systems have been schematically shown.

In the Figure 3.2, we can see different parts of the blood circulation in the body. In this figure, the red color indicates the blood which is rich of oxygen (O_2) and the blue color indicates the blood which is poor of oxygen. As we can see, the heart is located in the center of these two systems and they are connected via heart. Therefore, it can be asserted that the heart is the main part of the blood circulation in the body. The role of the heart looks like a pump in a hydraulic system in which the function of the other parts depends on the function of the pump. The heart is considered as two parallel pumps, the left one which pumps the blood into the systemic circulation and the right one which pumps the blood into the pulmonary circulation.

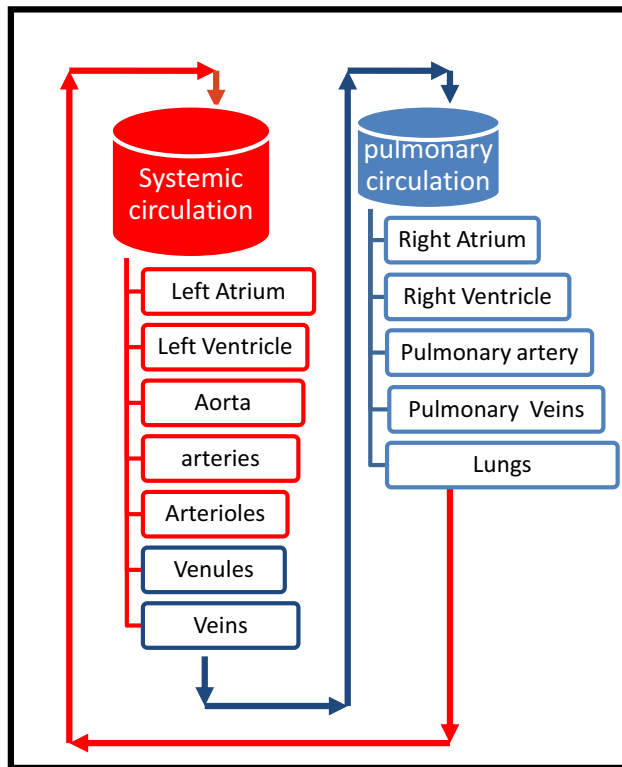
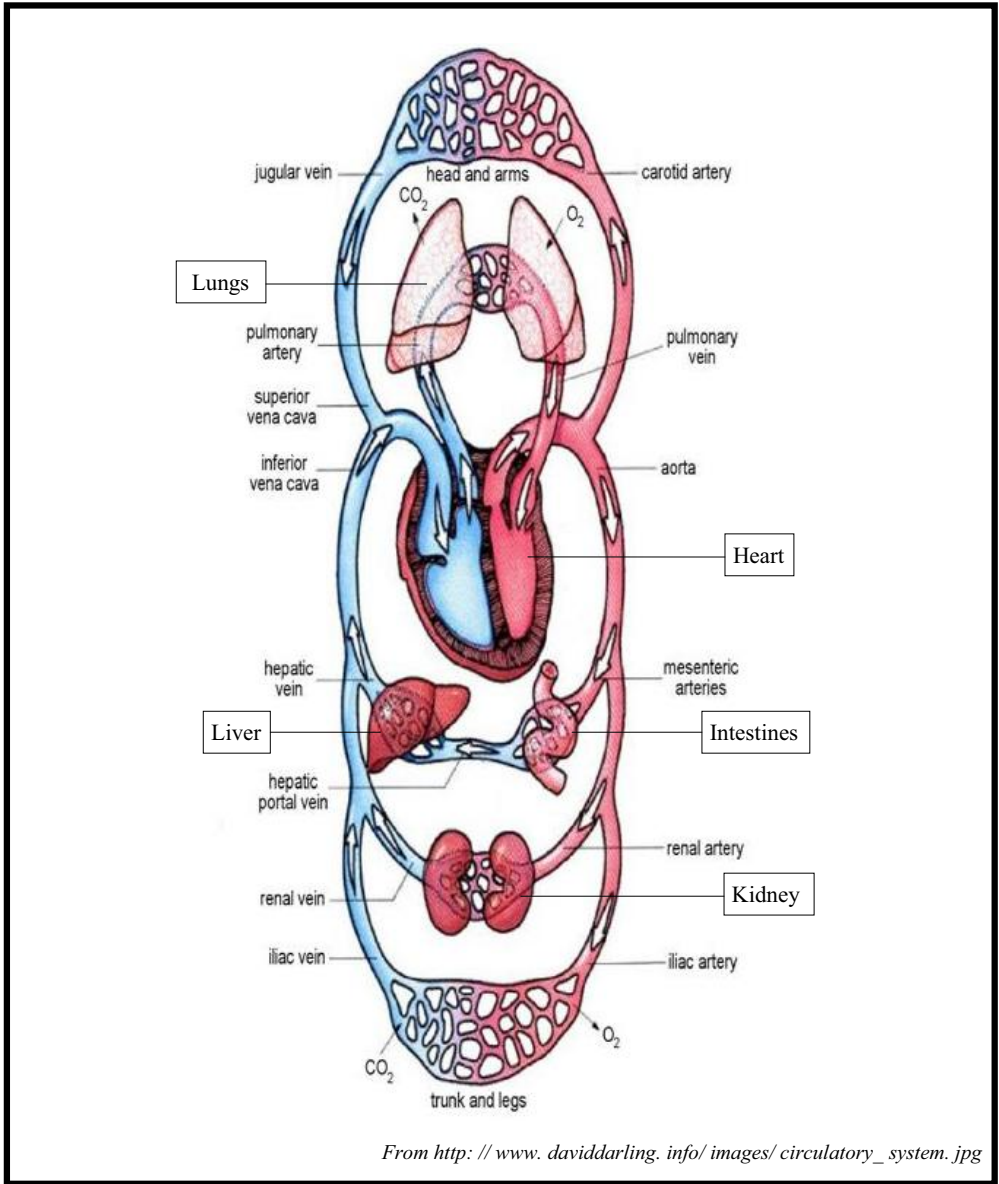


Figure3.1: Schematically overview of the systemic and pulmonary circulations and their different parts



From http://www.daviddarling.info/images/circulatory_system.jpg

Figure3.2: Distribution of the cardiovascular system in the body, connection of the systemic circulation (red color) and pulmonary circulation (blue color).

3.3. The heart

The heart is located in the middle of the chest, between two lungs and above the diaphragm. In the Figure 3.3, the position of the heart in the chest has been showed. It is surrounded by pericardium which holds the heart in the place which it is an inelastic membrane that limits the dilation of the heart.

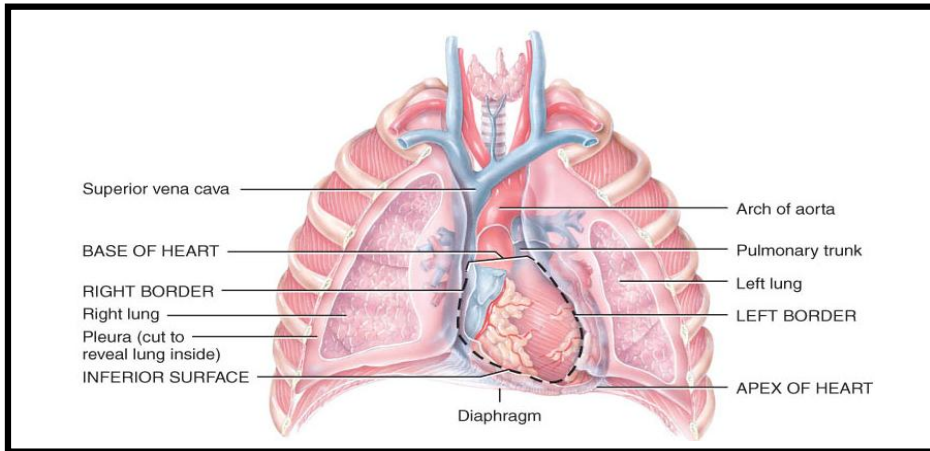


Figure3.3: Position of the heart in the chest. [21]

The heart has four chambers that have been addressed in Table 3.1. The septum between left and right ventricle divides the heart into the two sides. As we can see in the Figure 3.4, the thickness of left ventricle is more than the right one because the left ventricle has to pump the blood into the systemic circulation which is longer and there is more resistance against the blood flow in this part. The left and right atria have almost the same thickness and they are thinner than the ventricles because they pump the blood into a short distance (adjusts ventricles).

Chambers of the heart	Abbreviation	Input from	Output to
Right Atrium	RA	Deoxygenated blood from upper and lower part of the body	Right Ventricle
Right Ventricle	RV	Deoxygenated blood from right atrium	Pulmonary artery
Left Atrium	LA	Oxygenated blood from lungs	Left Ventricle
Left Ventricle	LV	Oxygenated blood from left atrium	Aorta

Table3.1: Chambers of the heart

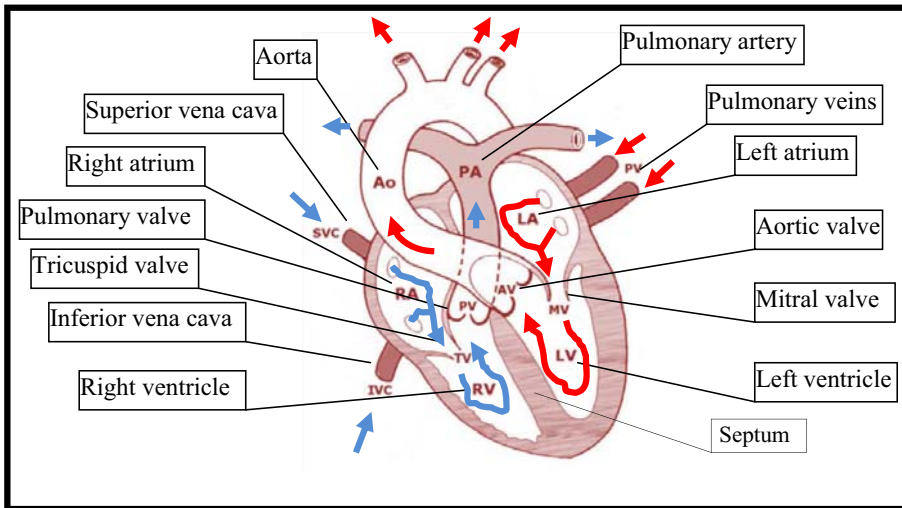
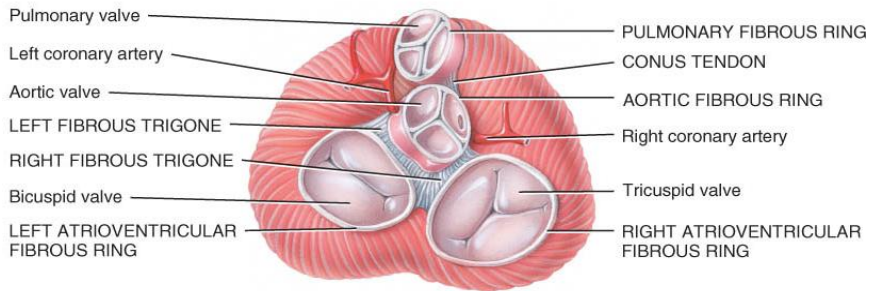


Figure3.4: Different parts of the heart and blood flow inside the heart; the blue color indicates the deoxygenated blood and the red one indicates the oxygenated blood. The difference between thickness of the left and right ventricle is observable.

The heart also has four valves (see Table 3.2 and Fig. 3.5). They are one-way valves and work according to the heartbeat. All of them are embedded in the fibrous skeleton of the heart (rings). These rings keep the valves in the place and also they are insulator between atria and ventricles when electrical signals are propagating. In the following sections, situation and function of these valves during the each heartbeat will be considered.

Valves of the heart	Abbreviation	Input	Output
Tricuspid Valve	TV	Right atrium	Right ventricle
Pulmonary Valve	PV	Right ventricle	Pulmonary artery
Bicuspid Valve (Mitral Valve)	MV	Left atrium	Left ventricle
Aortic Valve	AV	Left ventricle	Aorta

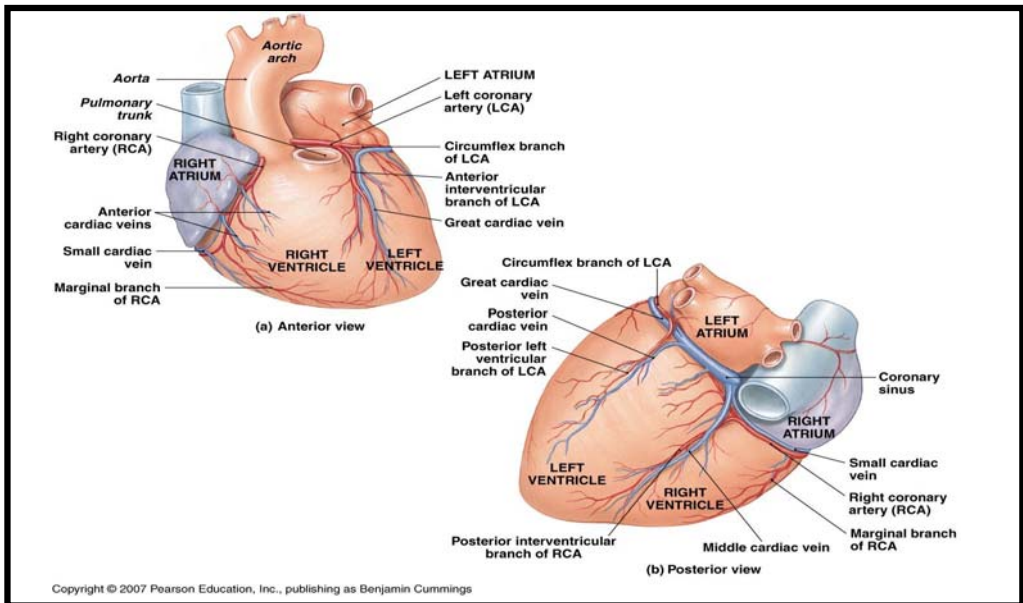
Table3.2: Valves of the heart



Superior view (the atria have been removed)

Figure3.5: The heart valves from superior view. The bicuspid valve (mitral valve) is situated between left atrium and left ventricle. [21]

The myocardium (cardiac muscles) is not able to contract without oxygen (anaerobically), thus it continuously needs oxygen and nutrients to function. They are provided by the left and right coronary arteries which are branched from the root of the aorta and distributed on the surface of the myocardium and finally penetrated inside the cardiac muscles (see Fig. 3.6).



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Figure3.6: Distribution of the coronary arteries and veins on the surface of the heart.

After pumping the blood by the heart, the vascular networks carry the blood to and from the various tissues. These networks consist of arteries, arterioles, capillaries, venules and veins. The main artery is Aorta that carries the blood from the heart and the main veins are Superior vena cava (SVC) that carries the blood from upper part of the body to the heart and Inferior vena cava (IVC) that carries the blood from upper part of the body to the heart (see Fig 3.3). Table 3.3, shows some of the characteristics of the vessels in the systemic circulation. Veins have valves that prevent backflow of blood away from the heart. Venous and arterial networks are roughly parallel to each other.

Vessels	Diameter of lumen (mm)	Wall thickness (mm)	Number of the vessels	Blood volume (%)	Mean pressure (kPa)
Aorta	25	2	1	2	12.5
Large arteries	1-10	1	50	5	12
Small arteries	.5-1	1	10 ³	5	12
Arteriole	.01-.5	0.03	10 ⁴	5	7
Capillary	.006-.01	0.001	10 ⁶	5	3
Venule	.01-.5	0.003	10 ⁴	25	1.5
Vein	.5-15	0.5	10 ³	50	1
Vena cava	30	1.5	2	3	.5

Table3.3: Some of the characteristics of blood vessels in the systemic circulation. The number of the vessels is a rough approximation. [22]

3.4. Regulation of the circulation system

The cardiac cycle is regulated by two simultaneous stimulations; sympathetic stimulation (from nerves connected to the brain) which speeds up the rate of impulse generation and parasympathetic stimulation which slows the rate. This variability allows the heart to respond to demands for higher or lower cardiac output (i.e. faster or slower heartbeat). In Figure 3.7, we have introduced the main mechanisms acting in the cardiovascular regulation. The cardiovascular centre which is located in the brainstem, receives nervous signals from many mechanical and chemical sensors (baroreceptors and chemoreceptors) around the body and then sends the regulation signals to the sino-atrial node (S-A) and also the myocardium, in the heart, to control the heart rate and the rate and strength of the myocardial contraction. And simultaneously, efferent nerves from this centre transfer the regulation signals to the smooth muscles in the blood vessel walls to control arterial tone, resistance in the microcirculation and blood volume in the large veins.

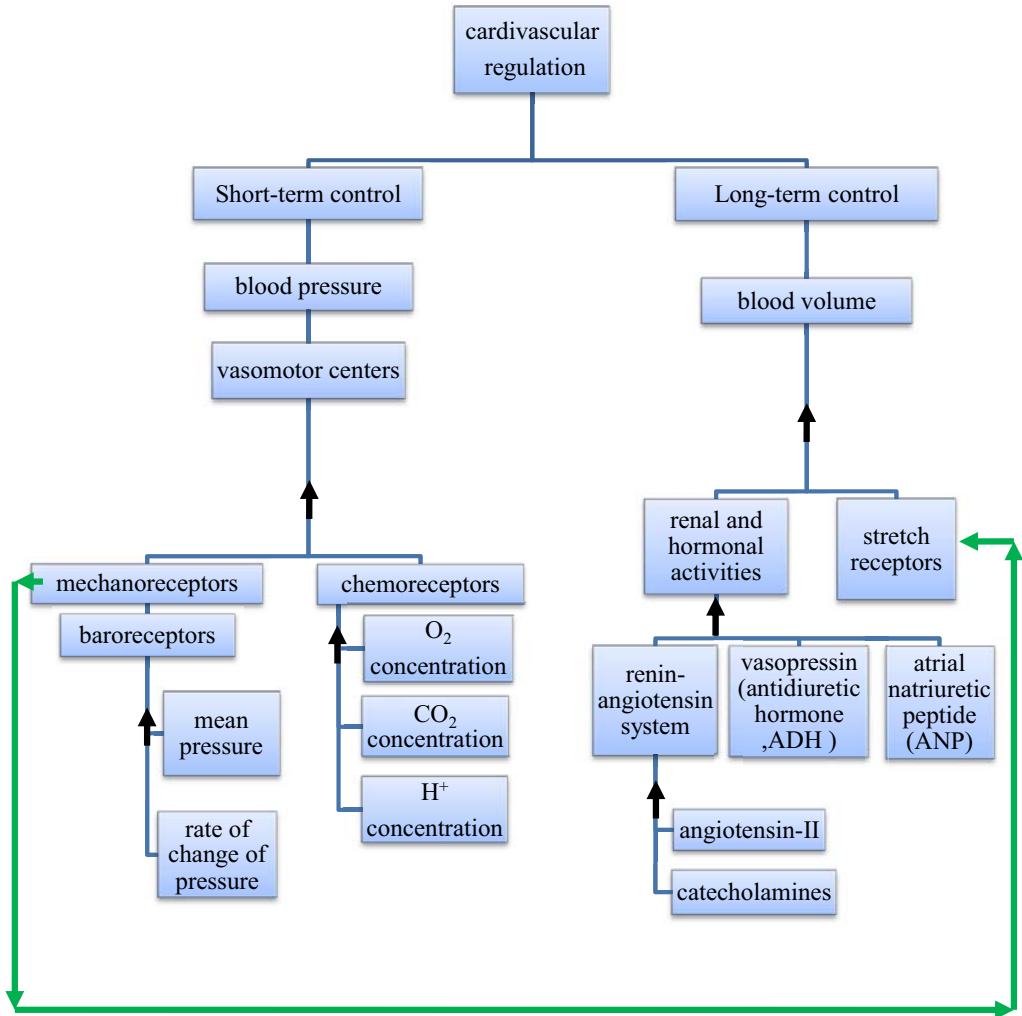


Figure 3.7: Diagram of the regulation of the circulation system; short-term factors and long term factors. The stretch receptors are located in the lower pressure parts of the circulation system such as vena cava and pulmonary artery and also in the ventricular walls.

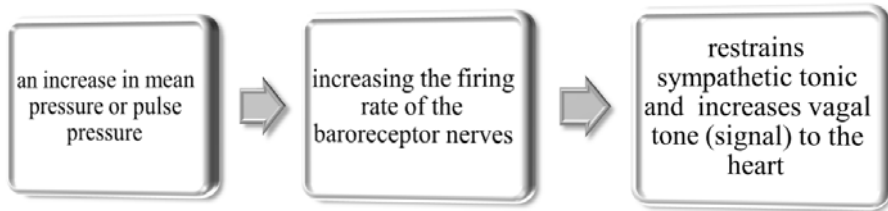


Figure3.8: The role of the baroreceptors in the control of heartbeat while the mean pressure increases.

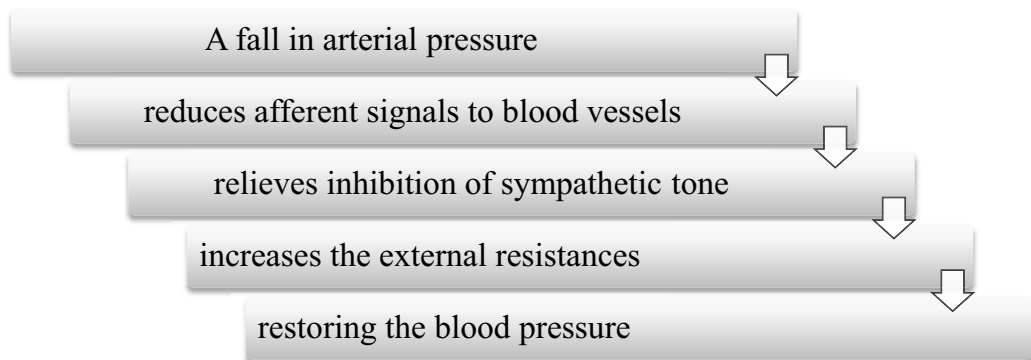


Figure3.9: The role of the baroreceptors in the control of heartbeat while the arterial pressure falls.

3.4.1. Role of hormones in long-term control of the heart function:

The main hormones in the long-term control of the cardiac cycle are: 1- the catecholamines (adrenaline and noradrenaline – also known as epinephrine and norepinephrine), secreted by the adrenal gland (above either kidney), 2- vasopressin or antidiuretic hormone, ADH, (any of the corticosteroids elaborated by the adrenal cortex, the major ones being the glucocorticoids and mineralocorticoids, and including some androgens, progesterone, and perhaps estrogens), secreted by the hypothalamus, 3- angiotensin-II, secreted by the kidney, and 4- natriuretic peptides, such as the atrial natriuretic peptide (ANP), secreted by atrial myocytes.

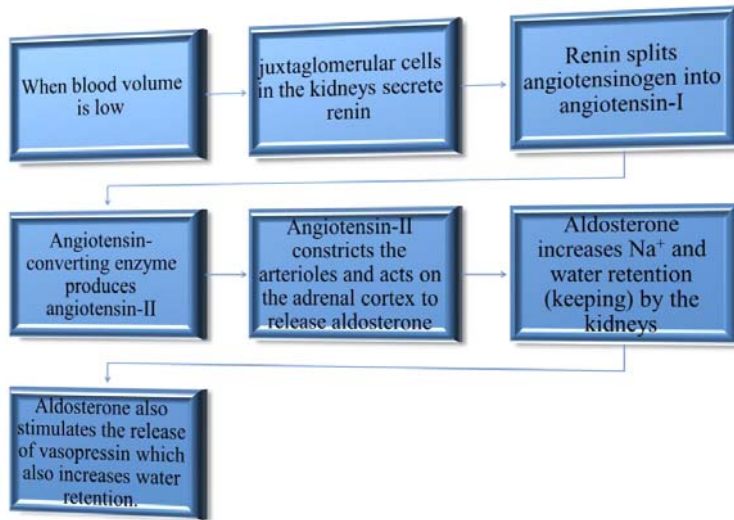


Figure3.10: Long-term control of the cardiac cycle; regulating of the blood volume which is done in the kidneys by regulating of the Na^+ and water retention.

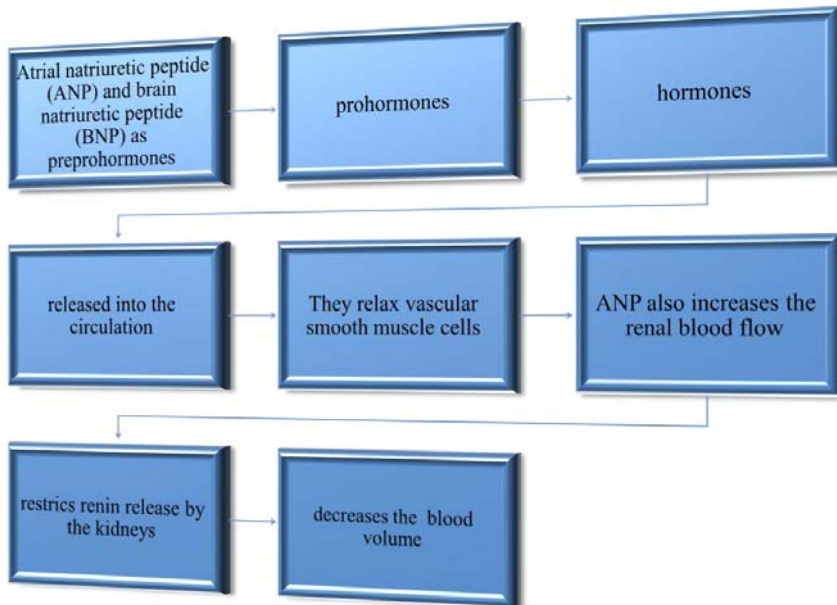


Figure3.11: Long-term control of the cardiovascular regulation: Internal function of the heart in regulation process.

3.5. The conduction system in the heart

The fundamental rhythm of the heartbeat is generated by the cardiac muscle cells which are self-excitable (autorhythmic cells). They do not need external stimulus to be excited. These cells act as pacemakers to set the rhythm for the entire heart. They repeatedly generate spontaneous action potentials and then trigger heart contractions. The signals from the sympathetic and parasympathetic nervous system and hormones modify the heart rhythm (modify the beating rate and strength of contraction). The heart beat starts with a self-excitable cardiac pacemaker which generates regular electrical impulses. The impulses are propagated as a wave that travel from cell to cell and spread through the conduction system of the heart and initiate contraction of the myocardium. This pacemaker is called the Sino-atrial node (S-A node) which is located in the upper wall of the right atrium (see Figure 3.12). The conduction system in the heart consists of the sinoatrial (SA) node, the AV node, the AV bundle (or bundle of His), the bundle branches, and conducting fibers called Purkinje fibers.

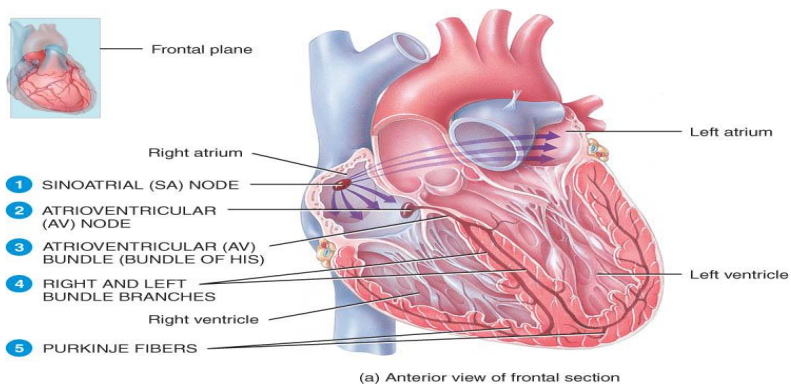


Figure3.12: Conduction system in the heart. [21]

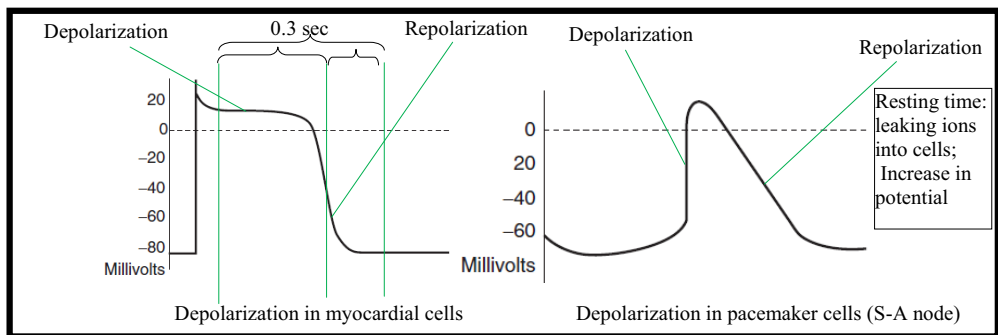


Figure3.13: Comparison of the action potential in the myocardial cells and pacemaker cells (S-A node). After [18]

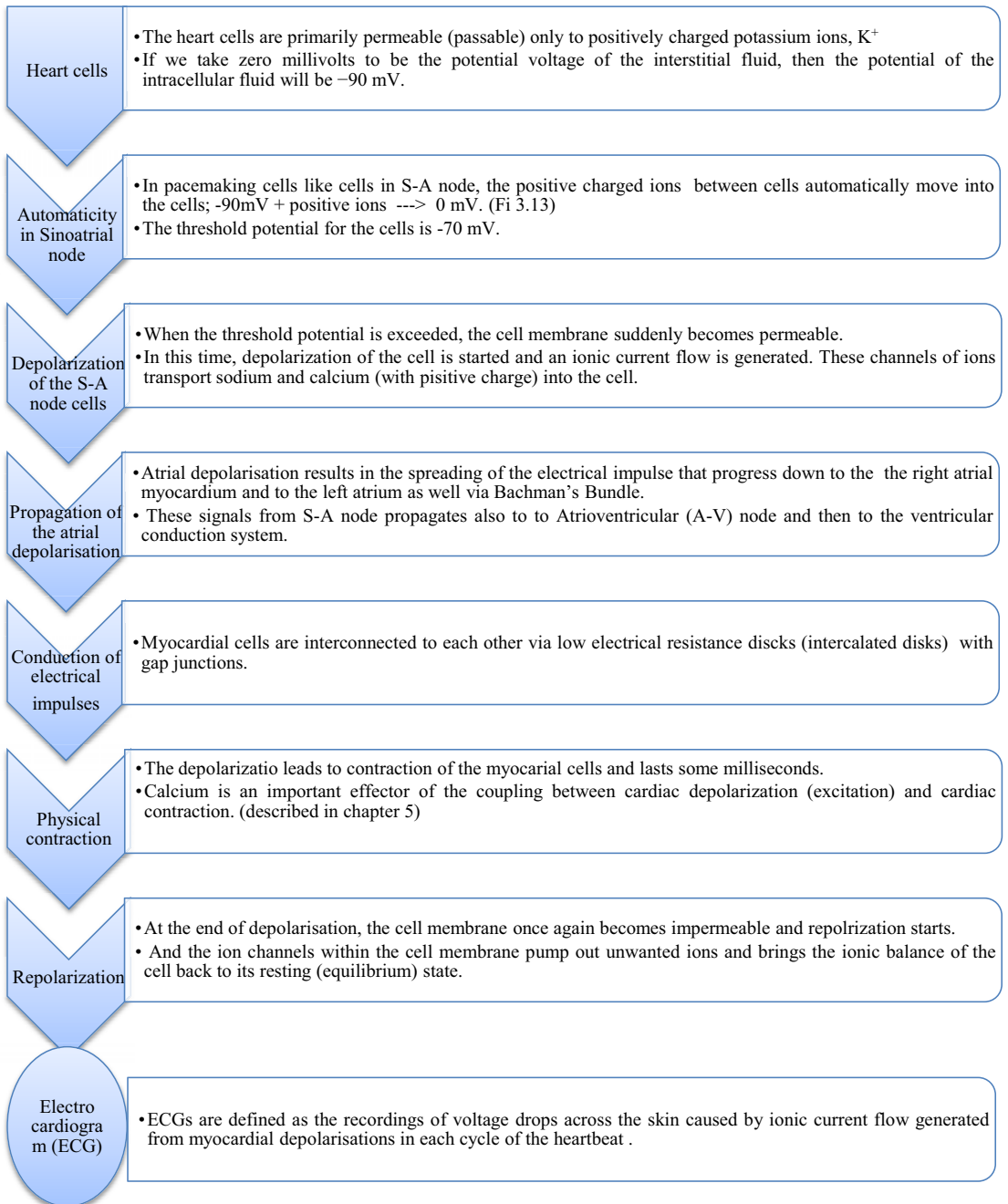


Figure3.14: The process of cardiac cell self-excitation and contraction. After [18] and [21]

3.6. The cardiac cycle

The cardiac cycle of the heart is based on two parts: Systole and Diastole. During the systole time, the myocardium contracts, and so blood is ejected from ventricle. And during the diastole time, myocardium relaxes which is defined as the time between the closing of the aortic valve and the closing of the mitral valve. When the body is in the rest, the diastole time is almost two thirds of the cardiac cycle period. The systole time is almost fixed, it means that with the increase of the heart beat, the time of the diastole period will be decreased and the time of the systole period remains constant.

The cardiac cycle (heartbeat) can be described in the four stages depending on the state of the inlet and outlet valves (see Fig. 3.15). In the Figure 3.16, the pressure, volume flow rate, electrocardiogram (ECG) and phonocardiogram (PCG) with respect to the time of heartbeat have been sketched.

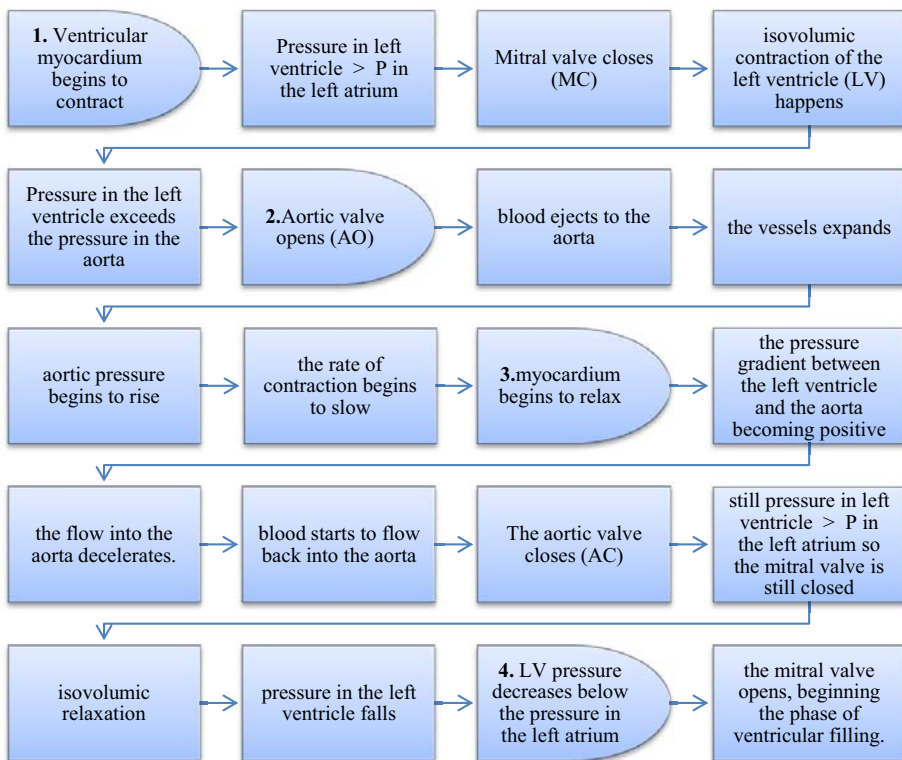
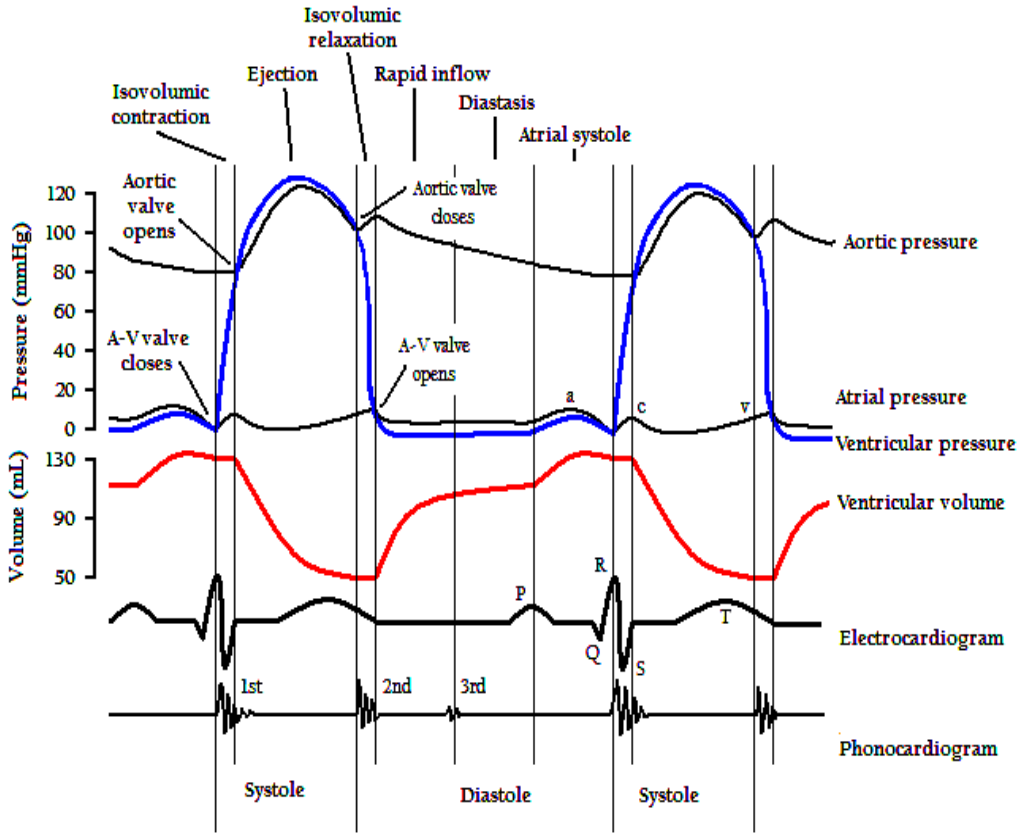


Figure 3.15: Four stages of the cardiac cycle.



http://en.wikipedia.org/wiki/Cardiac_cycle

Figure3.16: The cardiac cycle; Pressure, Volume, Electrical and Sound diagram off the cardiac cycle with respect to the time.

Stage	Duration (millisecond)	Starting event
1. Isovolumic contraction	50	MC: Mitral valve closure
2. Ventricular ejection	250	AC: aortic valve closure
3. Isovolumic relaxation	100	AO: aortic valve closure
4. Ventricular filling	400	MO: Mitral valve opening

Table3.4: typical duration of the four stages of the cardiac cycle (Left ventricle) in healthy young adult at rest, with heart beating 75 per minut. After [18]

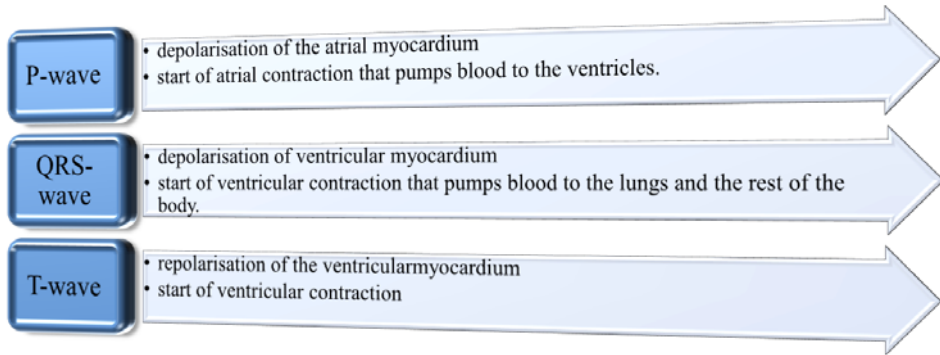


Figure 3.17: Peaks in the electrocardiogram (ECG)

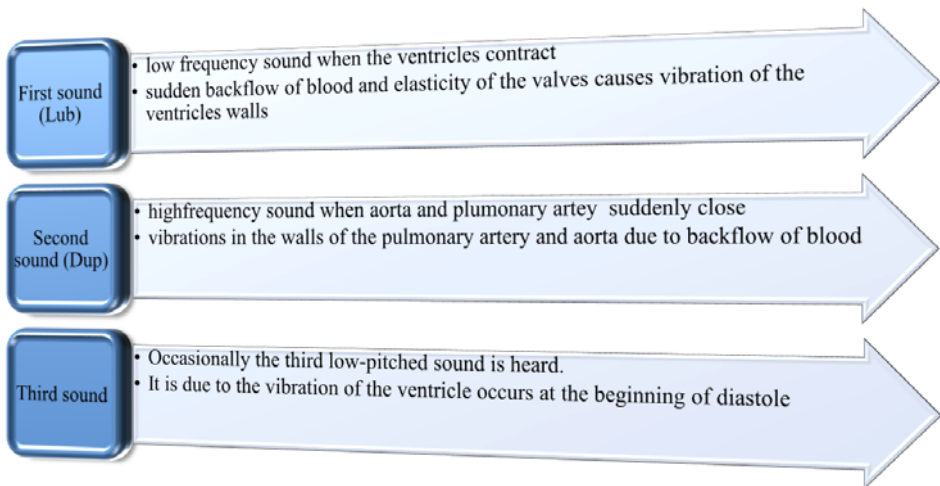


Figure 3.18: Sounds of the heartbeat (phonocardiogram)

3.7. Cardiac output

The cardiac output (CO) is defined as the average of the blood volume which is pumped from either ventricles of the heart. Regulating and adjusting the cardiac output is one of the main functions of the heart because it is proportional to the needs of tissues. For a healthy person at rest, cardiac output is

approximately 5 to 6 liter/min, [14]. The cardiac output (CO) equals to the stroke volume (SV), the volume of blood pumped by the ventricle during each contraction, multiplied by the heart rate (HR: the number of heart beats per minute); $CO = SV * HR$.

Here, SV is calculated from the difference of the ventricle volume at the end of diastole (EDV, filling phase) and systole (ESV)

Therefore, the cardiac output can be written as

$$CO = (EDV - ESV) * HR \tag{3.1}$$

For example, if SV equals 70 milliliter and HR is 75 beat/sec, the CO will be 5.25 liters/min. Anxiety and excitement can increase the cardiac output (CO) up to 50-100 percent and it can be increased up to fivefold by exercise [19]. In Figure 3.19, we can see the factors that affect the CO.

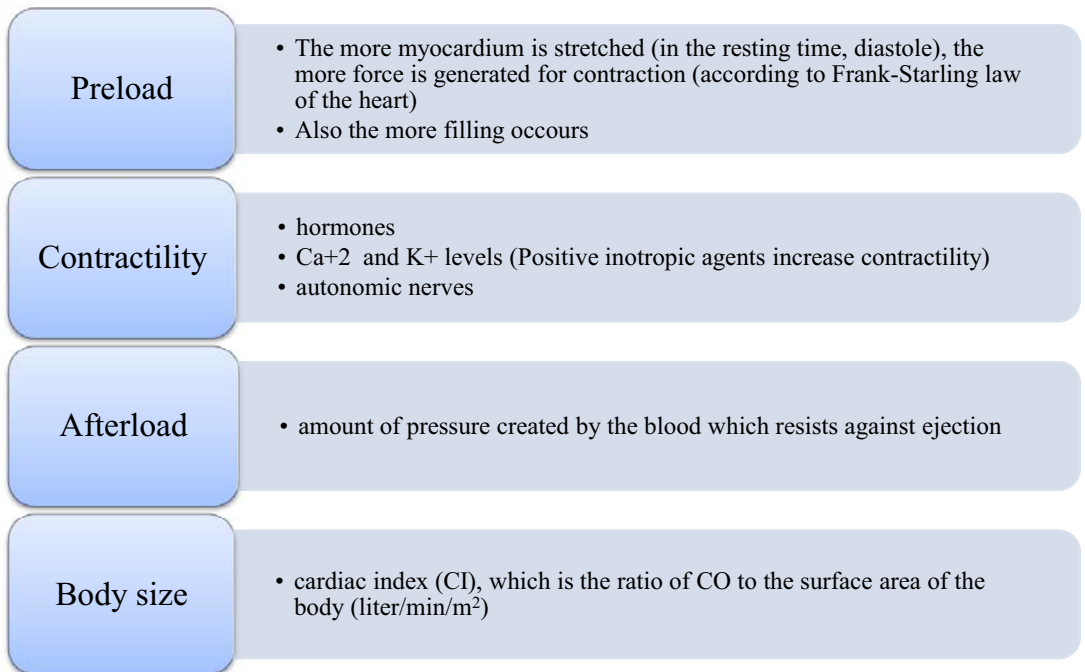


Figure3.19: Factors that affect the cardiac output (CO)

3.6.1. Frank-Starling Law of the heart

One of the main mechanisms in controlling the cardiac output (CO) is called Frank-Starling Law. According to this compensatory mechanism, the larger stretch of the myocardium at the end of resting time (diastole) results in a large force during the contraction time (systole) which results in the equalization of the output from right and left ventricle, because the same blood volume should flow in the both system circulation and pulmonary circulation. One explanation presented for the Frank-Starling mechanism is that stretching of the heart muscle fibers increases their sensitivity to Ca^{2+} [23].

The left and right part of the heart work with the same frequency while they are connected to the two different systems (systemic circulation and pulmonary circulation) so they have different performance and the amount of the blood that circulates in these two system should be in balance with their performance. In Figure 3.20, we can see the effect of the Frank-Starling law in the balance of right and left heart's performance.

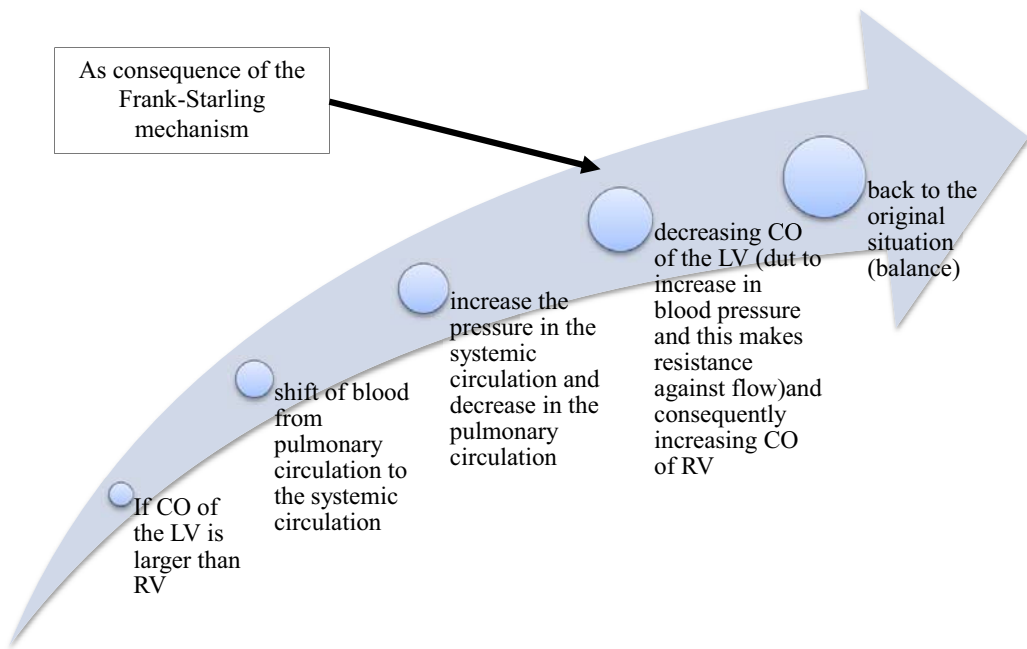


Figure 3.20: Role of Frank-Starling mechanics that makes a balance between left and right heart's performance. Here, CO represents the cardiac output, LV is the left ventricle and RV is the right ventricle.

3.8. Mechanical work of the heart function

Mechanical properties of the heart can be considered from different perspective. From example, fluid dynamic of the blood due to circulating in the heart and other parts of the circulation system, fluid-solid interaction of the blood with myocardium and blood vessels, dynamic behavior of the heart walls during the heart cycle, are some of the mechanical aspects of the heart function that can be tackled.

During considering dynamic systems, the mechanical work done by a system is one of the main subjects which are considered. In the fluid mechanics field, this can be measured from the pressure-volume (P-V) diagram and is defined as the bounded area of the P-V diagram:

$$W = \oint PdV \quad (3.2)$$

In the simulation of the heart function, many of the available models have been initiated by considering the pressure-volume relationship, because by considering this relation, we can understand many characteristics of the system and also the blood pressure is a parameter which can be measured easily with compare to other parameters of the system.

The first attempts to describe the P-V relationship during the heart cycle have been started from the 19th century and has been developed during the recent decays. Among of them, we can mention to the valuable investigations that have done by Suga et al. in the 1970's, [24, 25].

A simplified relation between pressure and volume can be assumed as equation 3.3. In this equation, E is called "elastance, [25], (in some literatures it is named C, "compliance", e.g. [23]);

$$P(t) = E(t) * (V(t) - V_0) \quad (3.3)$$

In this equation, "P" and "V" represent the pressure and volume of the ventricle, respectively, and "E" represents the elastance of the myocardium and all are depend on the time. V_0 is the volume of the ventricle at zero pressure. This equation has been applied as the basic equation in the most of lumped models. In the next chapter we consider this equation in more details.

In Figure 3.21, the P-V relationship of the left ventricle has been shown. As we can see, after closing of the mitral valve (beginning of the systole) and before the opening of the aortic valve, the isovolumic contraction of the left ventricle happens and we have a sharp increase in the pressure while the volume of the ventricle remains constant (because from inside of the myocardium, the blood is a incompressible fluid and from outside, the heart is limited by the inelastic pericardium). And there is also an isovolumic relaxation after closing the aortic valve (beginning of the diastole) and before the opening of the mitral valve.

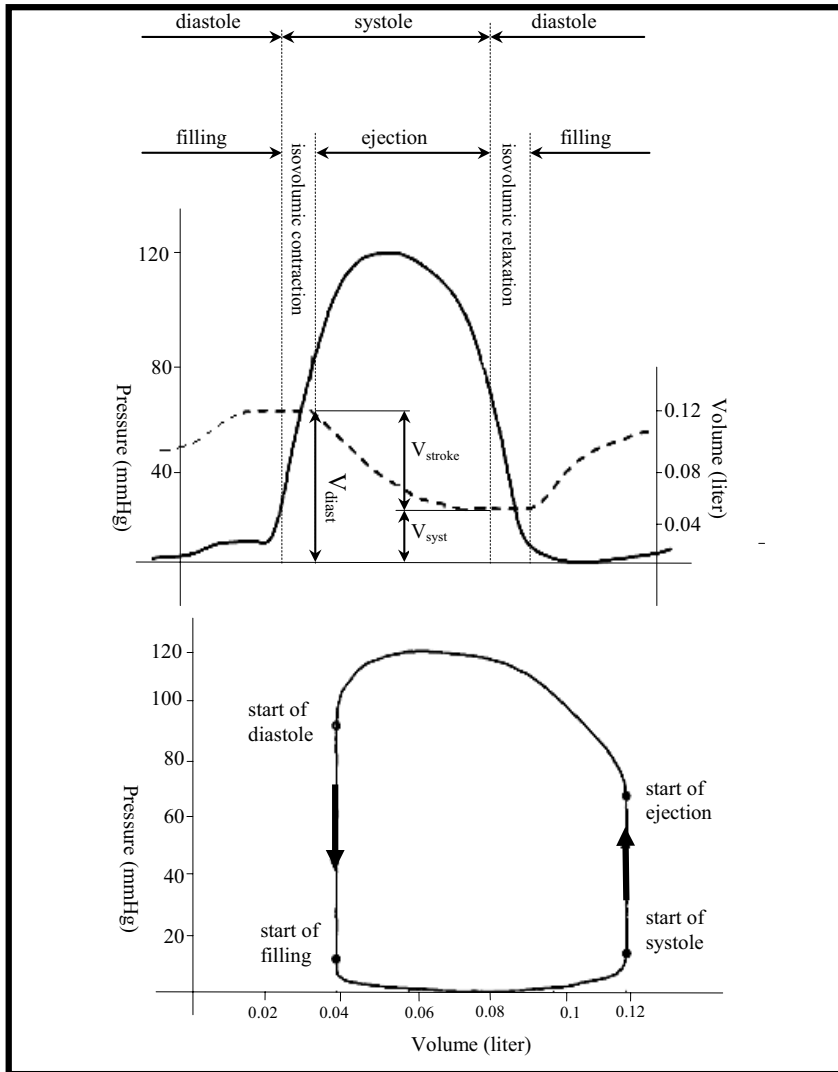


Figure 3.21: Pressure and volume behavior of the left ventricle during the heart beat.

3.9. Summery

In this chapter, the blood circulation system has been considered and some parts of this system have been introduced. We focused on the heart and its function to find out which components form the heart structure and how they interact. Then we have dealt with the regulation of heartbeat and introduced the conduction system for the electrical signals inside the heart. After that, we presented the cardiac output (CO) (and the role of Frank-Starling mechanism on it) which is one the important indicators to consider the quality of the heart function. At the end of this chapter, we pointed out the mechanical characteristics of the heart function.

During considering the heart's components, we have tried to simplify the method of the description by applying the diagrams and skip the complex texts.

As we have figured out, the heart function depends on different mechanical, electrical and chemical systems which work simultaneously to control the heart function during the short time and long time. Interdependency of different mechanisms makes this system as one of the complicated bio-systems to be dealt with.

4 Mathematical modeling of the heart function

In this chapter we consider the mathematical modeling of the heart function. First we introduce some general simulation strategies. Then we present a background about the mathematical simulation of the heart function that has been developed in the recent years with introducing different modeling approaches applied in this way. Three different simulation methods is considered; lumped-model, 2-D model and 3-D model. Then we consider the role of numerical method in these approaches and present some tools that can be applicable in this way.

4.1. Introduction

Many aspects of the cardiovascular system are still unknown for the physicians and with the help of simulation we can investigate some of these aspects. Mathematical modeling is a powerful tool in order to discover and describe the functions and interconnections in this system which are complex to understand and in many cases impossible to be investigated experimentally.

With the progress in the numerical methods and computer technology, we can solve many of mathematical problems obtained from the simulation of this system which were not possible for some decades ago. So, in this chapter we deal with these mathematical approaches.

Since one of the important parts of a simulation process is choosing a proper simulation approach, before dealing with the modeling methods of cardiovascular system, we represent a brief introduction about the simulation strategies applied in the area of the physical systems.

4.2. Simulation methods

A model can be defined as a representation of a system, function or process which describes some or all properties of the system. From one case to another one, according to the purpose of simulation, there are different strategies applied for the modeling.

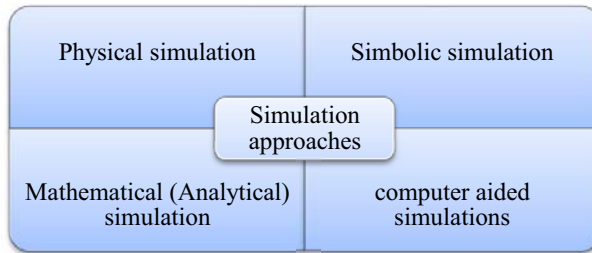


Figure 4.1. Some of the simulation approaches.

Some characteristics of a model can be listed as following;

1. Representation: A model should represent some characteristics of the system.
2. Simplification: In the case of complicated systems, some aspects or details are not easy to be described directly, so a simplified model of a system can represent these aspects.
3. Uniqueness: For each system there is not only one unique model and it will be flexible depends on the chosen way to consider the system as well as the modeling tools.
4. Adaptation: The model should be adaptable with the real system. In the case of I/O (Input/Output) systems, the adaptation of the output between real system and the model is a scale to consider the validity of the model.
5. Prediction: Sometimes we applying simulation approaches to predict the behavior of the system in the future or respond of the system for different outputs which are not easy to be examined in the real situation.
6. Manipulation: The model should be open to be manipulated and improved. With considering the advances in the different branches of science and technology, we can observe many new discoveries and creations in the terms of tools, methods and algorithms which help us to have more accurate data and understanding of the real systems and obtaining these accurate data can result also in more comprehensive and complete modeling of the real systems. Therefore a model should be flexible to be adopted with new findings.

4.2.1. Process of modeling

Various types of the problems in the science lead to the different taken ways to deal with those problems, consequently there are different approaches in the modeling and simulation that can be considered. One of the main parts of the modeling process is the selecting tools during the process which itself depends on the various factors such as availability, applicability, reliability, accuracy and cost of the tools. Many of the methods of the simulations are very impressive from the accuracy of the applied tools, for example, accuracy of the imaging tool in the medical applications plays the important role in the diagnostic results and also modeling of the structures and functions of the inner

organs of the human body. So the more accurate tools, the more accurate model of a system can be obtained.

4.2.2. Modeling languages

Depending on the applying method, the language which is used to present a model will be different. In Figure 4.2, we address some of these languages.

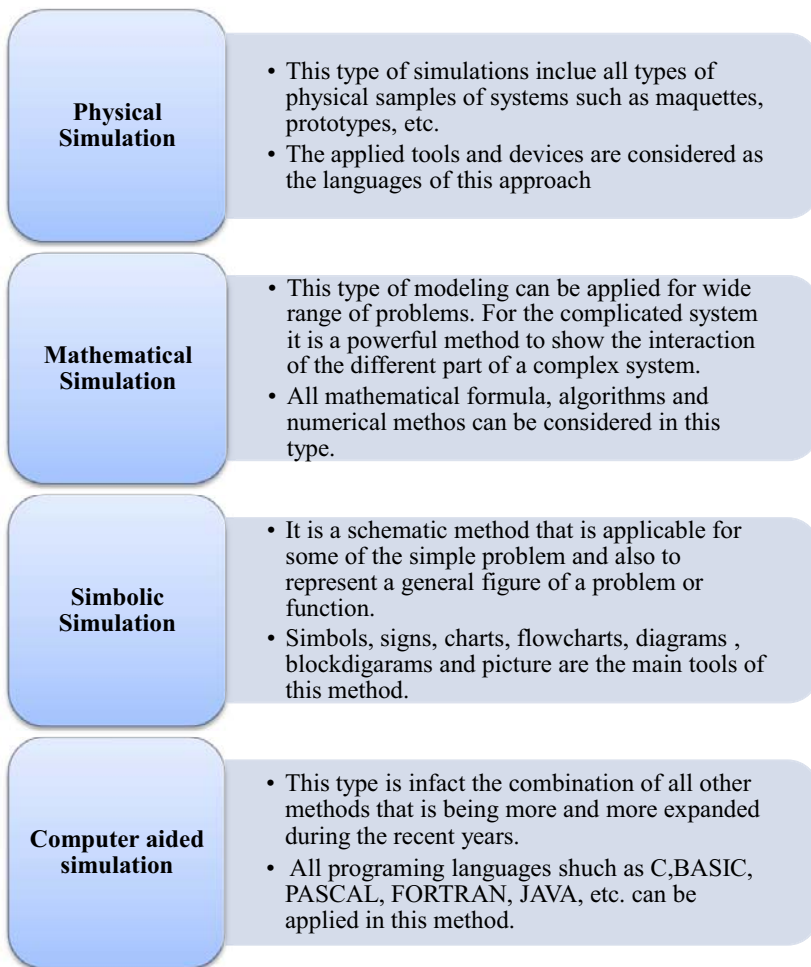


Figure 4.2. A brief introduction about some of the modeling approaches.

4.3. Mathematical modeling of the human heart function

As we have discussed before, the simulation approaches are powerful tools to describe the complicated systems. Because of the complexity in the structure and function, many of the bio-systems have been subject of mathematical simulations that is a powerful and flexible method among the other approaches of the simulation. In the recent years, because of development in the calculation systems such as computers and super-computers, the application of the mathematics in the simulation of the physiological systems has been widespread more and more. The human heart is one these complicated systems that has been investigated in the medical fields.

Recently, scientists have achieved impressive developments about the diagnostic or detective tools in the medical fields. The new techniques are mainly based on the imaging methods. Hence, the more powerful imaging tools give us the more detailed and accurate information about the inner organs of the body. These imaging techniques like X-ray (electromagnetic radiation), CT (X-ray computed tomography), US (Ultra-sonic) and MRI (Magnetic resonance imaging) are also applied to improve the accuracy of the mathematical models of the human heart. For instance, combination of the imaging measurements with mathematical modeling results in better evaluation of the stresses and strains of the heart structure. In the following section, we deal with the recent mathematical models of the human heart function and consider the application of the numerical methods in this way.

Generally, the modeling approaches of the heart function can be categorized in three main domains; (i) Lumped parameter models, (ii) 2-D models and (iii) 3-D models

4.3.1. Lumped models

The lumped-element model is a discrete representation of a distributed system under the certain assumptions. This type of modeling because of its simplicity in the application is widespread method of simulation in classical mechanical and electrical systems. Moreover, this approach is a powerful tool in the simulation of the sophisticated bio-systems such as human heart function. In Figure 4.4, we have compared the different compartments of the lumped models in the SDOF systems and electrical circuits with the corresponding compartment in the lumped model of the heart.

To consider the application of numerical methods in lumped-element models, first of all we need to know how a lumped model is made and about the governing equations on the model. So, in the following, we consider three different lumped parameter models of heart function presented in the recent decade.

The lumped parameter model is used to describe the behavior of distributed physical systems into discrete entities that simplifies the behavior of the distributed system under certain assumptions. This modeling approach is applicable for different systems such as mechanical systems, electrical systems, heat transfer, fluid dynamics, acoustics, rotational systems, etc (see Fig. 4.3).

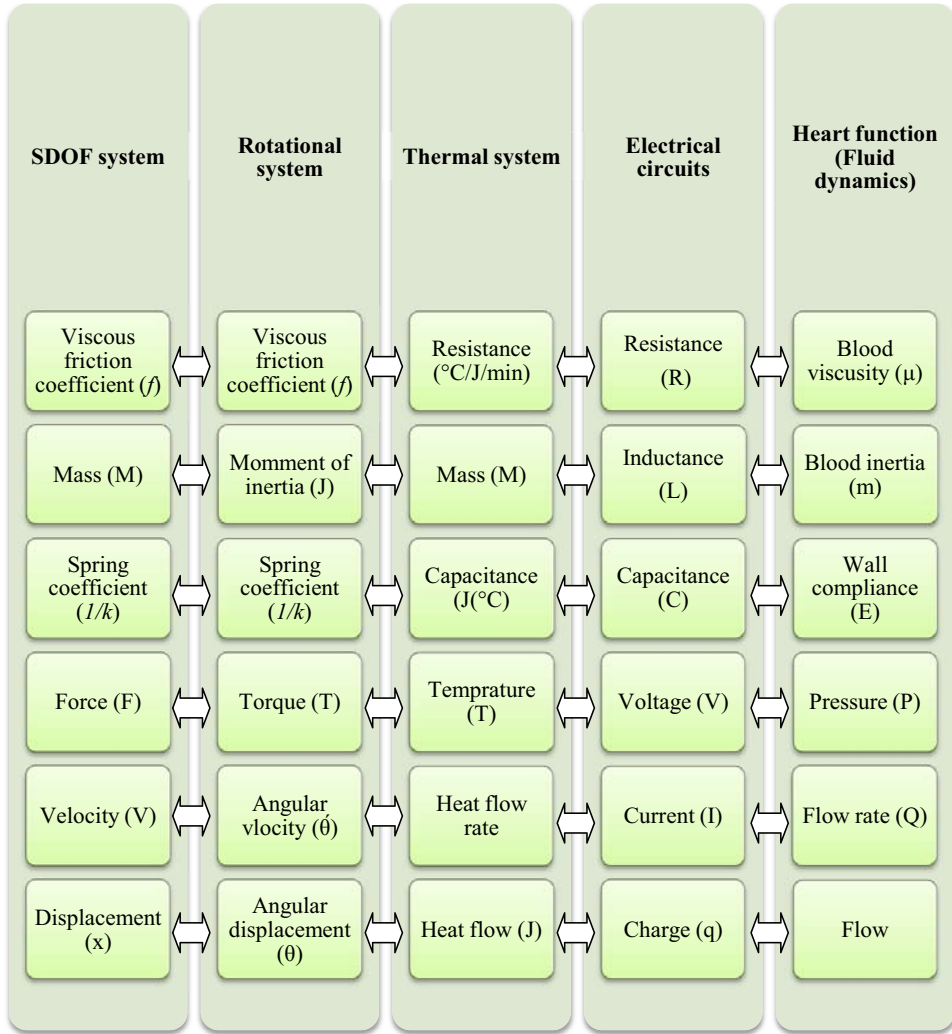


Figure 4.3. Comparison of the compartments in the different lumped models

The first lumped model that we mention here, has been presented by Alfio Quarteroni et.al. [14], 2009. They have modeled each ventricle as a vessel with a significant compliance that is time-varying. The model is begun with the relation between the internal pressure and the radius of an elastic spherical ball filled with fluid. In Figure 4.4 and 4.5, a brief representation of this simulation has been outlined.

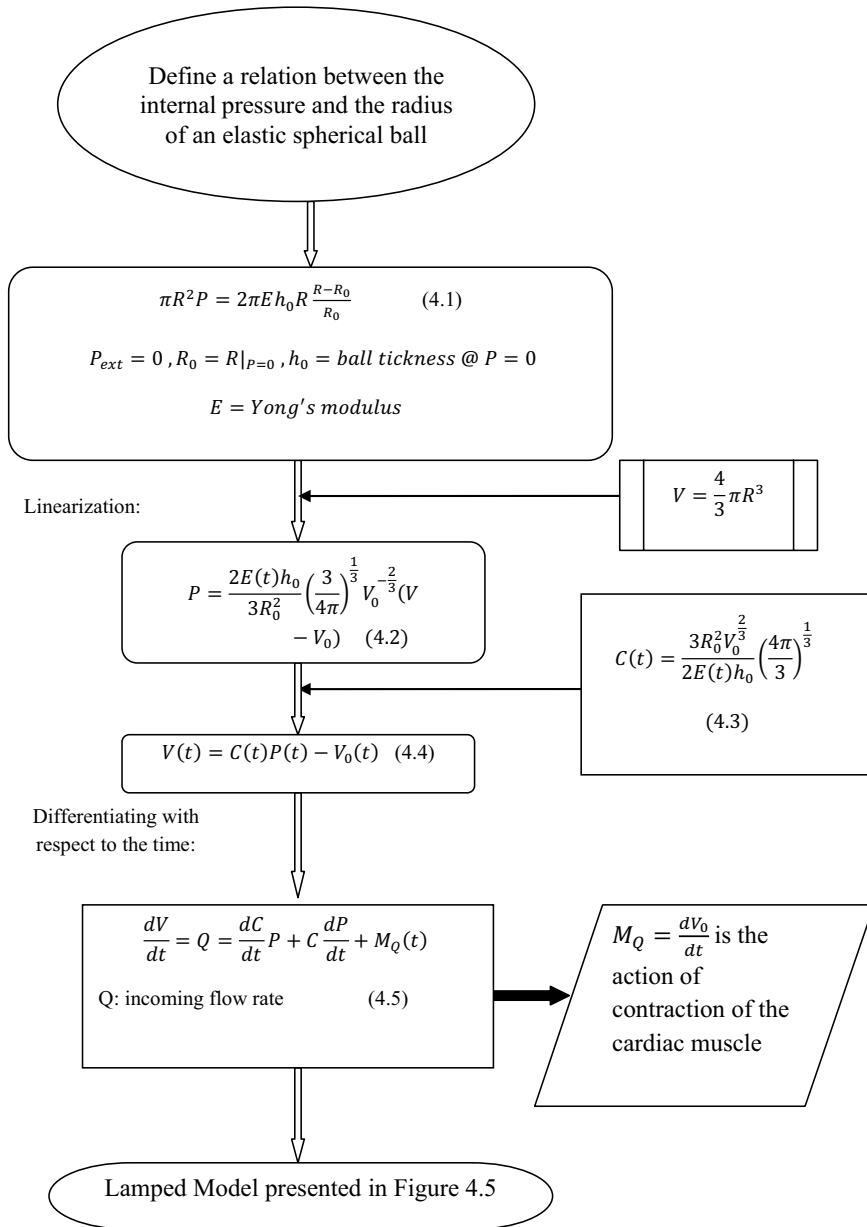


Figure 4.4. Flowchart of the simulating the ventricle presented by Alfio Quarteroni et al, 2009.

The heart valve in this simulation has been modeled by electrical diodes. Mathematically, diodes can be described as ideal model or as Shockley model. In both case, the presence of the diodes in this system introduces a nonlinear term.

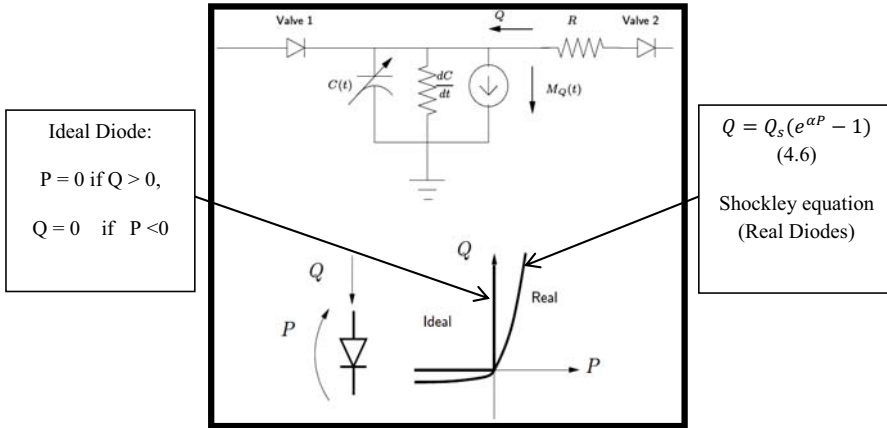


Figure 4.5. Lumped model of the ventricle simulated by Alfio Quarteroni et al., 2009, [14]. Where R : additional viscous resistance inside the ventricle, M_Q : current generator. Q_s : saturation flow rate or scale flow rate which is the magnitude of the flow rate for negative pressure, α : quality factor.

One of the diagrams presented for time-dependent compliance $C(t)$ in the equation (4.3), has been addressed in [26, 27].

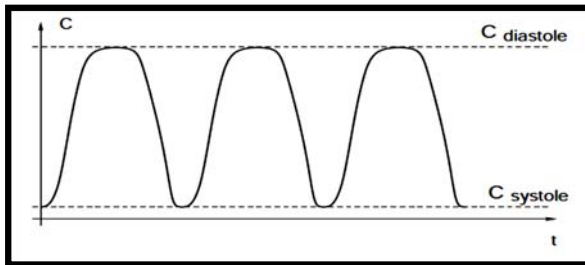


Figure 4.6. A representation of the compliance varying in the time [27].

A voltage generator for the same model (see Figure 4.7) can be another alternative for this type of modeling approach;

$$Q = \frac{dC}{dt} P^* + C \frac{dP^*}{dt} \quad \text{with} \quad P^* = P - M_P \tag{4.7}$$

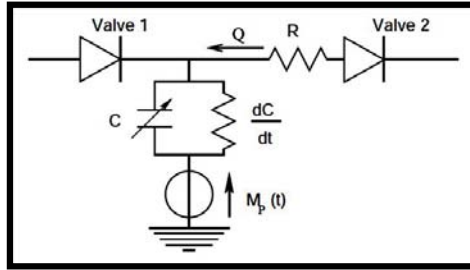


Figure 4.7. Alternative representation for the lumped parameters modeling of a ventricle; stimulating the circuit with a voltage generator, instead of a current one. After [27]

The second lumped model that we consider here has been introduced by Eunok Jung and Wanho Lee, 2006, [28]. They have applied the linear formulation according to the Ohm's law, volume conservation and the definition of the compliance to present the lumped parameter model of the whole blood circulation system (see Figure 4.8).

Three basic linear equations applied in this simulation are as following;

- Ohm's law: $Q(t) = \frac{\Delta P(t)}{R}$,
- Volume conservation: $\frac{dV(t)}{dt} = Q_{in}(t) - Q_{out}(t)$
- And Compliance relation: $V(t) = V_d + C(t)P(t)$.

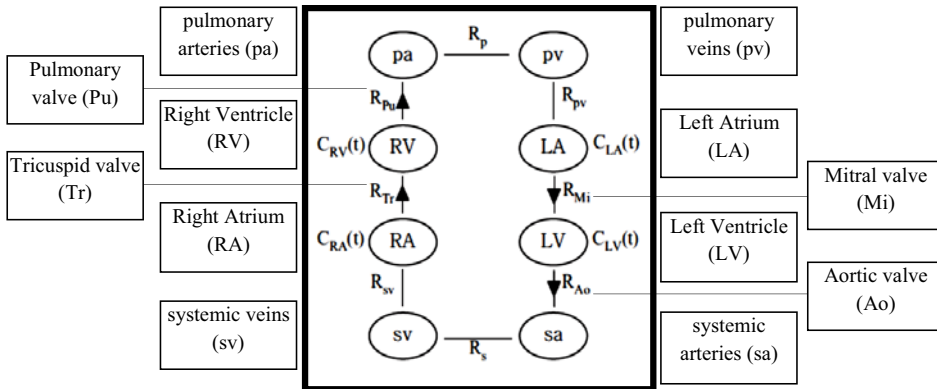


Figure 4.8. Lumped model of the cardiovascular system including heart, systemic circulation and pulmonary circulation; R_p , R_{pv} , R_s and R_{sv} are assumed resistance between related compartments [28].

For example if we apply these formulas for the left atrium and left ventricle with considering the mitral valve between them, the linear relation between volume and pressure is:

$$\frac{d(C_{LA}(t)P_{LA}(t))}{dt} = \frac{P_{pv}(t)-P_{LA}(t)}{R_{pv}} - \frac{S_{Mi}(t)(P_{LA}(t)-P_{LV}(t))}{R_{Mi}} \quad (4.8)$$

Where $S(t)$ is a step function which acts on the heart valves and is equal to one when the valve is open and zero when it is closed which means that the heart valves work as the ideal valves (i.e. as soon as the gradient of pressure is negative valves will be closed). So, in this type of modeling the nonlinear term (Shockley equation for modeling the real diodes as cardiac valves) is neglected. By the same way we obtain a system of eight linear ODEs which are transient in the time (eq. 4.9).

By extracting the values of the pressure and volume and calculating the compliance from the P-V diagram at the eight points (which are chosen at the end of each phase period (see Figure 2.10)), we obtain the initial values for the equations.

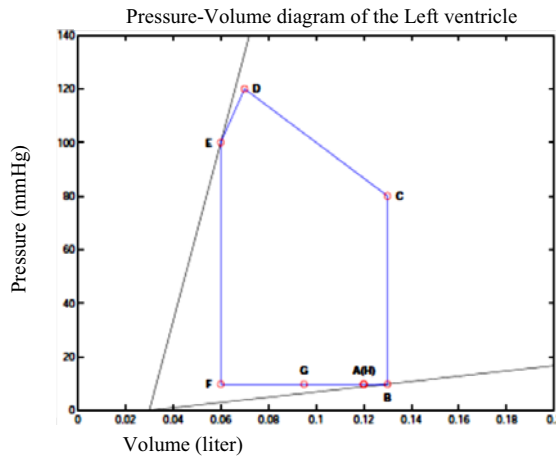


Figure 4.9. Pressure-Volume diagram of the left ventricle which shows the linear relation of the P-V in the 7 stages of the heart function; AB=Atrial Contraction, BC=Isovolumetric Contraction, CD=Rapid Ejection, DE=Reduced Ejection, EF=Isovolumetric Relaxation, FG=Rapid Filling, and GH=Reduced Filling [28].

In the next step, the backward Euler method has been applied to solve the system of equations (see equation 4.9). The time domain is discretized, so we have $t=n\Delta t$ and $P^n=P(n\Delta t)$. The obtained equations have been presented in Eq. 4.9. In these equations, the states of valves which are depend on the values of the pressure at the same time, have been found by try and error, so this system can be assumed linear, otherwise it is nonlinear system.

$$\left\{ \begin{array}{l}
\frac{C_{LA}^{n+1} P_{LA}^{n+1} - C_{LA}^n P_{LA}^n}{\Delta t} = \frac{P_{pv}^{n+1} - P_{LA}^{n+1}}{R_{pv}} - \frac{S_{Mi}^{n+1} (P_{LV}^{n+1} - P_{sa}^{n+1})}{R_{Mi}} \\
\frac{C_{LV}^{n+1} P_{LV}^{n+1} - C_{LV}^n P_{LV}^n}{\Delta t} = \frac{S_{Mi}^{n+1} (P_{LA}^{n+1} - P_{LV}^{n+1})}{R_{Mi}} - \frac{S_{Ao}^{n+1} (P_{LV}^{n+1} - P_{sa}^{n+1})}{R_{Ao}} \\
\frac{C_{sa} (P_{sa}^{n+1} - P_{sa}^n)}{\Delta t} = \frac{S_{Ao}^{n+1} (P_{LV}^{n+1} - P_{sa}^{n+1})}{R_{Ao}} - \frac{P_{sa}^{n+1} - P_{sv}^{n+1}}{R_s} \\
\frac{C_{sv} (P_{sv}^{n+1} - P_{sv}^n)}{\Delta t} = \frac{P_{sa}^{n+1} - P_{sv}^{n+1}}{R_s} - \frac{P_{sv}^{n+1} - P_{RA}^{n+1}}{R_{sv}} \\
\frac{C_{RV}^{n+1} P_{RV}^{n+1} - C_{RV}^n P_{RV}^n}{\Delta t} = \frac{P_{sv}^{n+1} - P_{RA}^{n+1}}{R_{sv}} - \frac{S_{Tr}^{n+1} (P_{RA}^{n+1} - P_{RV}^{n+1})}{R_{Tr}} \\
\frac{C_{RV}^{n+1} P_{RV}^{n+1} - C_{RV}^n P_{RV}^n}{\Delta t} = \frac{S_{Tr}^{n+1} (P_{RA}^{n+1} - P_{RV}^{n+1})}{R_{Tr}} - \frac{S_{Pu}^{n+1} (P_{RV}^{n+1} - P_{pa}^{n+1})}{R_{Pu}} \\
\frac{C_{pa} (P_{pa}^{n+1} - P_{pa}^n)}{\Delta t} = \frac{S_{Pu}^{n+1} (P_{RV}^{n+1} - P_{pa}^{n+1})}{R_{Pu}} - \frac{P_{pa}^{n+1} - P_{pv}^{n+1}}{R_p} \\
\frac{C_{pv} (P_{pv}^{n+1} - P_{pv}^n)}{\Delta t} = \frac{P_{pa}^{n+1} - P_{pv}^{n+1}}{R_p} - \frac{P_{pv}^{n+1} - P_{LA}^{n+1}}{R_{pv}}
\end{array} \right. \quad (4.9)$$

Another type of heart's function modeling has been presented by the C. Luo et al, 2008, [29]. This model is like the first presented model but in their model (see Figure 4.10), they have applied the role of the septum (the wall between two ventricles) in the ventricular interaction as a compartment and also the role of pericardium (which is surrounding the heart) as the compliance of non-activating pericardium.

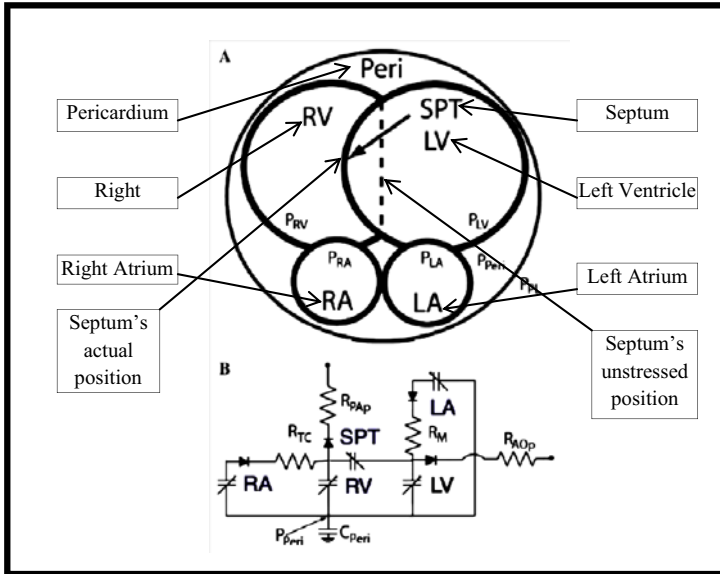
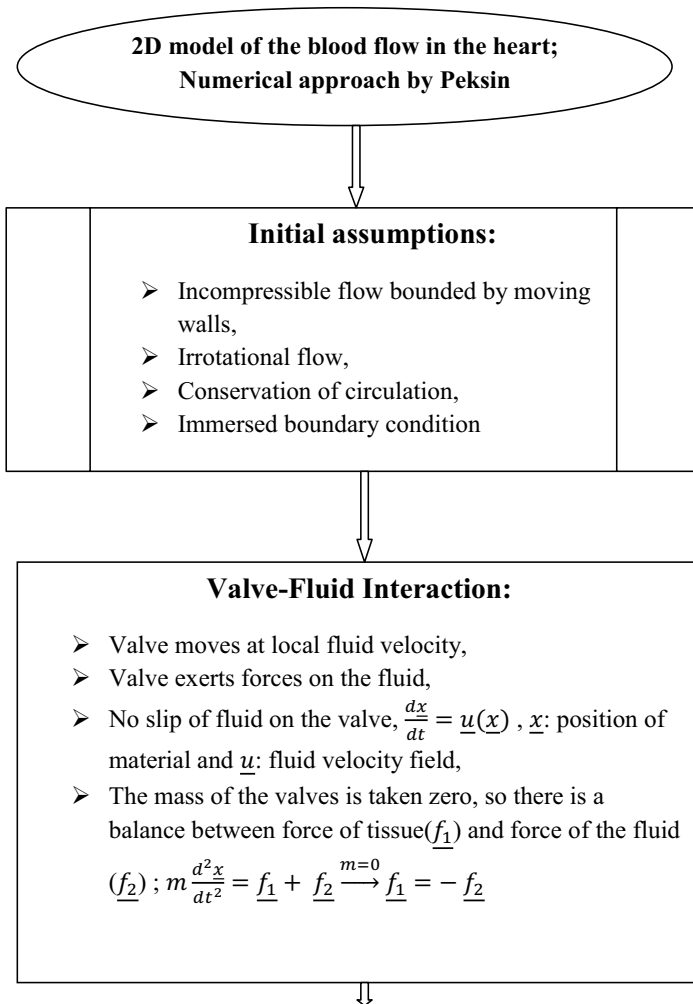


Figure 4.10. The lumped simulation of the heart function with the 8 compartment (SPT = interventricular septum, C_{Peri} = Compliance of non-activating pericardium). After [29]

4.3.2. Two dimensional models

One of the first multi-dimensional simulations of the heart function has been implemented by Charles S. Peskin 1973, [30]. He has introduced the immersed boundary method (IBM), [31], to simulate the interaction between fluid flow and the tissues of the dog's heart. In this method, the heart's model is immersed in a box filled with fluid of the same density and viscosity as blood and the governing equation on the fluid in the heart has been assumed as the Navier-Stokes equations. In the following, we have introduced the procedure that has been applied by Peksin to simulate the blood flow in the heart. We should mention that here we only outline this procedure in a very general way, in order to find more details about this subject and applied assumptions and formulations in this method, the reader can refer to [30], [31] and [35].





Boundary Conditions:

Boundary forces:
 Let “s” be a material parameter for the boundary curve $\underline{x}(s, t)$
 $f(s)ds$: transmitted force from boundary to the fluid,

$$\int_{s \in (B \cap R)} \underline{f}(s) ds = \int_{s \in B} \underline{f}(s) \begin{cases} 1 & \underline{x}(s) \in R \\ 0 & \underline{x}(s) \notin R \end{cases} ds =$$

$$\int_{s \in B} \underline{f}(s) \left(\int_{\underline{x} \in R} \delta(\underline{x} - \underline{x}(s)) \right) ds = \int_{\underline{x} \in R} \left(\int_{s \in B} \underline{f}(s) \delta(\underline{x} - \underline{x}(s)) ds \right) ds$$

, Note that the impulse function δ is two dimensional.

$$\underline{F}(\underline{x}) = \int_{s \in B} \underline{f}(s) \delta(\underline{x} - \underline{x}(s)) ds \quad (4.10) \approx \text{As the force density in the fluid due to the boundary.}$$


In the same way, we can rewrite the non-slip condition:

$$\frac{d\underline{x}}{dt} = \underline{u}(\underline{x}) \xrightarrow{\text{rewrite}} \frac{d\underline{x}(s)}{dt} = \int_{\underline{x} \in D} \underline{u}(\underline{x}) \delta(\underline{x} - \underline{x}(s)) d\underline{x} \quad ,$$

D=fluid domain (4.11)

In the discrete domain we can also rewrite the equation (4.10) in the following form:

$$\underline{F}(\underline{x}) = \lim_{N \rightarrow \infty} \frac{1}{N} \sum_{k=1}^N \underline{f}_k \delta(\underline{x} - \underline{x}_k) \quad (4.12) \quad ; \text{ force density for the sample points in the fluid.}$$


The Governing equations of fluid forced by the boundary:

$$\frac{\partial \underline{u}}{\partial t} + \underline{u} \cdot \nabla \underline{u} = -\nabla p + \eta \nabla^2 \underline{u} + \underline{F} ; \quad (4.13)$$

Navier – Stokes equations

$$\nabla \cdot \underline{u} = 0 ; \quad (4.14)$$

Incompressible flow orthogonal to the gradient of the arbitrary vector in the same region.

$$\underline{F}(\underline{x}) = \lim_{N \rightarrow \infty} \frac{1}{N} \sum_{k=1}^N \underline{f}_k \delta(\underline{x} - \underline{x}_k) ; \quad (4.15)$$

Force density in the fluid due to the boundary

$$\frac{d\underline{x}_k}{dt} = \int_{fluid} \underline{u}(\underline{x}) \delta(\underline{x} - \underline{x}_k) d\underline{x} ; \quad (4.16)$$

No slip of fluid on the boundary

$$\underline{f}_k = \underline{f}_k(\underline{x}_1, \underline{x}_2, \dots) ; \quad (4.17)$$

Material properties of the boundary (for the active boundaries, this relation will vary with the time.)

- 4.13-14 are fluid equations, equations 4.15-17 couple boundary and fluid.

One sample of numerical scheme for the Navier-Stokes equations based on the finite difference method has been presented in by J. Chorin [32]. Here, we skip to deal with the details of this scheme. The next step is coupling the boundary conditions with the Navier-Stokes equation. Peksin has presented new procedure to combine the boundary conditions which involves equations 4.15-17 with the governing equations on the fluids (equations 4.13-14). In the following, we consider this procedure.

Coupling the boundary and fluid equations:

This procedure has been represented in order to applying the forces of the boundary to the fluid and considering the effect of local fluid velocity on the boundary.

Defining a function $D_{ij}(\underline{x}_k)$ to replacing 2-dimensional impulse $\delta(\underline{x} - \underline{x}_k)$ such as:

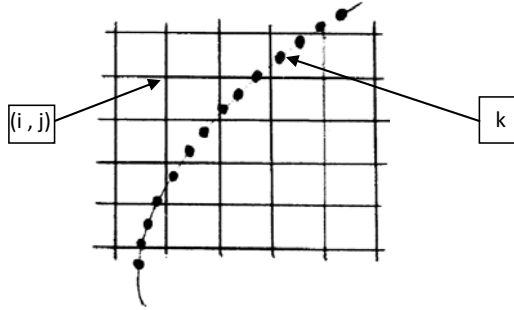


Figure 4.11. Coupling of the boundary and fluid points. [30]; i, j : fixed mesh points of the fluid, k : movable sample points of the boundary.

$$\left\{ \begin{array}{l}
 (4.15): \quad \underline{F}(\underline{x}) = \lim_{N \rightarrow \infty} \frac{1}{N} \sum_{k=1}^N f_k \delta(\underline{x} - \underline{x}_k) \\
 \rightarrow \quad \underline{F}(\underline{x}) = \frac{1}{N} \sum_{k=1}^N f_k D_{ij}(\underline{x}_k) \quad (4.18) \\
 (4.16): \quad \frac{d\underline{x}_k}{dt} = \int_{fluid} \underline{u}(\underline{x}) \delta(\underline{x} - \underline{x}_k) d\underline{x} \\
 \rightarrow \quad \underline{x}_k^{n+1} = \underline{x}_k^n + \delta t \sum_{ij} (\delta x)^2 \underline{u}_{ij} D_{ij}(\underline{x}_k^n) \quad (4.19)
 \end{array} \right.$$

$\delta t = \text{time step} \quad \delta x = \text{mesh width}$

$$\text{Let } \varphi(r) = \begin{cases} \frac{1}{4} \left(1 + \cos \frac{\pi r}{2} \right) & |r| \leq 2 \\ 0 & |r| > 2 \end{cases},$$

$$\text{Then } D_{ij}(\underline{x}) = h^{-2} \varphi(x - i) \varphi(y - j)$$

Where $\underline{x}(xh, yh)$ and $h = \delta x$.

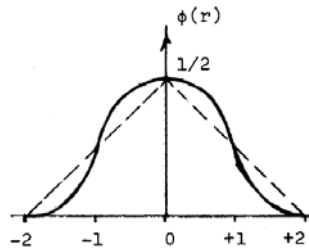


Figure 4.12. representation of the ϕ function

Properties of φ ;

$$\left\{ \begin{array}{l} \text{(i) } \int \varphi(r) dr = 1 \\ \text{(ii) } \varphi(r) \geq 0, \text{ and } \varphi(r) = 0 \text{ for } |r| \geq 0 \\ \text{(iii) For all } r \quad \sum_{k_{\text{even}}} \varphi(r-k) = \sum_{k_{\text{odd}}} \varphi(r-k) = \frac{1}{2} \rightarrow \\ \quad \sum_k \varphi(r-k) = 1 \\ \text{(iv) For all } r \quad \sum_k \varphi^2(r-k) = \frac{3}{8} \\ \text{(v) } \sum_k \varphi^2(r-k) \geq \sum_k \varphi(r-k) \varphi(s-k) \end{array} \right.$$

Properties (i) and (ii) show that applying arbitrary function $D_{ij}(\underline{x}_k)$ instead of impulse function in equations 4.18 and 19 which “can be interpreted as a local interpolation of the velocity field from the mesh to the boundary and the local distribution or spreading of the boundary forces onto mesh, with conservation of the total force. [30]”

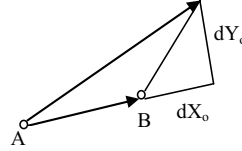
The next step is to describe the forces between boundary points (equation 4.17) in a more detailed way. We define \underline{x}_{AB} which represents the link between points A and B in the boundary material and we have

$$\left\{ \begin{array}{l} \underline{x}_{AB} = \underline{x}_B - \underline{x}_A \\ R_{AB} = |\underline{x}_{AB}| \\ T_{AB}(R_{AB}); \text{ tension in link } AB \\ \hat{a}_{AB} = \frac{\underline{x}_{AB}}{R_{AB}} \text{ unit vector of } \underline{x}_{AB} \\ \underline{f}_A = N \sum_{B=1}^N T_{AB} \hat{a}_{AB} \end{array} \right.$$

And \underline{f}_A is transmitted force from the point A at the boundary to the fluid.

To consider the changes of \underline{f}_A due to the perturbation of the other points ($B=1, 2, \dots, N$) at the boundary, the Q_{AB} function is introduced which represents a rotation in coordinate of link AB. So Q can be defined

$$d \underline{f}_A = \sum_{B \neq A} Q_{AB} d \underline{x}_{AB} = \sum_{B \neq A} Q_{AB} (d \underline{x}_B - d \underline{x}_A)$$



$$\frac{d \underline{f}_A}{N} = \begin{bmatrix} T' & 0 \\ 0 & \frac{T}{R} \end{bmatrix} \begin{pmatrix} d x_o \\ d y_o \end{pmatrix} \text{ where } T' = \frac{dT}{dR} \tag{4.20}$$

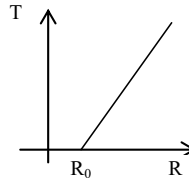
Generally Q can be presented as $Q = N \tilde{S} \begin{bmatrix} T' & 0 \\ 0 & \frac{T}{R} \end{bmatrix} S$, where S ($\tilde{S}S = I$) is the rotation between global coordinates system and local coordinates system of link AB which is parallel to the link.

In this way, three types of material properties for the links between the boundary's points (physical behavior of the boundary) can be considered;

1) Passive flexible links: no resistance to bending

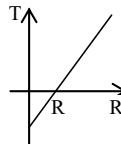
$$T = \begin{cases} K(R - R_0) & R \geq R_0 \\ 0 & R < R_0 \end{cases} \tag{4.21}$$

K=Stiffness, R_0 =Unstretched length



2) Prosthetic links: resistance to extension and compression (due to the arrangement of the links)

$$T = K(R - R_0) \quad R > 0 \tag{4.22}$$



For example the “railroad bridge”, can be a pattern to represent the links between points in the boundary materials.

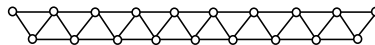


Figure 4.13. Model of “Railroad bridge” connection between nodes.

3) Heart muscles: this type of connection will be considered in the next chapter.

In Figure 4.14, the heart model geometry applied in the Peksin's simulation has been shown.

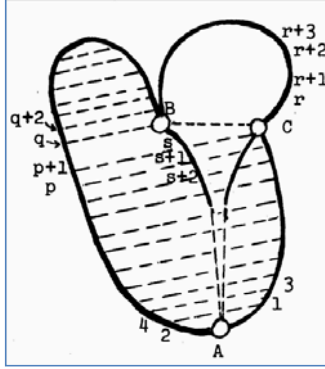


Figure 4.14. Simulation of the heart structure by Peksin in the immersed boundary method. [30]

As it has been mentioned, this modeling approach was one of the first mathematical multi-dimensional models of the animals' heart function (dog's heart) which has been used by some other researchers in modeling the human heart function. Another research with the same procedure has been done by T.Ottesen et al, 2004, [22]. Their model is based on the Peksin's model with some modifications. The boundary conditions, has also been analyzed by immersed boundary method. In the following, we have pointed to the mathematical background of this modeling approach.

This 2-dimensional modeling is started by applying the Newton's second law for the fluid;

$$\rho \frac{Du}{Dt} = -\nabla p + \mu \nabla^2 u + F \quad (4.23)$$

In fluid dynamics, $\frac{D}{Dt}$ is defined as the time rate of change for a fluid element (material derivative or Lagrangian derivative). Thus

$$\frac{D\gamma}{Dt} \equiv \frac{\delta\gamma}{\delta t} + u \cdot \nabla \gamma \quad , \quad \text{div} u = \nabla \cdot u = \frac{\partial u}{\partial x} + \frac{\partial u}{\partial y} + \frac{\partial u}{\partial z} \quad (4.24)$$

Then we have

$$\rho \left(\frac{\partial u}{\partial t} + u \cdot \nabla u \right) = -\nabla p + \mu \nabla^2 u + F \quad (4.25)$$

This is the Navier-Stokes equation for incompressible fluid flow. Based on the continuity equation (Chorin and Marsden, 1998) for incompressible fluid flow in the presence of the source-sink effects, we have;

$$\nabla \cdot u = \psi(x, t) \quad (4.26)$$

Applying the equation 4.26 is one of the modification done comparing with the mentioned Peksin's model ($\nabla \cdot \underline{u} = 0$; 4.14).

The function $\psi(x, t)$ represents the area flow rate density distribution of the sources and sinks and derived from the momentum of the fluid leaving or entering the sources or sinks, which is a function of $Q_k(t)$ (the flow rate) and is been expressed in equation 4.27.

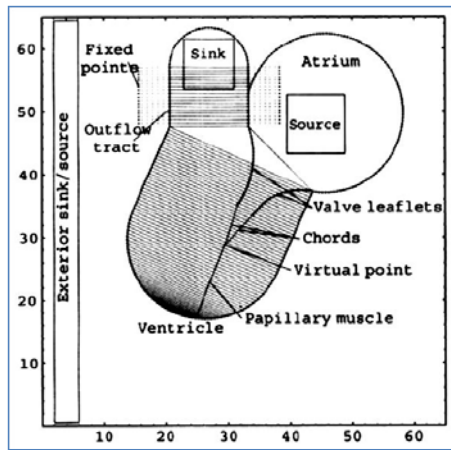


Figure 4.15. The heart model Modified by T. Ottesen et al, which shows the source location in the atrium and sink in the aorta. The key parameters for the geometry are: 1) The diameter of the mitral ring (2.97 cm), 2) The diameter of the aortic outflow tract (2.58 cm), 3) The angle between these two (45°), 4) The length of the ventricle (5.42 cm) [22].

$$\psi(x, t) = \psi(p(t), t)(x) = \sum_{k=1}^2 Q_k(p(t), t) \psi_k(x, t) \quad (4.27)$$

$k = 1 \equiv \text{source}, k = 2 \equiv \text{sink}$

For the source ($k=1$) in the atrium, a linear relationship between $Q_1(t)$ and $P_1(t)$ can be chosen;

$$Q_1(t) = \frac{P_{src} - P_1(t)}{R_{src}} \quad (2.28)$$

Where R_{src} represents the resistance against the flow through the source.

The second modification can be implemented on the P - Q relationship in the sink, by applying the three-element Windkessel model of the arterial impedance shown in Figure 4.16, which is also linear but with a time-varying pressure reservoir.

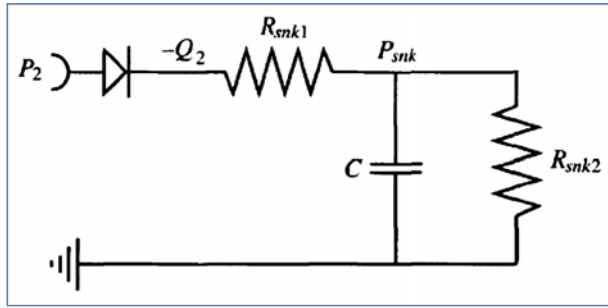


Figure 4.16. The 3-element Windkessel model coupled to a diode valve

$$-Q_2(t) = \begin{cases} \frac{P_2(t) - P_{snk}(t)}{R_{snk1}} & \text{if } P_2(t) \geq P_{snk}(t) \\ 0 & \text{if } P_2(t) < P_{snk}(t) \end{cases} \quad (4.29)$$

$P_2(t)$: pressure at the aortic outflow,

R_{snk1} : proximal arterial resistance to the flow,

$P_{snk}(t)$: pressure at the beginning of the arterial system, which is governed by the differential equation

$$C \frac{dP_{snk}}{dt} = -Q_2(t) - \frac{P_{snk}(t)}{R_{snk2}} \quad (4.30)$$

R_{snk2} : represents the peripheral (boundary) resistance,

C : arterial compliance which can be a function of $P_{snk}(t)$, results in a nonlinear impedance model.

So we have

$$C(P_{snk}) \frac{dP_{snk}}{dt} = -Q_2(t) - \frac{P_{snk}(t)}{R_{snk2}} \quad (4.31)$$

These differential equations have been solved by the help of finite difference method. To see the procedure, reader can refer to [22,32].

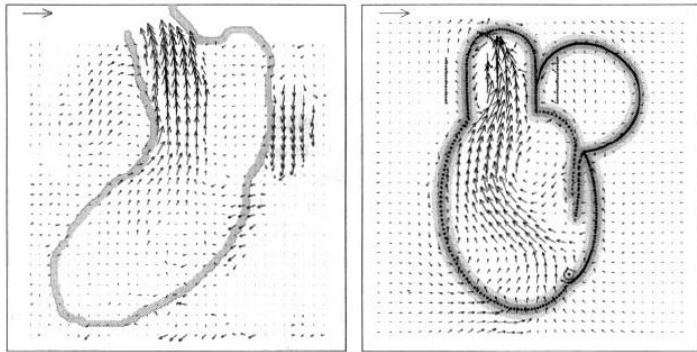


Figure 4.17. Comparison of the results of the mathematical model and the experimental data obtained from MRI. This figure referred to the peak aortic outflow at 702 ms after the beginning of the early mitral inflow.[22]

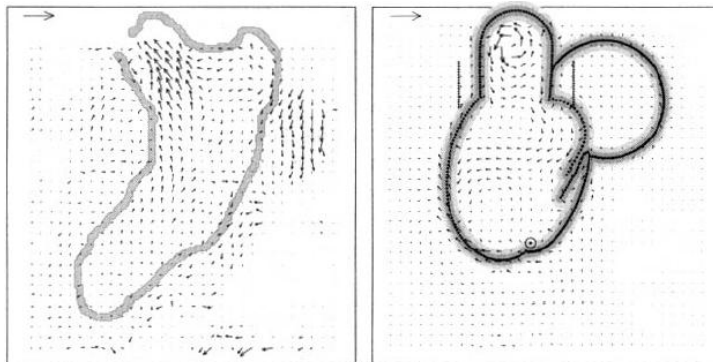


Figure 4.18. End of systole: 882 ms after the beginning of the early mitral inflow. The left part show MR data and the right one shows the data obtained from the mathematical simulation. [22]

The third modification is regarding to the dimensions of the heart's geometry. The geometry of the first model was set based on the dog's heart, while in this model new dimensions is more matched with the data obtained from the MR recordings.

The fourth improvement of the model is about the using of linear springs from the boundary points on the straight part of the outflow tract to fixed points in the domain in order to prevent excessive translational and rotational movements during the ejection phase, while in the original model it was freely floating in the surrounding domain.

Since in this simulation consists of several parameters, the improvement in these values can give the better-matched results. The finite difference method applied on differential equations in 2-D model, can be applied also for the 3-D model. Another alternative is to apply finite element model to solve the differential equations, which is a more time-consuming approach of the simulation, but can give more accurate results.

2.3.3. Three dimensional modeling

During the recent years, some researchers have presented different 3-D models of the human heart structure. Some these models have been based on the development of 2-D models specially Peksin's model and immersed boundary method such as the E. Griffith researches, [33]. In the following, we introduce some of these models which are based on the numerical methods.

The first considered model is a computational model of the heart structure based on the contraction waves in the spiral elastic bands [34]. This type of modeling has been presented by Anna Grosberg, 2008, [34]. According to the previous researches (Torrent-Gausp models) and MIR data, A.Grosberg has modeled the complex arrangements of the helical fibers into a simple model by simplifying the helical arrangements of the myofibrils as well as the way that they bundle together and it is based on the assumption in which the heart muscles behave as an elastic tissue.

The initial idea of this model has been proposed to answer the paradox between the amount of the myofibrils contraction (which is 15% of its volume which consequently shall result in 28% contraction of internal volume) and ejected blood from the left ventricle (which is 50% of the left ventricle volume).

In Figure 4.19, we can see the basic shape of the spiral tubes for different angles, but the structure of the heart is more complex than this. The introduced structure by A.Grosberg [34], which contains ventricular volumes is not axis-symmetric and shapes a parabolic chamber for the left ventricle and half-parabolic one for the right ventricle shown in Figure 4.20.

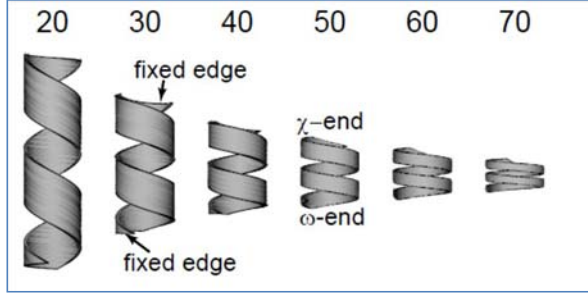


Figure 4.19. The shape of spiral muscles bands (tubes) for different angles [34].

The mathematical structure of the non-axi-symmetric spiral chamber model of the heart in Cartesian coordinate described as following;

$$\left. \begin{aligned}
 z &= z_{cent} + \xi, \quad \text{while} \quad z_{cent} = C_1 - C_2 \frac{\theta^{A_1}}{A_2} \exp \left[-\frac{\theta}{B_2} \right] \\
 r &= \sqrt{z + C_3} [Factor 1] [Factor 2] + \zeta \\
 Factor 1 &= 1 + C_4 \cos \left(\frac{\theta - \theta_{crossing}}{2} \right), \\
 Factor 2 &= 1 + C_5 \exp \left(-(\theta - \theta_{right})^2 \right) \\
 \theta_{crossing} &= \pi \left(-1 + \cot \frac{\pi}{A_1 B_2} \right) \\
 x &= r \cos \theta, \quad y = r \sin \theta \\
 -\frac{w}{2} < \xi < \frac{w}{2}, \quad 0 < \zeta < t, \quad 0 \leq \theta \leq \theta_{max}
 \end{aligned} \right\} \quad (4.32)$$

Where A, B and C are constant, “ z_{cent} ” represents the long-axis coordinate, $\theta_{right}=3.8\pi$, w is width and t is the thickness of the band.

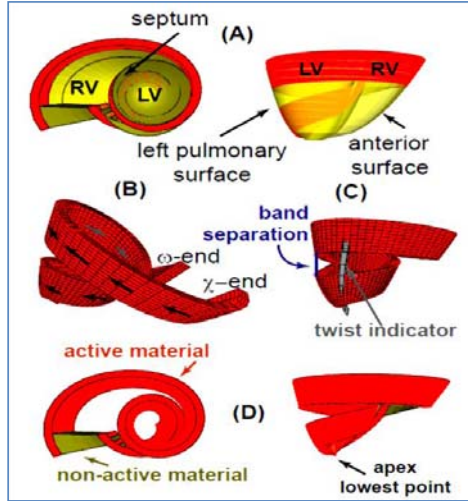


Figure 4.20. Model of the ventricles based on the non-axi-symmetric spiral chambers represented by A.Groberg [34].

In the following table, the values of the geometrical parameters in the former formulas for the adult heart are given.

Parameter	Value	Remarks
θ_{max}	4.08π	Indicating the number of turns
C_2	7	Indicating the long axis dimension
C_1	4.9	Indicating the fiber angle
A_1	1.3	
A_2	0.5	
B_2	2	
C_4	$\frac{1}{6}$	Fiber orientation at the myocardium
C_3	-0.77	Fiber orientation at the apex (lowest point)
C_5	1	Right ventricle size
w	2.5 cm	Band width
t	0.5 cm	Band thickness

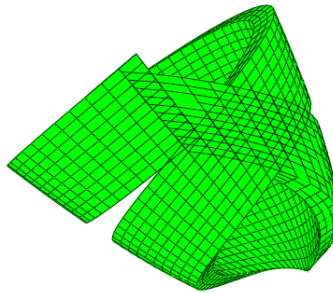
Table 4.1. Values of the geometrical parameters introduces in the equations 4.32.

The assumptions about the material properties applied in this model are:

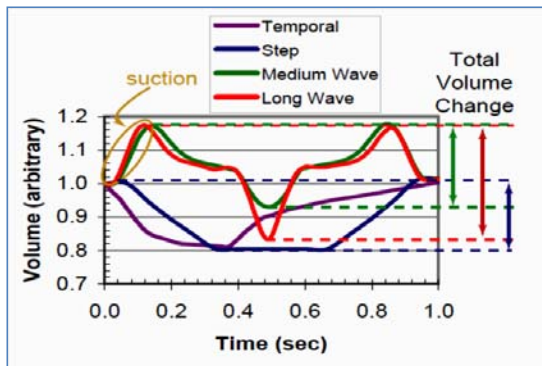
- Incompressible materials
- Poisson ratio $\nu=.48$
- E_Y =Young's modulus of the muscle fiber for active materials (producing the forces) (i.e. linear elasticity behavior when they are not excited)
- Young's modulus of the non-active materials (not producing force) is one fourth of the active materials.

The next step of this modeling process is to apply the boundary conditions on the model. Comparing with the medical data, the non-active materials were constrained in the x-y-directions and the lowest point of the chambers (called apex) was restrained in z-direction.

This model has been analyzed by the finite element method in the ABAQUS/Standard in which each node excited independently. In Figures 2.21 and Figure 2.22 we can see some results obtained from the simulation.



(a)



(b)

Figure 4.21. simulation of the heart structure; (a): discretization of the domain, (b): the volume changing of the model with different excitation functions represented in the [34].

In this work, some other approaches (such as double helical band method shown in Figure 4.22) for this type of modeling have been also considered by the finite element method and then the model has been applied to simulate some of the heart diseases such as defects in the heart muscles. This failure simulation has been exerted on the FE- model by changing the mechanical properties of the damaged muscles from flexible to rigid elements.

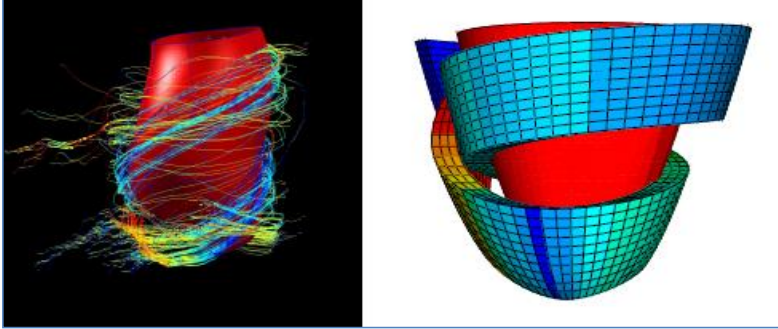


Figure 4.22.double helical model of the heart: The left part shows the muscle fiber and the right part is the simplified model by the double helical band method [34].

By the progress of numerical methods, the first 2D-model presented by Peksin has been improved from some aspects and the Immersed Boundary Method (IBM) been developed in 3D-model. As we have mentioned before, in the immersed boundary method, the structure and blood flow in the heart is considered at the same time, i.e. the simulation of the heart function includes analyzing the material behavior of the heart walls, heart valves, fluid dynamic of blood and the interactions between the fluid and heart tissues. The assumptions of the fluid flow are still the same ones which chosen for the simulation in 2-D immersed boundary method [30], although few changes implemented than the initial models specially by considering sink-source effect of the fluid flow on the governing Navier-Stokes equations. But the geometry of the model has been improved rapidly because of the more powerful numerical method and more powerful imaging techniques.

Peksin and McQueen [35], have developed their 2-D Immersed Boundary model of the heart to a 3-D model and solved the governing equations by second-order Runge-Kutta method. Besides that, some modifications have been implemented on the governing equations related to the material behavior of the heart's fibers. By comparing the following equations with equations 4.13-17, we can find these modifications.

$$\rho\left(\frac{\partial u}{\partial t} + u \cdot \nabla u\right) + \nabla p = \eta \nabla^2 u + f \quad (4.33)$$

$$\nabla \cdot u = 0 \quad (4.34)$$

$$f(x, t) = \int F(q, r, s, t) \delta(x - X(q, r, s, t)) dq dr ds \quad (4.35)$$

$$\frac{\partial X}{\partial t}(q, r, s, t) = u(X(q, r, s, t), t) = \int u(x, t)\delta(x - X(q, r, s, t))dx \quad (4.36)$$

$$F = \frac{\partial}{\partial s}(Tt); \text{ force balance on the mass-less fiber} \quad (4.37)$$

$$T = \sigma\left(\left|\frac{\partial X}{\partial s}\right|; q, r, s, t\right) \quad (4.38)$$

$$t = \frac{\partial X/\partial s}{|\partial X/\partial s|} \quad (4.39)$$

Where equation 4.35 is the relationship between the force densities $f(x,t)dx$ and $F(q,r,s,t)dqdrds$ and equation 4.36 represents the no-slip condition of the viscous fluid, i.e. fibers move at the local fluid velocity. And equations 4.37-39 are fiber equations. And

$u(x,t)$: fluid velocity,

$p(x,t)$: fluid pressure : Unknown functions,

$f(x,t)$: force per unit volume applied by the fibers to the fluid,

$x=(x_1,x_2,x_3)$: spatial position (in Cartesian coordinates),

(q,r,s) : material curvilinear coordinates aligned with the fibers, (if we hold (q,r) and t fixed but let s vary, then the equation $x = X(q,r,s,t)$ defines the space curve that happens to be occupied by the fiber whose coordinates are (q,r) at the time t)

$T(q,r,s,t)$: fiber tension (fiber stress) as a function of fiber strain $\left(\left|\frac{\partial X}{\partial s}\right|\right)$ in equation (2.37); constitutive law of fibers.

$F(q,r,s,t)$: fiber force density,

$t(q,r,s,t)$: unit tangent vector; since (q,r) are constant along any given fiber, the vector $\frac{\partial X}{\partial s}$ is tangent to the fibers.

$$\delta x = \delta(x_1)\delta(x_2)\delta(x_3); \quad \text{3-D Dirac delta function} \quad (4.40)$$

We know $\int_{\Omega} \delta(x - X)dx$ equals to 1 if X is within Ω otherwise is 0.

Here, the connection of fluid and fiber meshes is done by a auxiliary function (φ) replacing the Dirac delta function;

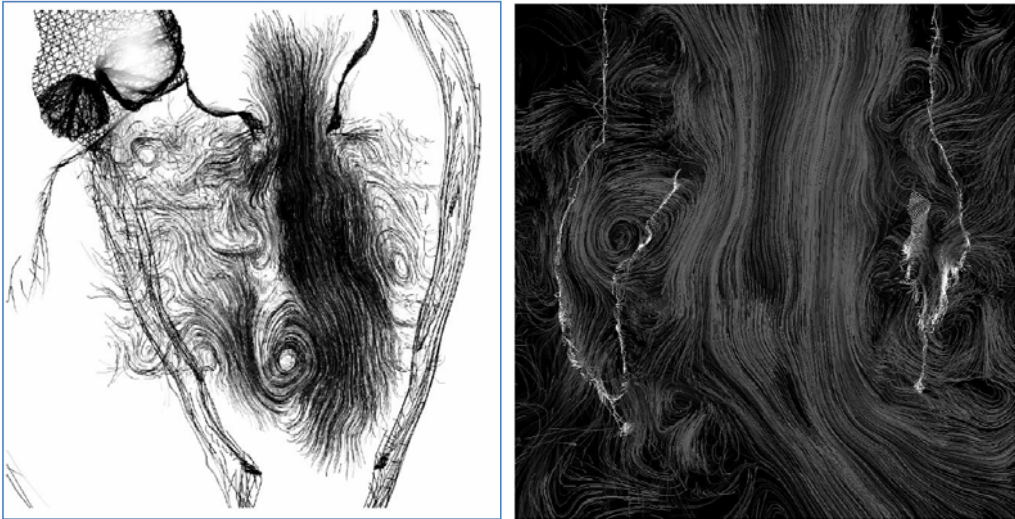
$$\delta_h(x) = \frac{1}{h^3} \varphi\left(\frac{x_1}{h}\right) \varphi\left(\frac{x_2}{h}\right) \varphi\left(\frac{x_3}{h}\right) \quad (2.40)$$

Where h is meshwidth and φ is defined as

$$\varphi(r) = \begin{cases} \frac{3-2|r|+\sqrt{1+4|r|-4r^2}}{8} & |r| \leq 1 \\ \frac{5-2|r|-\sqrt{-7+12|r|-4r^2}}{8} & 1 \leq |r| \leq 2 \\ 0 & 2 \leq |r| \end{cases} \quad (2.41)$$

For each time-step, implementing the Runge-Kutta for former equations involves the four calculation stages;

1. Calculation of the force due to material activation, (excitation function)
2. Calculation of the force applied to the fluid from material, (eq. 4.35)
3. Calculation of the Navier-Stokes equations, (eq. 4.33-34)
4. Calculation of the material movement due to fluid force, (eq. 4.36)



(a)

(b)

Figure 4.23. (a): Numerical results of analyzing the left ventricle at the filling time; the mitral valve is open and the aortic valve is closed. (b): The cross-section of the aortic valve while opening.[35]

In the last years, this model has been also developed. K.Yelick in [36], has reviewed the recent progresses in the simulation of heart based on the immersed boundary method and introduced the algorithm of the simulation with the new language program Titanium (based on the Java).

Although, the new models of the heart are more accurate, but to numerically solve the differential equations governing on such models requires more powerful and effective calculation tools. This new object-oriented language has some special characteristics that facilitate these computation processes. This language supports the following performances: (i) Multidimensional arrays, (ii) small objects, (iii) Semi-automatic memory management and (iv) optimization on parallel code.

In Figure 4.24, the latest model of the heart structure (By Peksin et al) based on the recent obtained data from the CT scans (Computed tomography) on a healthy human has been addressed. In this figure we can observe the complexity of the new model of the heart.

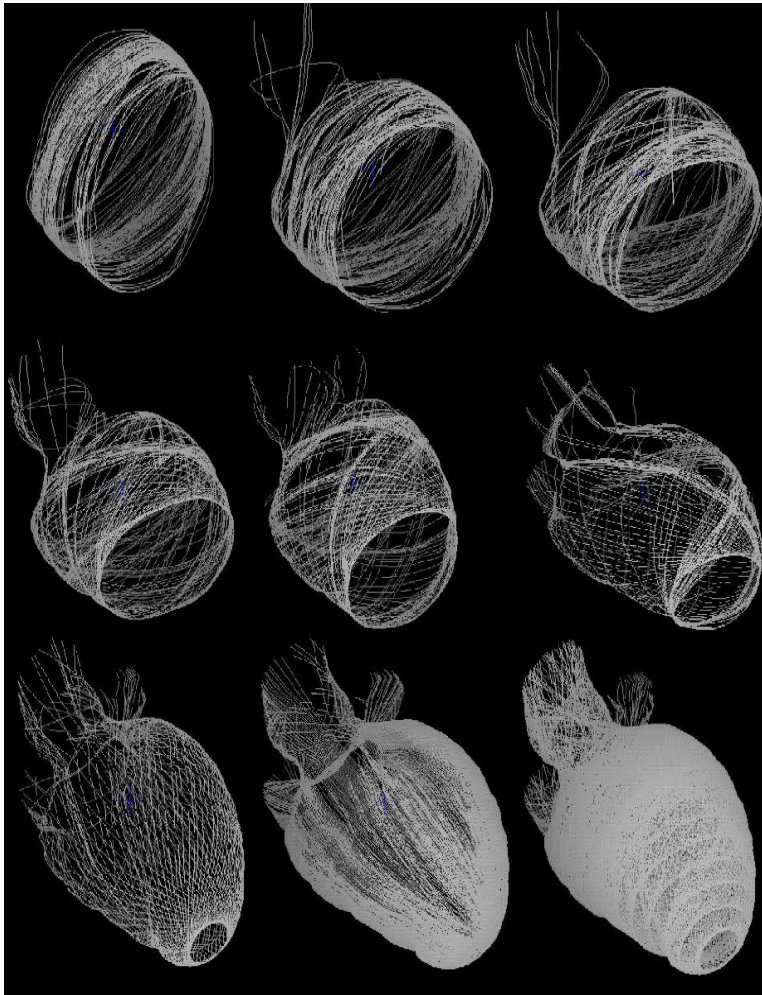


Figure 4.24. The recent heart model based on the CT scans data [36]

4.4. Application of numerical methods in imaging techniques

As we have observed, during the last years, many great advances have been achieved in the modeling of heart. These achievements are partly because of the advances in the imaging equipments such as MRI (Magnetic Resonance Imaging) that give us the more real and accurate data about the heart geometry, and also because of the advances in the numerical methods that give us this ability to handle these massive data in a more effective way. For example, the Volumetric Finite Element (see Fig 4.25) is one of the applicable numerical method to convert the obtained data from MR-imaging to the 3-D model (4-D with considering the time) of the heart geometry [37]. For more information reader can refer to [37, 38, 44].

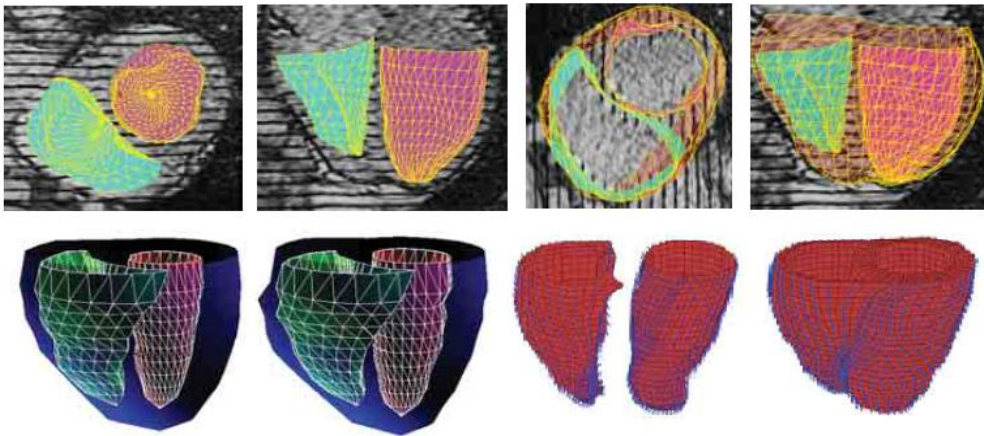


Figure 4.25. Numerical analysis of the obtained data from imaging process from the heart; applying the 2-D SPAMM images (SPAtial Modulation of Magnetization) to build a volumetric Finite Element model of the heart, [37].

4.5. Applicable tools for numerical analysis of the heart function

In this section, we address some of available tools which are based on the numerical methods and can be applied to simulate the heart structure and function;

I) PHYSBE is one of the initial models of the circulatory system written in the block-diagram format and implemented in the Simulink, [39]. This model is a lumped parameter model and is relatively

simple to understand and work with. In [40], we can find several applications of PHSBE about the simulation of different parts of the heart or simulating the defects in the heart function.

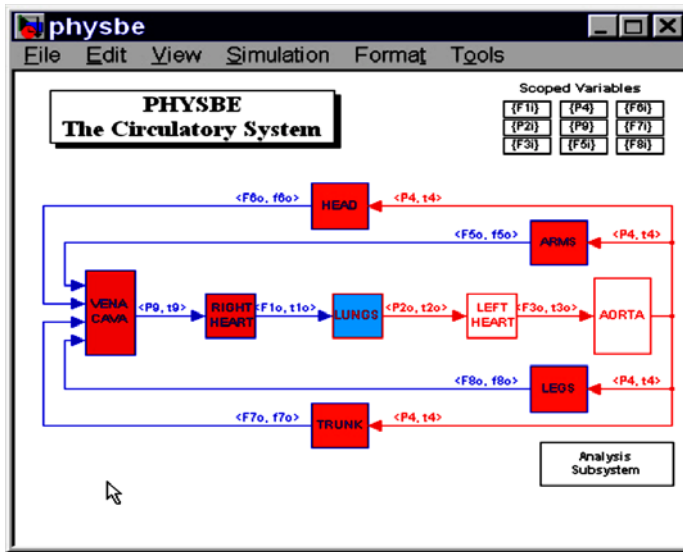


Figure 4.26. Block Diagram of PHYSBE simulation. Three main circulatory system components to the nine individual subsystem blocks; (i) The pulmonary system (lungs), (ii) The coronary system (vena cava, right heart, left heart, aorta), (iii) The systemic system (arms, head, trunk, legs). [39]

II) ADINA FSI is a program to analyze the fluid-structure interaction (FSI) and nonlinear behavior of fluid and structure and their interactions can be analyzed (<http://www.adina.com/fluid-structure-interaction.shtml>). This program is based on the finite element method (with available shell, 2D and 3D solid, beam, iso-beam, contact surfaces, etc. elements) and is applicable for consideration of the large deformations, inelasticity, contact, temperature-dependency, incompressible, slightly compressible and low-speed or high-speed compressible.

III) FEBiO is a program to solve the nonlinear large deformations in solid biomechanics based on the implicit finite element method. This program has been developed to model and analyze 3D nonlinear problems and supports quasi-static and dynamic analysis. With this program, two other programs are needed, one is a preprocessor (*PreView*) and the other one is a postprocessor (*PostView*) [41, 42 and 43]. This software is relatively user-friendly and can be also modified and extended by the users. ABAQUS input files can also be imported to this program.

IV) The Heart Simulator is a Java-based online heart simulator according to the mathematical model of the heart function to consider the different aspect of ventricular properties, for example, P-V loop, effect of preload, contractility, afterload, heart rate, valves, Frank-Starling Law, etc. Daniel Burkhoff and Marc Dickstein at the Columbia University have developed this program for medical students (<http://ccnmtl.columbia.edu/projects/heart/>).

This program was provided to help the students to understand and explore the dynamic interactions in the cardiovascular system and cardiac function in health and disease. In this simulator, the relationship between pressure and volume of blood flow in the heart can be investigated by manipulating different parameters in the P-V diagram.

4.6. Summary

In this chapter, we have dealt with simulation of the heart function. Three different strategies of modeling have been considered: Lumped parameter models, two and three dimensional models. And for each modeling strategy, application of numerical methods has been investigated. 2D model presented by Peksin has been considered in details, and then we perused the immersed boundary method in this way which is the basic approach for many of new 2D and 3D models and should be solved numerically. Then, we have dealt with 3D models. Two different models have been considered; one based on immersed boundary method and the other one based on non-axi-symmetric spiral chamber. The solutions of the mathematical models for both cases are solved numerical with finite element method and Range-Kutta or finite difference method. After that, the application of numerical methods in the imaging techniques has been also addressed. At the end, some of the applicable softwares for simulation of the heart function have been presented.

5 Mathematical modeling of the heart muscles

In this chapter, we describe the anatomy and physiology of the heart muscles in details. Then we consider the mechanical behavior of the heart muscles and deal with the cross-bridge theory about the heart muscles. And finally we consider one of the numerical approaches applied to analyze the mechanical behavior of the heart muscles.

5.1. Introduction

To consider the simulation approach of the heart muscles and application of numerical methods in this way, firstly we need to know about their structure. Because of the complexity of heart structure, describing the behavior of the heart muscles is one of the most complex and challengeable subjects in the study of the cardiovascular system. Although, the cells of the heart muscles are similar to the skeleton muscles, but the force development within the heart muscles is different and depends on the length of the muscles, so these muscles have more complicated characteristics than skeleton muscles. On the other hand, due to the different stage of the heart beat, different boundary condition is present on the heart muscles (as opening and closing the heart valves). Other challenges can be considered as high nonlinearity in the property and geometry of the heart structure, coupling of the chemical-electrical-solid-fluid reactions during a heart beats and irregularity in time steps of heart function, etc.

5.2. Anatomy of the heart muscles

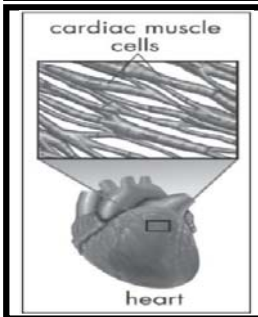
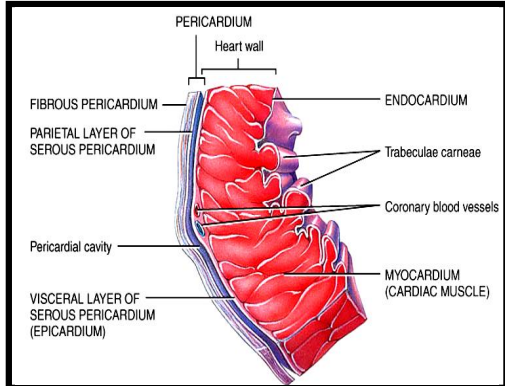
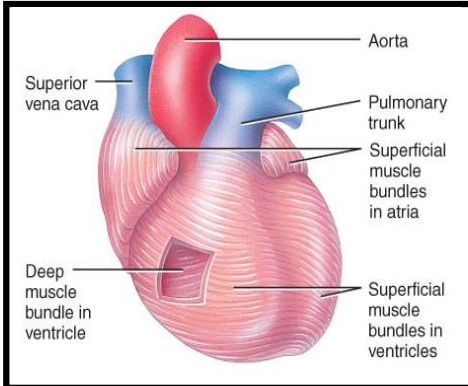
As the general characteristics of the muscle cells we can mention to the ability of potential conduction through their membrane surface and translation of electrical signals to the mechanical contractions. Generally, muscle cells are categorized into two groups; Smooth muscles and Striated muscles. The smooth muscles are located in the walls of blood vessels and contractile visceral organs.

Both cardiac muscles and skeleton muscles belong to the striated muscles category. Though they have much similarity in the structure, but they do not have the identical behavior. Striated muscles consist of parallel cylindrical units which work together in very smart way to make the contraction force in the muscles.

The main model representing the behavior of the movement of the striated muscles is called cross-bridge. In the following diagram we have outlined the structure and mechanism of the heart muscles contraction. Figures are derived from [19, 21, 22, 45, 46].

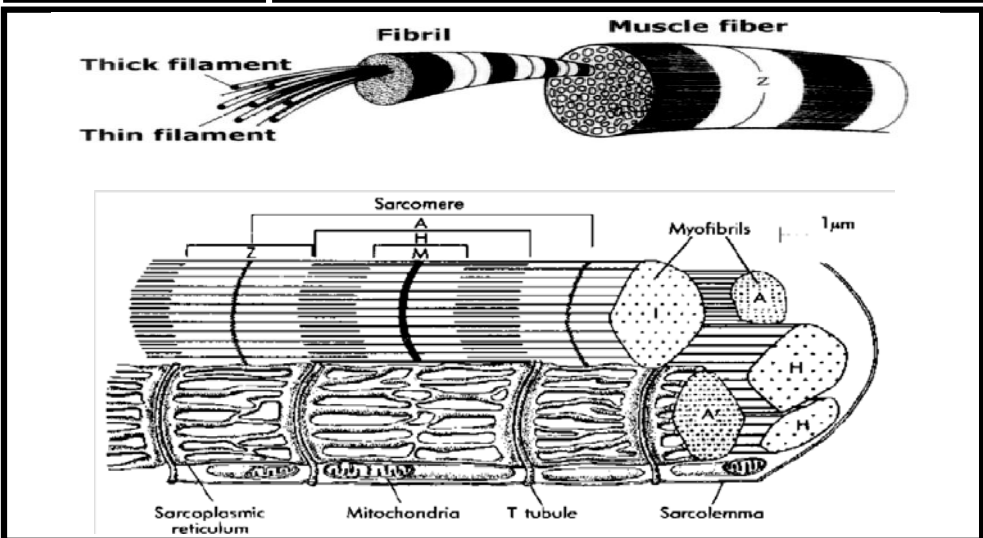
Three layers of the heart wall:

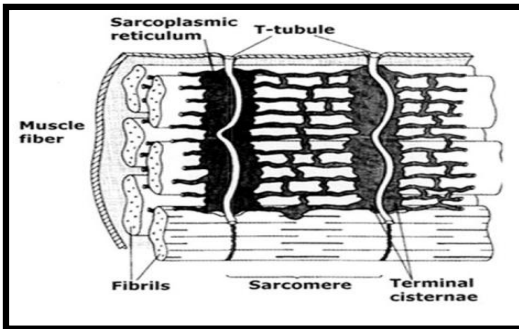
1. Epicardium (outer layer), 2. Myocardium (middle layer), 3. Endocardium (inner layer)



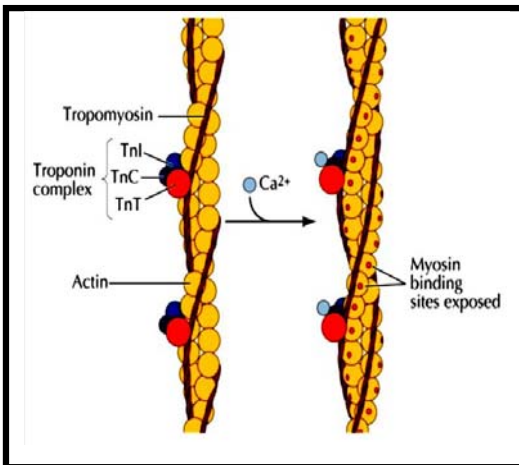
Cardiac muscle cells are called **Myocytes** and they have tubular structures.

Contractile units are called **Sarcomeres** consist of two parallel contractile filaments (proteins) known as **actin** (thin filament) and **myosin** (thick filaments). The sarcomere is found between two Z lines (or so-called Z discs, about 2.5 μm long) in a muscle fibre.





Tropomyosin is a thin protein strand that under normal resting conditions covers the actin-myosin binding site. **Troponin** is a macromolecule with three subunits: troponin T (TnT) which binds the troponin complex to tropomyosin, troponin C (TnC) which has binding sites for calcium and troponin I (TnI) binds to actin.



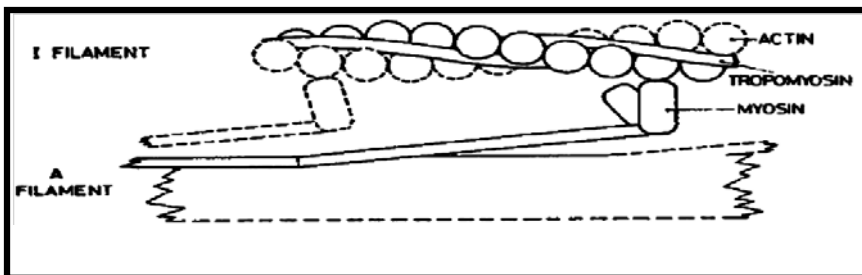
Process of muscle contraction:

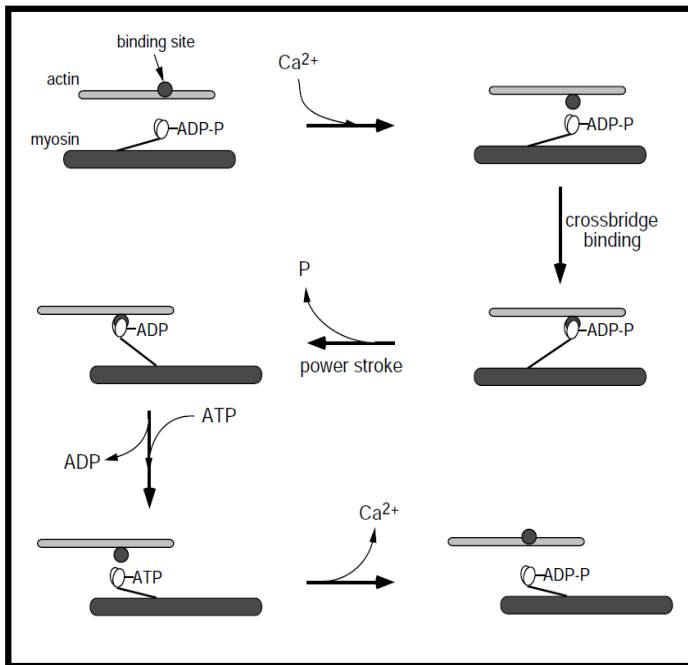
1. Action potential (electrical depolarization of the cell) is transmitted across a synapse from a neuron and spreading into the interior of the cell via T-tubules.

2. Then, by the action potential voltage-gated Ca^{2+} channels are opened and Ca^{2+} enters into the cell, triggers the release of further Ca^{2+} from the sarcoplasmic reticulum: increasing in the concentration of calcium.

3. Calcium binds to TnC and then TnI releases from actin allowing the tropomyosin molecule to be pulled away from the actin-myosin binding site.

4. Myosin binds to actin and due to the hydrolysis of ATP (which is located on the head of myosin), the head rotates and extends the hinge region (between head and tail).
(Adenosine-5'-triphosphate (ATP): transports chemical energy within cells for metabolism. Adenosine diphosphate (ADP): is the product of ATP).

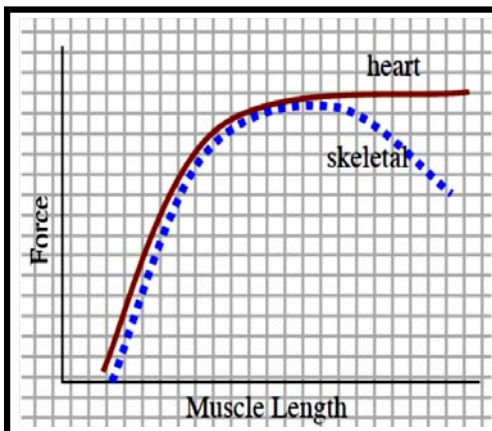




5. Force is produced when the crossbridges bind and then causing the thin filaments to slide along the thick filaments (results in the contraction). The movement of the crossbridge to its new position is called the **power stroke**.

The greater the peak calcium the greater the number of potential actin-myosin bonds, the greater the amount of force production.

6. During the relaxation time the uncoupling of the actin-myosin bond occurs which is immediately upon reaching the preferred bent configuration and the crossbridge releases its ADP (hydrolyzed ATP) and binds another ATP molecule, causing dissociation from the actin binding site and return to its initial perpendicular and unbound position and a new ATP molecule binds to the ATP site on the myosin head.



The force production is depends on:

1. The amount of calcium during contraction phase,
2. The cardiac muscle length which is proportional to average sarcomere length. The optimal length to have the optimal overlap is about 2.3-2.3 microns and more than this value, the force decrease because fewer myosin heads can reach and bind with actin. This situation can happen in skeleton muscles, but cardiac muscles are restricted to stretch beyond

5.3. Modeling of the Force-Velocity relationship: The Crossbridge Theory

As we have mentioned in the previous section, the ability of a muscle to produce the tension force depends on the size of overlap between thick and thin filaments (myosin and actin). A.V Hill (1983) has presented one of the first models of muscle contraction. Hill observed that under isometric tension (the tension generated by a muscle contracting at a fixed length), the force-velocity equation (5.1) governing the relationship between v and p , where v is the constant rate of shortening in the muscle and p is the load;

$$p = p_0 f(v); \quad (p + a)v = b(p_0 - p) \tag{5.1}$$

Where a and b are parameters which are fitted to experimental data (a and b are constants with dimensions of force and velocity, respectively) and p_0 is the isometric tension which is constant for skeletal muscle cells, dependent on length in cardiac cells. We can write also

$$v = b \frac{(p_0 - p)}{(p + a)} ; \text{ Velocity as function of force and } p = \frac{bp_0 - av}{b + v} ; \text{ Force as function of velocity.}$$

Inserting $p=0$, we have $v_0 = bp_0/a$ and represents the maximum contraction velocity of the muscle. By this value we can replace the b in the equation (5.1);

$$\frac{v}{v_0} = \frac{p_0 - p}{p + a} \tag{5.2}$$

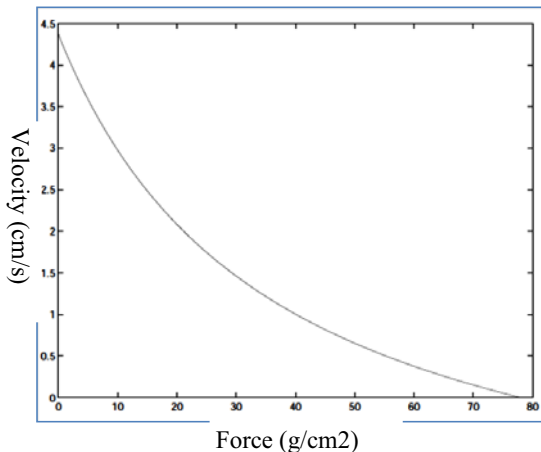


Figure 5.1. A typical Hill-curve representation [48].

In Figure 5.2, the muscle fiber has been modeled as a contractile element in term of an elastic element.

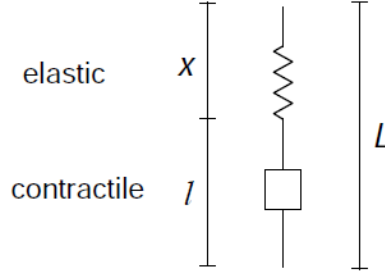


Figure 5.2. Two-element model of muscles fiber; l : the length of the contractile element, x : the length of the elastic element, $L = l+x$: the total length of the fiber. [46]

Let define the velocity of the contraction, v , as

$$v = -\frac{dl}{dt} \tag{5.3}$$

Assuming the load is a function of length of elastic element $p=P(x)$ we have

$$\frac{dp}{dt} = \frac{dp}{dx} \frac{dx}{dt} = \frac{dp}{dx} \left[\frac{dL}{dt} - \frac{dl}{dt} \right] \xrightarrow{eq.(5.2)} = \frac{dp}{dx} \left[\frac{dL}{dt} + v \right] \xrightarrow{eq.(3.1)} = \frac{dp}{dx} \left[\frac{dL}{dt} + b \frac{(p_0-p)}{(p+a)} \right] \tag{5.4}$$

If we assume the linear elastic property for the elastic element, we can write

$$P = \alpha(x - x_0) \tag{5.5}$$

Where x_0 is the length at resting.

Replacing equation 5.5 in the equation 5.4, we can rewrite

$$\xrightarrow{\frac{dp}{dx}=\alpha} \frac{dp}{dt} = \alpha \left[\frac{dL}{dt} + b \frac{(p_0-p)}{(p+a)} \right] \tag{5.6}$$

As it has been mentioned, this model is one of the primary and simple models of the muscle fiber. In the recent years, with the help of new measurement techniques, more exact formulation for force–

velocity relation has been presented which fits also with experimental data, for example, equation 5.7 presented in [48];

$$v = \frac{(p_0^* - p)b}{p+a} \left(1 - \frac{1}{1 + e^{-k_1(p - k_2 p_0)}} \right) \quad (5.7)$$

Where p_0 is the measured isometric force and p_0^* is the predicted isometric force according to the Hill model. In this equation, there are two constant correction terms k_1 and k_2 ; k_1 [1/force] is related to the steepness of the high-force curvature and k_2 [dimensionless] determines the relative force at which the correction term reaches its half value.

The former models consider only the mechanical factors in the muscle fiber behavior while there are some other chemical factors such as concentration of the calcium which play important roles in contracting muscle fiber and should be taken into account.

For example, in Hunter-McCulloch-TerKeurs (HMT) model (1998) [48], the effect of calcium concentration into the Hill's model is considered:

$$\frac{d[Ca^{2+}]_b}{dt} = f_1([Ca^{2+}]_i, [Ca^{2+}]_b, p_{active}, p_0) \quad ; \text{ Calcium binding description} \quad (5.8)$$

$$\frac{dz}{dt} = f_2(z, \lambda, [Ca^{2+}]_b) \quad ; \text{ The proportion of actin sites available for cross-bridge binding} \quad (5.9)$$

$$p_0 = f_3(\lambda, z) \quad ; \text{ Isometric tension} \quad (5.10)$$

$$p_{active} = f_4(p_0, \lambda, t) \quad ; \text{ Force-velocity relation given by a Hill function} \quad (5.11)$$

Where $[Ca^{2+}]_i$ represents the intracellular calcium concentration, $[Ca^{2+}]_b$ represents the concentration of calcium bound to Troponin C (TnC) which itself depends on the tension force p , $[Ca^{2+}]_i$ and λ (length). For more information the reader can refer to [48].

5.4. Application of numerical methods to analyze the heart muscles

As we have observed in the previous section, mathematical modeling of the heart muscles (myocardium) results in some differential equations [50, 51], and the procedure of solution for these equations is mostly based on numerical methods [18, 52]. For instance, in [18], one the solution procedures to analyze the mechanical behavior of left ventricle muscles as poroelastic fluid-structure problem based on Darcy's law for flow through porous tissue, has been numerically solved.

5.5. Summary

In this chapter we have described the structure of the heart muscles and then we considered the mechanical behavior of the heart muscles according to the Hill's model and the effect of the calcium concentration on the force-velocity relation of heart muscle fiber. We observe that in the consideration of the heart's muscle fibers several factors should be taken into account such as

- Rate of crossbridge binding and detaching between myosin and actin,
- Length of Sarcomere,
- History of changes of length,
- The intracellular calcium concentration and calcium bound to Troponin C,
- ...

In the considered model, the linear elastic behavior was taken as a mechanical property of the muscle fiber which makes the modeling simpler but on the other hand neglects the nonlinearity of the fibers which happens due to nonlinear geometry and large deformation of the heart muscles. Furthermore, the deformation of the muscle is not only as the results of active force developed in the cells and passive forces developed by the elastic properties of the tissue but also depends on the history of the deformation. Therefore, the accurate consideration of the heart muscle fibers require advanced continuum mechanics knowledge as well as consideration of the fluid-structure reactions between heart walls and blood. On the other side, the more complete model of heart muscles, the more complicated differential equations are obtained which are difficult to be solved analytically. Hence, the effective numerical methods play important role to solve these equations.

6 Discussion and conclusion

The aim of present work was to consider the mathematical modeling of the human's heart function and investigation in the numerical methods applied for this simulation. The present work has been done from the scratch to answer the basic questions about this topic. To satisfy this purpose, first of all we have studied the structure of the heart to figure out which components constitute the heart structure and how they are interconnected to each other. Besides, the regulation system of the heartbeats and mechanical characteristics of the heart's muscles have been considered. In this part, instead of complex texts, we have provided the comprehensive charts, figures and diagrams to explain the structure of the heart in a simpler way for the beginners in this field.

Then we have done a literature study on the related researches about the mathematical simulation of the heart function. We have dealt with the different simulation approaches which have been applied in this way. They are categorized as three types of modeling; lumped models, 2-D models and 3-D models. For each approach, some sample models have been studied and application of numerical methods in these examples has been investigated.

It is found that the lumped parameter models are mostly applied to consider the specific parameters of the heart function, e.g. P-V loop. In this approach, some simplifications should be done to convert this distributed structure to the discrete components. This modeling approach takes less time for modeling comparing to the other approaches and does not need deep knowledge about the different parts of the heart's structure, and the model can often be run in a typical computer, but to find the assumed parameters and have the applicable results, it is need to adjust the model with the experimental data which is the most challengeable part of this approach.

Although, the obtained differential equations in this modeling approach are often linear and first order, but since the heartbeat is function of time (transient), so the equations should be solved numerically by marching in the time, and the Euler methods are typically used for this purpose. For nonlinear lumped models which are due to considering the nonlinearity of the heart valves, the numerical methods would play more significant role.

During the 2D and 3D modeling of the heart function which are based on the geometry of the heart the role of numerical methods is more significant. We have found that the immersed boundary method (IBM) presented by Peksin, is one of the powerful tools to numerically simulate the heart structure. This method which is applicable for the solid-fluid interactions makes a coupling between blood flow and heart muscles as well as heart's valves. So, we have studied this method in more details to find out that how it is defined and have it has been applied for the heart simulation. This method has been developed in the recent years and adopted for more realistic geometry of the heart and analyses results based on this method has been applied to make some artificial heart's valves. The obtained equations in this method are solved by numerical such as Runge-Kutta or finite difference method. For the recent 3D model of the heart based on this method, a new coding approach has been developed to optimize the computations of fluid-fiber interactions.

This work is the first step of the writer in the field of biomechanics. As we have observed this interdisciplinary science is very complicated and requires not only vast knowledge of micro and macro-structures of the bio-system (in this case the human heart) but also advanced knowledge about the mathematical modeling, numerical methods and coupled mechanical systems such as solid-fluid interactions.

For who are interested to step in this way, beside the study of the present work, the following topics are suggested to be studied to go further in this way;

- The mathematical modeling of the force generation in the heart muscles
- The mathematical modeling of the heartbeat regulation
- Application of numerical methods in the imaging processes for the inner human organs such as the heart to extract the more exact geometry of the heart
- Consideration of the applicable methods to calculate the elastic module (elastance/compliance) of the nonlinear elastic materials and for the case study it can be the elastance of the heart muscles
- Investigation about the application of immersed boundary methods (IBM) and for the case study it can be consideration of mechanical behavior of a cantilever beam located in a fluid flow to simplify the modeling of the leaflets of the heart valves
- Consideration of the role of sinks and source in the Navier-Stokes equations to study this role during the modeling of the blood flow in the heart.

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